Atrial Fibrillation

Lead Article

Atrial fibrillation: advances and perspectives - A. J. Camm, I. Savelieva

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The prevalence of atrial fibrillation (AF) continues to increase worldwide, largely affecting the elderly, but also occurring in younger patients as a result of structural heart disease, autonomic imbalance, genetic abnormality, or previous cardiac surgery. Despite major advances in the understanding of the diverse pathogenesis, electrophysiological mechanisms, and triggering factors contributing to AF, the management of this arrhythmia is still palliative in most cases. It consists of anticoagulation prophylaxis and pharmacological therapy aimed at either maintenance of sinus rhythm or merely ventricular rate control and lifelong anticoagulation. Sinus rhythm can relieve symptoms, improve cardiac function, and theoretically lessen the risk of thromboembolic events. However, prophylactic antiarrhythmic drug therapy has limited efficacy and is associated with a significant risk for proarrhythmias or noncardiac adverse effects. These limitations of antiarrhythmic drugs have led to the development of nonpharmacological approaches such as the dual-chamber atrial pacemaker or defibrillator and surgical and catheter ablation techniques. Despite all these advances, a successful curative therapy for AF is, however, relatively unusual, and preventative therapies are rarely contemplated. A fundamental question is whether “upstream” therapy of the causes of AF may increase the likelihood of successful treatment. Prevention of AF is an attractive possibility that will rely on general prevention of cardiac disease, identification of those at risk of AF, and the development of specific therapeutic strategies to prevent the evolution of an electrophysiological milieu that will support the arrhythmia.

Keywords: atrial fibrillation; epidemiology; elderly; anticoagulation; sinus rhythm; antiarrhythmic drug; pacemaker; defibrillator; catheter ablation; prevention

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Dialogues Cardiovase Med. 2003;8:183-202

HISTORY OF ATRIAL FIBRILLATION

Chaotic irregularity of the pulse has long been recognized by physicians and has been referred to as “rebellious palpitations,” “ataxia of the pulse,” “pulsus irregularis perpetuus,” “arrhythmia perpetua,” and “delirium cordis.” In 1908, taking advantage of the newly invented string galvanometer, Hering recorded an electrocardiogram of a patient with atrial fibrillation (AF) and firstly noted the absence of “action of the auricles,” meaning the P waves, although f waves were visible.1 Rothberger and Winterberg,2 in 1909, finally identified “arrhythmia perpetua” and “fibrillation of the auricles,” and in the same year, Lewis3 described various aspects of AF and demonstrated f waves corresponding to fibrillatory activity of the atria (Figure 1, page 184).4

There was controversy regarding the exact mechanisms of AF. In 1894, Engelmann reported AF caused by multiple foci in the atria and provided the first evidence for the “multiple heterotopous centers” theory, which later was supported and further developed by Lewis who suggested that such multifocal atrial activity might account for both atrial tachycardia and AF.5 Rothberger and Winterberg6 advocated a “single focus” theory when a rapidly fired single focus produced, depending on the rate, atrial flutter or AF, a predecessor of contemporary understanding of the mechanism of “focal” AF triggered by atrial tachycardia originating from pulmonary veins. In 1920, Lewis7 assumed that the atria were involved in one constant reentrant circus traveling through the vena cava and crista terminalis and suggested a “circus movement” theory for atrial flutter (and AF) that prevailed for nearly four decades, although certain refinements were added, such as a concept of a “mother” wave and “daughter” waves. Reentry in atrial tissue was initially explained on the basis of fixed anatomic circuits, but, in 1959, Moe and Abildskov8 suggested that electrical activation in AF proceeded as multiple reentrant wavelets separated by lines of functional conduction block that continuously initiate themselves (leading circle reentry) or each other (random reentry), thus creating conditions for the perpetuation...
of the arrhythmia (multiple wavelet hypothesis). Moe’s hypothesis has been further explored and substantiated by Allessie and colleagues; the first results were published in 1977.

Two main approaches to the management of AF also began to form early. In the mid-1800s, Bouillaud observed that digitalis reduced the ventricular rate dramatically even though pulse irregularity persisted, and referred to it as “opium for the heart.” In 1920, Mackenzie commented on the effects of digitalis in patients with heart failure: “The best effect of digitalis is seen in cases of heart failure with dilatation of the heart and dropsy. Eighty or ninety percent of such cases suffer from auricular fibrillation.” William Evans and Peter Swann, in 1953, observed 20 patients with mildly symptomatic AF and no identifiable underlying heart disease and concluded that “…continuous digitalization . . . is ideal treatment” and “an urge to reinstate sinus rhythm . . . should be suppressed.” However, the discovery of antiarrhythmic properties of quinidine in the early 1920s and the introduction of cardioversion for AF by Lown in 1961 boosted the role of rhythm control in the management of patients with AF. The benefits of cardioversion were summarized by Lown in his Thomas Lewis lecture “Electrical Reversion of Cardiac Arrhythmias” to the British Cardiac Society in 1967. He noted symptom relief in patients with severe palpitations and a “calm in the chest” in those who had not been aware of the presence of arrhythmia, observed hemodynamic improvement in heart failure, and called restoration of sinus rhythm “the best guarantee” against recurrent stroke in patients who had already had thromboembolic events. The Framingham Study initiated in 1948 has explored the epidemiological importance of AF and cardiovascular disease associated with this condition.

Epidemiology of Atrial Fibrillation

Twenty years ago, the prevalence of AF was said to be 0.4% of the general population. Now AF has become more common and it is present in about 1.5% of the population. While relatively unusual in the young, it is found in 5% of 65- to 70-year-olds, rising to over 20% of those over 90 years. The increased prevalence of AF is largely due to the increasing age of the population. However, even when corrected for age, there still appears to be an increase in the likelihood of AF, much of which is silent and revealed only by routine medical
examinations and electrocardiograms (preoperative checks, insurance examinations, screening medicals, etc). People now grow old with a significant degree of heart disease that once was fatal, but is now survived. Such residual heart disease provides a substrate for AF. Projected data from the North-American ATRIA (AnTicoagulation and Risk Factors In Atrial fibrillation) study of adults aged 20 years or older have shown that the number of patients with AF is likely to increase 2.5-fold during the next 50 years, with more than 50% of affected individuals aged 80 years or older (Figure 2).

ASSOCIATION WITH DISEASE AND RISK FACTORS

AF is often found in association with underlying heart disease, such as hypertension, which can be present in half or more of the patients with AF, and heart failure (Figure 3). The prevalence of AF associated with left ventricular dysfunction and con-

Figure 2. Projected number of patients with atrial fibrillation in the United States between 2000 and 2050. Data from the ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study. Upper and lower curves represent the upper and lower numbers based on sensitivity analysis.

Figure 3. (A) Prevalence of hypertension as an underlying cardiovascular disorder in patients with atrial fibrillation. (B) Prevalence of atrial fibrillation in heart failure studies.
gestive heart failure varies from 4% to 50% depending on New York Heart Association (NYHA) class. Although AF is classically caused by mitral stenosis,16 thyrotoxicosis,17 and alcohol,18 these are relatively minor associations. AF is a common complication of acute myocardial infarction19 and hypertrophic cardiomyopathy.20 Congenital heart disease21 and preexcitation syndromes due to accessory pathways22 are also associated with AF. Idiopathic or “lone” AF is commonly seen in relatively young patients presenting with the paroxysmal form of the disease. It is uncertain whether idiopathic AF occurs in the elderly, since underlying disease, although not necessarily causative, is almost always present. Idiopathic AF, which constitutes about half the cases of paroxysmal AF and 20% of persistent AF, is a diagnosis of exclusion, although patients with small hearts, normal valvular function, and no hypertension are not usually much investigated besides routine thyroid function tests. When studied in detail, some have evidence of inflammation and atrial myocarditis,23 mild diastolic ventricular dysfunction,24 subclinical thyroid disease,25 autoimmune disorders,26 autonomic imbalance,27 sinus node dysfunction,28 or a genetic basis29 for the disease. Significant progress in treatment and aggressive strategies of primary and secondary prevention of cardiovascular diseases have resulted in changes in the structure and distribution of risk factors for AF. Valvular heart disease, particularly of rheumatic etiology, one of the most common causes and a powerful risk factor for AF in the Framingham and other early studies, no longer holds its leading role in more recent surveys,30 but is still important in the developing countries. On the other hand, an increasing number of surviving patients with chronic heart failure, a significant proportion of whom develop AF, has led to recognition of congestive heart failure as an extremely important risk factor for AF. The EuroHeart survey conducted in 2000-2001 in 24 countries has reported the overall prevalence of new-onset AF in patients hospitalized for heart failure to be 13%, varying from 8 to 36% in different regions.31

PATHOPHYSIOLOGY OF ATRIAL FIBRILLATION

Electrophysiological mechanisms

AF is now recognized as a nonuniform clinical and electrophysiological entity with different mechanisms, triggers, and substrates for the initiation and perpetuation of the arrhythmia, and it may, therefore, need multiple treatment modalities for either prevention or reversal. One of the first attempts at electrophysiological classification of different types of the arrhythmia was a simple electrocardiographic differentiation based on fine, coarse, and flutter-fibrillation f waves during AF, suggested by Culler32 in the early sixties and subsequently elaborated by others.33,34 Using right atrial high-density mapping, Konings and colleagues33 described three patterns of atrial activation with the right atrium being activated by a single wavefront propagating uniformly without significant conduction delay (type I), by one or two nonuniformly propagating wavelets showing a more pronounced intratrical conduction block (type II), or by multiple slowly conducting wavelets separated by multiple lines of functional conduction delay.
block (type III). An increase in complexity of atrial activation is generally associated with a decreased regularity of atrial activation and an increased incidence of continuous atrial electrical activity. A relatively ordered atrial activation and a slow atrial rate are observed in type I and II atrial electrograms with atria activated by relatively uniformly propagating wavelets, and corresponds to coarse AF or flutter-fibrillation on the surface ECG (72% of patients in Konings’ series). A type III electrogram is likely to be associated with fine AF. There is evidence that AF with an organized pattern of atrial activation may coexist with atrial flutter as the dominant arrhythmia.35 These observations have given rise to nonpharmacological therapeutic methods, such as ablation of cava-tricuspid isthmus to interrupt the reentrant circuit of typical atrial flutter as a potential trigger of AF, and institution of antitachycardia pacing to interrupt organized atrial activity and to prevent progression to sustained arrhythmia.

The other two major findings were demonstration of the presence of an excitable gap and the ability to entrain AF36,37 and the discovery of arrhythmogenic foci in the pulmonary veins giving rise to unusually rapid atrial tachycardia, which, when the atria are unable to respond in a 1:1 fashion, initiates AF (Figure 4).38 In accordance with the “critical mass” theory, maintenance of AF depends on adequate atrial mass to encompass sufficient wavelets to perpetuate the arrhythmia. Local capture around the stimulation site may decrease the amount of tissue available for multiple wavelet reentry necessary for maintenance of the arrhythmia, and thus, AF may be interrupted by local pacing. Pulmonary vein isolation is aimed at interruption of the connection between arrhythmogenic foci in the pulmonary veins and the rest of the atrial myocardium.

Electrical and structural remodeling

AF results from an advanced and complex pathophysiological process, which promotes the triggers and forms the electrophysiological substrate that will support the arrhythmia. Sustained AF in turn induces further electrophysiological and structural alterations of the atrial myocardium, a process known as atrial remodeling, which further favors arrhythmogenesis.39 Early in the development of AF, tachycardia-induced calcium overload of atrial myocytes prompts alterations in gene expression leading to downregulation of the L-type calcium current. This results in shortening of the atrial effective refractory period to compensate for calcium overload at the expense of a decrease in the wavelength, promoting multiple reentry.40 Changes in the atrial refractory period have been observed as early as the first two days of AF. Activation of stretch-mediated channels in the fibrillating atria enhances calcium binding to cellular myofilaments, generating calcium currents that produce delayed afterdepolarizations and triggered activity. Increased dispersion of refractoriness and a loss or reversal of rate adaptation of the effective refractory period are two other features of electrophysiological remodeling.40,41

If AF persists, ultrastructural changes may occur, tending to shift atrial myocytes to a more fetal phenotype, so-called dedifferentiation.42 Atrial myocytes show increased cellular volume, sarcomere misalignment, loss of contractile elements, and accumulation of glycogen (Figure 5).43 Further changes involve gap-junctional remodeling with the reduction in expression of connexins Cx40 and Cx43. Electrophysiological and structural changes may, however, lessen or completely reverse after restoration of sinus rhythm. The atrial effective refractory period restores within a few weeks, but structural changes, such as the appearance of small elongated mitochondria and loss of myofilament alignment, may persist after several months. Chronic stretch and calcium overload during fast AF are likely to contribute to sustained proteolysis, resulting in slow recovery of contractile elements. More advanced changes include atrial hibernation, myolysis, and hypertrophy, followed by irreversible fibrosis and cell death in long-standing arrhythmia, making restoration and/or maintenance of sinus rhythm unattainable.44 Of interest, AF-induced atrial myopathy may also cause remodeling of the sinus node, resulting in depressed sinus node function and the development of tachycardia-bradycardia syndrome.45
PROGNOSIS OF ATRIAL FIBRILLATION

Because AF is so common as age advances, often not obviously associated with underlying heart disease and seemingly asymptomatic, it is still regarded by some to be an acceptable alternative to sinus rhythm. However, AF may be associated with a significant degradation of quality of life, even when “asymptomatic.” It is clear that AF is associated with an increased morbidity and mortality related to thromboembolic complications such as cerebrovascular accident and to aggravation of heart failure (Table 1). Lone AF, not linked with any apparent underlying heart disease, may also have an adverse prognosis. This common arrhythmia is therefore a significant public health risk and the management of the arrhythmia itself and its complications represents a major cost to the health care system.

**Atrial fibrillation numbers**

<table>
<thead>
<tr>
<th>Risk of stroke</th>
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<td>In the Framingham Study, the annual risk of stroke attributable to AF among patients aged 50 to 59 years is 1.5% and increases to 23.5% in those over 80 years of age. The presence of AF has been estimated to increase the risk of stroke by about 2- to 7-fold. Strokes associated with AF are more severe and nearly twice as likely to be fatal. Including transient ischemic attacks and silent cerebral thromboembolic events, the annual risk of ischemic stroke exceeds 7%. The risk is considerably higher (about 12%/year) for recurrent stroke in patients with a previous cerebrovascular accident.</td>
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**Risk of heart failure**

Data from the Cardiovascular Health Study (CHS) and the Digitalis Investigation Group (DIG) have shown that the presence of AF is associated with a 1.65-fold risk for developing congestive heart failure in individuals older than 65 years and a 3-fold risk of worsening heart failure. In the Framingham study, the development of AF later in the course of heart failure was associated with increased mortality, particularly in women (2.7-fold risk). In patients with lone AF, left ventricular dysfunction may result from poor rate control during AF, irregularity of ventricular response, and loss of atrial contribution. Such ventricular dysfunction associated with significant heart dilatation and symptoms of heart failure is termed tachycardia-induced cardiomyopathy and may reverse completely after sinus rhythm is restored or adequate ventricular rate control is achieved (Figure 6). The rate and duration of the arrhythmia required to cause cardiomyopathy are unknown, but it is generally accepted that sustained ventricular rates of above 120 beats/min may pose a risk.

**PRINCIPLES OF MANAGEMENT**

The fundamental principles of therapy of AF include: (i) electrical or pharmacological restoration and maintenance of sinus rhythm (predominantly in persistent AF); (ii) rate control if restoration and maintenance of sinus rhythm is impossible (permanent AF); (iii) identification of the arrhythmia amenable for nonpharmacological treatment, including radiofrequency catheter ablation and maze procedure, ie, paroxysmal AF induced by rapid pulmonary vein tachycardia; (iv) risk stratification and prevention of thromboembolic complications and stroke; (v) identification and prevention or reduction of risk factors; (vi) “upstream” therapy of the underlying pathology (eg, hypertension) and specific atrial pathophysiology (eg, fibrosis) and elimina-
tion of precipitating agents; and (vii) identification of patients with AF who may benefit from implantable device therapies (antitachycardia pacing and preventative atrial pacing, atrial defibrillators).

**RHYTHM CONTROL VERSUS RATE CONTROL**

Atrial fibrillation is classified according to the temporal pattern of its presentation: first detected, paroxysmal, persistent, and permanent. Triggers, such as atrial premature beats, bursts of atrial tachycardia, atrial flutter, and sinus bradycardia, are particularly important in the prompting of an episode of paroxysmal AF, while the substrate presented as structural changes of atrial myocardium (fibrosis, hypertrophy, and dilatation) is a key factor for perpetuation of the sustained arrhythmia. The onset of AF may be asymptomatic and the “first detected episode” should not be regarded as necessarily the true onset. After its first recognition, the arrhythmia may not convert spontaneously and may be refractory to cardioversion, in which case “permanent” AF is diagnosed. However, with new interventional techniques and hybrid therapies, most AF is probably not resistant to being satisfactorily restored to sinus rhythm or an atrial paced rhythm, in which case the term “permanent” may be a misnomer. Nevertheless, the physician or the patient may choose not to treat the arrhythmia by a cardioversion technique and allow AF to remain. The term “accepted” AF has been applied to this situation.

AF that has been converted to sinus rhythm may recur. In patients with the paroxysmal variety, most episodes convert back to sinus rhythm spontaneously, whereas the persistent form of the arrhythmia requires an active intervention to restore sinus rhythm. There are mixed forms where the recurrence may or may not cardiovert spontaneously and there is often, but not always, a progression of the disease from the paroxysmal to the persistent and eventually the permanent (or accepted) form.

It seems obvious that continuation of AF will be disadvantageous compared with restoration and maintenance of sinus rhythm. Sinus rhythm theoretically offers physiological rate control, normal atrial activation and contraction, the correct sequence of atrioventricular activation and normal hemodynamic and atrioventricular valvular function, and a regular rhythm. However, normal sinus rhythm with normal atrioventricular conduction may not be the alternative to AF since sinus node disease with or without atrioventricular conduction abnormality may be the underlying problem and chronotropic incompetence may well be present. Atrial conduction and mechanical function may be seriously impaired and atrial contraction may not contribute much to the cardiac output. It is not unusual for patients to be relieved of their symptoms due to underlying sinus node disease when AF supervenes. When AF is established and becomes nonrecurrent, many of the patient’s symptoms, such as palpitations, anxiety, chest pain, and the like, become less prominent. Often the only symptoms that remain are a minor limitation of exercise tolerance and a subtle reduction in the quality of life.

The cardioversion of AF with electrical or pharmacological techniques carries some hazard, particularly from thromboembolism consequent upon restoration of mechanical activity to previously fibrillating and “stunned” atria in which thrombi accumulated. Other hazards relate to the risks of anesthesia and underlying heart disease, especially sinus node dysfunction (bradycardia and asystole) and other arrhythmias. Maintenance of sinus rhythm is not without its problems, especially when antiarrhythmic drugs must be used. Class I antiarrhythmic drugs may aggravate sinus node and conduction system disease, precipitate congestive heart failure, or slow AF to such an extent that the arrhythmia results in a faster ventricular rate and a symptomatic deterioration. A particular risk of class IA and III antiarrhythmics is their potential to impair ventricular repolarization, prolong the QT interval, and promote torsades de pointes, a fast and potentially fatal ventricular tachyarrhythmia. These complications are especially likely to occur when hy-
pokalemlia, bradycardia, underlying heart disease, or impaired drug metabolism or excretion are present or occur shortly after cardioversion from AF. Amiodarone is least likely to cause acquired long QT syndrome, but its use is fraught with other complications such as photosensitivity, thyroid dysfunction, and pulmonary fibrosis.

There is, therefore, a genuine equipoise as to whether it is best to leave the patient in AF while controlling the ventricular rate and preventing thromboembolic complications with anticoagulant therapy, or to restore and maintain sinus rhythm. A galaxy of clinical trials has been instigated with a central hypothesis centered on the resolution of this important question. PIAF (Pharmacological Intervention in Atrial Fibrillation), STAF (Strategies of Treatment in Atrial Fibrillation), RACE (RAte Control versus Electrical cardioversion for persistent atrial fibrillation), and AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) have reported in full and the HOT CAFE (How to Treat patients with Chronic Atrial Fibrillation - Polish Study) and Delhi trials have reported in abstract form. All trials consistently report that there is no clear advantage to rhythm control (Table II). Generally, there has been a trend toward improved survival and less serious cardiovascular adverse events in association with rate rather than rhythm control. Torsades de pointes, cerebrovascular accidents and other thromboembolic events, and hospital admissions for the acute management of AF or because of heart failure have been less with rate control than with rhythm control strategies. On meta-analysis, the reduction in cerebrovascular accident rate was significantly less with rate control, but this was largely because anticoagulation was often omitted when the patient seemed to be in stable sinus rhythm with an effective antiarrhythmic agent. Despite the appearance of freedom from AF, the patients may well have suffered asymptomatic episodes, or thromboembolism associated with AF was not actually dependent on recurrence of AF, but related to some other associated factors such as aortic atherosclerotic plaques.

The closely similar primary end point results from the rhythm and rate control strategies were probably due to a general failure to achieve a clear difference with respect to rhythm and rate status in the two arms of the trials. Ideally, the rhythm control arm should have primarily comprised patients who were in sinus rhythm, whereas the rate control arm should have consisted mostly of patients in AF. This was not usually the case, for example, in the AFFIRM trial, only 60% of patients of the rhythm control arm were maintained in sinus rhythm, whereas 40% of those of the rate control arm had reverted spontaneously to sinus rhythm. The RACE trial included patients with persistent AF who may have had the arrhythmia as long as 1 year and who may have already undergone serial electrical cardioversions. Despite an aggressive rhythm control strategy, the likelihood of maintenance of sinus rhythm in this selected group of patients is expected to be low, thus favoring

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*Not assessed prospectively.

Table II. Evidence of superiority of rhythm control in atrial fibrillation.

*Abbreviations: AF, atrial fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; CHF-STAT, Congestive Heart Failure–Survival Trial of Antiarrhythmic Therapy; HOT CAFE, How to Treat patients with Chronic Atrial Fibrillation (Polish Study); N/A, not assessed or reported; PIAF, Pharmacological Intervention in Atrial Fibrillation; RACE, RAte Control versus Electrical cardioversion for persistent atrial fibrillation; STAF, Strategies of Treatment in Atrial Fibrillation.*
the rate control strategy. At the 2003 Annual Session of the American Heart Association (AHA), the AFFIRM investigators presented a retrospective analysis of mortality in patients who remained in sinus rhythm and those in AF, irrespective of the treatment strategy. They found that being in sinus rhythm was associated with a 47% reduction in risk of death. Furthermore, in the RACE and STAF trials, 72% to 95% of end point events occurred when patients were in AF. This gives rise to the most serious criticism of this clutch of recent trials. It is argued that the impression that rate control is marginally better than rhythm control is entirely due to the inadequacy of the rhythm control therapy and that newer, potentially much more effective therapies are now available, which can effectively cure AF.

Comparison between these interventional, non–drug-based strategies for rhythm control and drug-based approaches are now under way (Jais, personal communication), but as yet it has not been proposed to repeat the rate versus rhythm trials utilizing nonpharmacological rhythm control methods. Rightly, it is believed that the ablation techniques, in particular, can be further improved and that major trials comparing their efficacy should be deferred until sufficient well-trained physicians and centers are available to conduct a large study.

**ANTICOAGULATION FOR ATRIAL FIBRILLATION**

Absence of organized mechanical contraction of fibrillating atria with a consequent increase in atrial pressure, atrial stretch, and dilatation due to multiple pathophysiological mechanisms compensating for reduced cardiac output generate conditions for blood stasis and thrombus formation. Abnormalities of hemostasis, endothelial function, and platelet activation are often associated with AF further increase the risk of thromboembolic events. With transesophageal echocardiography, left atrial thrombi can be found in about 14% of patients with AF, and spontaneous echo contrast can be seen in 52% of patients.

Anticoagulation has now become imperative in a significant proportion of patients with AF. Meta-analysis of pooled data from 5 large randomized clinical trials of oral anticoagulation for primary prevention and 1 trial for secondary prevention of thromboembolic events in patients with nonrheumatic AF has shown a 61% risk reduction in the incidence of stroke with adjusted-dose warfarin compared with placebo and a 36% risk reduction compared with aspirin.

**Risk stratification for stroke**

The number of patients needed to be anticoagulated to prevent 1 cerebrovascular event has been estimated to be 100 patient-years for those at low risk of stroke compared with 25 patient-years for those at high risk. The SPAF (Stroke Prevention in Atrial Fibrillation) Investigators have defined 3 risk groups of patients with AF. According to this stratification, patients over 75 years old, with prior cerebrovascular events and hypertension, may present with an annual incidence of stroke as high as 7% and have unequivocal indications for anticoagulation. Patients under 75 years of age, but with a history of hypertension or diabetes, would have a 2.5% annual risk of stroke and may, therefore, require anticoagulation, while those with none of these factors are considered to be at low risk (1% per year). These patients can be treated with an antiplatelet agent, usually aspirin, but the study exploring the efficacy of a combination with clopidogrel (the ACTIVE trial [Atrial Fibrillation Clopidogrel Trial with Irbesartan for the prevention of Vascular Events]) is under way. This study will enroll 14,000 patients with AF, and the efficacy of combination therapy over warfarin will be assessed by the first occurrence of cardiovascular death, myocardial infarction, stroke, or a vascular thromboembolic event.

There is clinical evidence suggesting that paroxysmal AF confers the same risk for stroke as a permanent form of the arrhythmia, but the risk-benefit ratio for anticoagulation therapy in paroxysmal AF remains uncertain as many randomized controlled trials generally enrolled patients with permanent AF. Thus, the AFASAK (Atrial Fibrillation, ASpirin AntiKoagulation)
and SPINAF (Stroke Prevention In Nonrheumatic Atrial Fibrillation) studies exclusively enrolled patients with permanent AF, whereas the proportion of patients with intermittent AF was 7% in CAFA (Canadian Atrial Fibrillation Anticoagulation), 16% in BAATAF (Boston Area Anticoagulation Trial for Atrial Fibrillation), and 34% in SPAF. However, standard anticoagulation is strongly recommended in patients with frequent and prolonged episodes of AF, especially in the presence of other risk factors for stroke.

**Transesophageal echocardiography**

Transesophageal echocardiography (TEE) has emerged as the most sensitive and specific imaging technique for detection of left atrial thrombi, also permitting assessment of left atrial appendage flow. Several TEE criteria have been associated with thromboembolism: thrombi in the left atrium and left atrial appendage, reduced flow velocity in the left atrium appendage, spontaneous echo contrast, and complex atheroma of the aorta. A number of studies, including the ACUTE (Assessment of Cardioversion Using Transesophageal Echocardiography) trial, have shown that the TEE-guided strategy with short-term anticoagulation is a safe and effective alternative in patients with AF for whom early cardioversion is deemed to be clinically beneficial. It is ideal for inpatients with recent onset AF or individuals at high risk of bleeding complications during prolonged anticoagulation therapy. The rate of embolic events did not differ between patients assigned to TEE-guided cardioversion or the conventional strategy of anticoagulation for 3 weeks prior to cardioversion, but the incidence of hemorrhage was significantly lower in the TEE-guided group.

**Future perspectives for prevention of stroke in atrial fibrillation**

Despite the proven benefit of anticoagulation therapy for the reduction of risk for ischemic stroke associated with AF, less than half eligible patients with contraindications for warfarin therapy receive this prophylactic treatment, probably due to patients’ concerns regarding bleeding complications and the difficulties related to the need for regular international normalized ratio (INR) monitoring in order to control warfarin dosage. In addition, many foods and drugs, including commonly used antiarrhythmic agents, interact with warfarin to either increase or decrease its potency. In the recent SPORTIF (Stroke Prevention using an Oral Thrombin Inhibitor in atrial Fibrillation) III and V trial, treatment with the oral direct thrombin inhibitor ximelagatran proved to be at least as effective as warfarin in the prevention of stroke in high-risk patients with AF based on the intention-to-treat analysis (preliminary data). The greatest advantages of ximelagatran are the absence of interactions with other medications, rapid achievement of the therapeutic effect, and no need for coagulation monitoring. There are concerns about liver enzyme elevation in 6% of patients, which requires regular liver function tests.

A device for percutaneous left atrial appendage transcatheter occlusion (PLAATO) via transseptal catheterization can offer effective protection from cardiogenic thromboembolism in patients with contraindications for or poor tolerance of long-life oral anticoagulation. The device, which is currently under investigation, consists of a self-expanding nitinol cage covered with an occlusive polymeric membrane, which serves both to occlude the orifice of the left atrial appendage and to allow tissue incorporation into the implant. The initial clinical experience was successful in 31 patients with AF and experimental histological examination demonstrated the surface of the implant to be completely smooth and free of mobile thrombi at 1 month after the implant. Left atrial appendectomy via thoracoscopic or limited sternotomy may also be considered for prevention or reduction of thromboembolism.

**NONPHARMACOLOGICAL THERAPY**

Nonpharmacological treatment alternatives for management of AF include atroventricular node ablation or modification to abolish frequent fibrillatory conduction to the ventricles, catheter ablation of “focal” AF originating from remnants of the atrial myocardium in the pulmonary veins, surgical and catheter-based maze procedure aimed at decompartmentalization of the fibrillating atria, implantation of a stand-alone atrial defibrillator, or dual-chamber cardioverter defibrillators and pacemakers capable of providing preventative and antitachycardia pacing therapies (Figure 8).

The “ablate and pace” strategy, which was first introduced in 1982, is now an established effective treatment in patients with symptomatic drug-refractory AF. A meta-analysis of 21 studies in 1181 patients has shown that it significantly improved cardiac symptoms, quality of life, and health care resource utilization, but had a neutral effect on survival compared with conventional therapy. To date, there is no well-powered, randomized study to show long-term survival benefit of the “ablate and pace” strategy over pharmacological rate control or rhythm control.
Ablation in or around the pulmonary veins, often in combination with isthmus ablation, and a modified catheter-based maze procedure can effectively accomplish the aim of the curative treatment of AF, but these techniques are limited to a selected patient population with “focal” AF or patients with AF undergoing heart surgery. The surgical maze procedure was the first curative approach to AF conceived with the idea of modifying the substrate for the arrhythmia by creating lines of conduction block in order to interrupt all possible reentrant circuits responsible for maintenance of AF. Although it was firstly conducted to cure lone AF, it is presently used in association with mitral valve or coronary bypass surgery, with long-term success rates of 74% to 90% and perioperative mortality less than 1%.

The considerable limitations of existing therapeutic options and new experimental evidence of electrophysiological mechanisms and triggers of AF have led to the development of specific atrial pacing algorithms aimed at either prevention or termination of AF. Atrial preventative pacing and antitachycardia pacing may reduce the incidence of AF by either eliminating the triggers and/or by modifying the substrate of the arrhythmia. Firstly, the presence in the atria of zones with consistently prolonged activation times, such as coronary sinus ostium and Bachmann’s bundle, resulting in nonuniform atrial conduction, has been linked to the initiation and perpetuation of AF. It has been suggested that pacing from these sites or multisite atrial pacing may prevent AF due to improved synchronized atrial depolarization. Secondly, recognition of potential triggers for AF, such as atrial premature beats, producing short-long sequences, bradycardia, and bursts of atrial tachycardia, have led to the development of specific algorithms capable of providing dynamic atrial overdrive pacing and antitachycardia pacing. Table III summarizes the presently available evidence base for the utilization of atrial pacing for the control of AF.

Although theoretically very attractive, preventative atrial pacing for the treatment of AF remains a debatable indication because existing data are too limited to provide sufficient evidence for definitive management guidelines. In general, randomized clinical trials have shown a neutral or slightly positive effect of specific pacing algorithms in the prevention of AF in addition

<table>
<thead>
<tr>
<th>Presentation of AF</th>
<th>Case studies</th>
<th>Small studies</th>
<th>Medium studies (≈100 patients)</th>
<th>Large RCTs (250-000s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia with little AF</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓/+</td>
</tr>
</tbody>
</table>
| AF with bradycardia | Usual pacing | ✓ | ✓ | ✓ | ±ve/ongoing
| Multisite pacing | ✓ | ✓ | ✓ | none |
| AF with left atrial delay | Multisite pacing | ✓ | ✓ | ±ve | none |
| Usual pacing | ✓ | ✓ | –ve | –ve/ongoing |
| AF without bradycardia or left atrial delay | Overdrive pacing | ✓ | ✓ | ongoing | ±ve/ongoing
| Multisite pacing | ✓ | ✓ | ✓ | none |
| Usual pacing | ✓ | ✓ | ✓ | ±ve |

Table III. Pacing for control of atrial fibrillation.

Abbreviations: AF, atrial fibrillation; RCT, randomized controlled study; ±ve, positive; –ve, negative.
to physiological pacing. The results of these trials are not conclusive with respect to the definition of an AF population that would obtain the most advantage from pacing strategies and which of these strategies are the best. An attempt to identify such patients has been undertaken by the PIPAF (Pacing In Prevention of Atrial Fibrillation) investigators. They found that patients with left atrial enlargement and patients with relatively preserved atrioventricular conduction conferred the most benefit from dynamic overdrive pacing.110

**“HYBRID” THERAPY AND “UPSTREAM” THERAPY FOR ATRIAL FIBRILLATION**

There is now an increased interest in combination, or “hybrid,” therapy, which emerges from the understanding that different mechanisms may be responsible for the initiation and maintenance of AF. Theoretically, the use of multiple different therapies allows more specific mechanisms of arrhythmia to be directly addressed (Table IV). The term “hybrid” implies fundamental different qualities of treatment, which together provide some form of synergism. Antiarrhythmic drugs that have proven effective in treating AF either slow intratrial conduction and convert poorly conducting regions to regions of block, or act to increase refractoriness, and may have an intermediate effect of organizing the arrhythmia into a fixed circuit reentry arrhythmia, such as atrial flutter, instead of fully terminating the arrhythmia. Atrial flutter can be subsequently cured by catheter ablation or terminated by antitachycardia pacing, but antiarrhythmic drug therapy should usually be continued. Dual-site atrial pacing appears to have a synergistic relationship with antiarrhythmic class I and III drug therapy, supporting the benefit of a “hybrid” therapy approach.112 The final option of using modification of the arrhythmia substrate by atrial linear ablation in combination with antitachycardia and preventative pacing has also anecdotally proven an effective therapeutic approach. Sometimes, all three modalities, of pacing, drugs, and linear ablation may be required. However, this is largely a theoretical concept that has only been strictly evaluated in a small number of studies. Studies of multiple therapies are difficult to perform unless the combination therapy is regarded as a strategy that can be compared with baseline, conventional treatment or one or more single constituent therapies from the combination.

The “upstream” approach to pharmacologic therapy of arrhythmias is a treatment strategy targeting the underlying disease process that may favor the atrial

**Examples of hybrid therapy in atrial fibrillation**

- Two or more independent antiarrhythmic actions
  - Pacemaker-induced reduction of atrial premature beats and antiarrhythmic drug modification of substrate
- One therapy neutralizes a proarrhythmic effect of the other
  - Pacemaker prevents the bradycardia complication of antiarrhythmic drug therapy
- One therapy facilitates the antiarrhythmic action of another
  - Antiarrhythmic drugs organize atrial fibrillation such that antitachycardia pacing will be successful
- Hybrid therapy provides an opportunity to monitor antiarrhythmic therapy
  - Device monitors rate/rhythm control in atrial fibrillation treated by pacing or antiarrhythmic drugs

<table>
<thead>
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<th>Table IV.</th>
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**Figure 9.**

(A) Kaplan-Meier curves showing the incidence of atrial fibrillation with trandolapril versus placebo in the TRACE (TRAndolapril Cardiac Evaluation) trial.

(B) The proportion of patients free from atrial fibrillation with enalapril versus placebo in the SOLVD (Studies Of Left Ventricular Dysfunction, Treatment and Prevention arms).
arrhythmia by disorganized hemodynamics or the development of atrial pathology. Effective conventional treatment of congestive heart failure has been shown to delay progression of left ventricular dysfunction and reduce mitral regurgitation and, consequently, to prevent left atrial dilatation and stretch. These are important constituents of the substrate for atrial tachyarhythmias as they create “a critical mass” necessary for multiple wavelet reentry and induce stretch-related abnormal automaticity and triggered activity in the atria. In the TRACE (TRAndolapril Cardiac Evaluation and SOLVD (Studies Of Left Ventricular Dysfunction) studies, therapy with angiotensin-converting enzyme (ACE) inhibitors trandolapril or enalapril was associated with a remarkable 55% to 78% risk reduction of AF in patients with left ventricular systolic dysfunction and patients with overt heart failure (Figure 9).113,114

ACE inhibitors and, potentially, angiotensin II receptor blockers appear to achieve their beneficial effects in the prevention of AF not only because of the hemodynamic improvement and reduction of atrial stretch, but also due to their blockade of local electrophysiological effects of angiotensin II and direct action on the reduction in the accumulation of collagen and interstitial fibrosis in the atria.115,116 There is now increasing evidence that ACE inhibitors can be effectively used in patients with AF in the absence of overt heart failure. The beneficial effect of an ACE inhibitor on the development of AF was more marked in the less symptomatic patients.114 Pretreatment with irbesartan in addition to amiodarone before electrical cardioversion for persistent AF increased a likelihood of successful cardioversion and prevented recurrence of the arrhythmia.117

Alternatively, early identification and treatment of hypertension may reduce the incidence of AF. Similarly, in the setting of coronary heart disease, complete revascularization may have antiarrhythmic action by virtue of improvement of left ventricular function and prevention of left atrial dilatation and stress, whereas use of antiarrhythmic drugs may further depress left ventricular function and may produce proarrhythmic effects in tissue with inhomogeneous perfusion.

### CONCLUSIONS

AF is a very significant health care problem with a prevalence rising to an epidemic proportion. Although it has held some interest for cardiac electrophysiologists and arrhythmologists, it was generally regarded, for obvious reasons, as of less importance than ventricular fibrillation and ventricular tachycardia. The invention of the implantable cardioverter defibrillator has provided at least a temporary solution to the serious problem of ventricular tachyarrhythmia and has led to refocused attention on AF. The number of references concerning AF has increased substantially in recent years (Figure 10) to such an extent that the number of important unresolved questions related to this arrhythmia has escalated dramatically. Among these, three important issues are in urgent need of solution, which will be looked into in the following section.
THREE KEY QUESTIONS

Stroke occurs 2- to 7-fold more frequently in the presence of atrial fibrillation (AF), and silent cerebral infarcts can be detected in nearly half the patients with AF. Overall, patients with AF face a 7% annual risk of ischemic stroke. The risk is considerably higher (about 12%/year) in patients with previous stroke or transient ischemic attack. The absence of organized mechanical contraction of fibrillating atria with consequent increase in atrial pressure, atrial stretch, and dilation creates conditions for blood stasis and thrombus formation. In addition, AF is associated with abnormalities of hemostasis, endothelial function, and platelet activation, adding to increased risk of thromboembolic complications. Bethan Freestone and Gregory Lip will give a detailed account of the thrombogenic mechanisms that operate in patients with AF and the ways of reducing the risk of stroke in their review “Why does thromboembolism occur in atrial fibrillation and how can it best be prevented?”

The management of heart rhythm in patients with AF has always been the subject of intensive investigation as increased morbidity and probably mortality conveyed by AF provide a clear impetus to restoration and maintenance of sinus rhythm as the first-line strategy. However, until recently, the benefits of rhythm control over rate control have not been rigorously tested but merely assumed. Over time, lack of direct evidence of improved survival or reduced risk of thromboembolic complications, poor efficacy in the long-term and adverse effects of antiarrhythmic drug therapy, a remarkable efficacy of anticoagulation for the prevention of stroke, and the emergence of nonpharmacological treatment options, have finally led to a series of randomized trials that showed at least noninferiority of the rate control strategy. However, the issue is not settled, as the population of patients with AF is not a homogenous entity for which a single therapeutic approach can be recommended. This leads Isabelle C. Van Gelder and Harry Crijns to answer the question: “What are the potential and proven advantages for rate or rhythm control of atrial fibrillation?” and to discuss theoretical benefits and the results of trials that have failed to confirm theoretical advantages of the rhythm control strategy. At present, a broad array of new nonpharmacological approaches has emerged from better understanding of the substrates, mechanisms, and triggers of AF. The use of different catheter ablation techniques to modify the substrate or to abolish the triggers of AF is an area of increasing investigative activity. Numerous, yet unresolved, clinical and methodological difficulties challenge the common use and benefits of this treatment. The first results with dual-chamber pacemakers and defibrillators equipped with a comprehensive array of atrial tiered therapies have been encouraging, but the selection of patients with AF who would benefit from such therapy remains an unresolved question. In general, the potential for curing AF currently involves costly interventional treatment, and the long-term success of such therapy is not known. David Keane and Jeremy Ruskin expertly assess these novel sophisticated approaches to answer a tantalizing question: “Is catheter isolation of the pulmonary veins a curative procedure for atrial fibrillation?” In the final analysis, the wide range of patients with AF and multiple mechanisms for the initiation and perpetuation of the arrhythmia suggest that no single therapeutic strategy is completely effective and introduce the concept of “hybrid” therapy in which multiple different therapeutic options allow specific mechanisms of arrhythmia to be directly addressed.
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Atrial fibrillation is associated with increased risk of thromboembolism, as illustrated by an increased incidence of stroke and thromboembolic events. Hemostatic abnormalities have been demonstrated in patients with atrial fibrillation in numerous studies, with increased markers of coagulation and fibrinolysis, and altered levels of plasma markers of platelet and endothelial origin have been reported. Nevertheless, the mechanism by which atrial fibrillation causes these abnormalities has yet to be fully elucidated. In order to reduce risk of thromboembolism in atrial fibrillation, anticoagulant and antithrombotic therapies have been assessed in randomized control trials, with dose-adjusted warfarin showing a clear reduction in stroke rate in “at-risk patients” in metanalysis. However, stroke risk in atrial fibrillation is heterogeneous, and, currently, risk stratification on clinical grounds is used to decide the best therapeutic strategy in individual patients.

Atrial fibrillation (AF) is associated with increased risk of stroke and thromboembolism. Indeed, nonvalvular AF is associated with an approximate 5-fold increase in the risk of thromboembolic stroke, although the precise level of risk is dependent on the presence of other risk factors. Despite the latter, AF has in fact been demonstrated to be an independent risk factor for stroke, again in the Framingham population, and is therefore not just an indicator of the presence of coexistent diseases that are considered to be risk factors for both stroke and AF.

The proportion of strokes attributable to AF increases with age, accounting for 23.5% of strokes in the 80- to 89-year-olds in the Framingham population, this is in direct contrast to other identifiable risk factors for stroke, which decreased with age, indicating the importance of this cardiac arrhythmia as a causative factor in stroke, particularly in the elderly. AF is also an independent risk factor for mortality, probably due to this increased risk of thromboembolism as well as hemodynamic consequences of AF and the presence of underlying heart disease contributing to heart failure or cardiac events. Indeed, the Framingham data estimate an odds ratio of 1.5 (95% confidence interval [CI] 1.2-1.8) for death in men and 1.9 (95% CI 1.5-2.2) in women with AF compared with the general population. Data from other studies support this observation. Furthermore, stroke severity appears to

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**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AF</td>
<td>atrial fibrillation</td>
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<tr>
<td>AFASAK</td>
<td>Atrial Fibrillation, ASpirin AntiKoagulation</td>
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<tr>
<td>EAFT</td>
<td>European Atrial Fibrillation Trial</td>
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<tr>
<td>ESPS II</td>
<td>Second European Stroke Prevention Study</td>
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<td>LAA</td>
<td>left atrial appendage</td>
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<tr>
<td>LASAF</td>
<td>Low-dose Aspirin, Stroke and Atrial Fibrillation study</td>
</tr>
<tr>
<td>NNT</td>
<td>number needed to treat</td>
</tr>
<tr>
<td>SEC</td>
<td>spontaneous echo contrast</td>
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<tr>
<td>SIFA</td>
<td>Studio Italiano Fibrilazione Atriale</td>
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<tr>
<td>SPAF</td>
<td>Stroke Prevention in Atrial Fibrillation</td>
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<tr>
<td>TEE</td>
<td>transesophageal echocardiography</td>
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<tr>
<td>UK-TIA</td>
<td>United Kingdom–Transient Ischaemic Attack trial</td>
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<tr>
<td>vWF</td>
<td>von Willebrand factor</td>
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</table>
be worse in patients with AF compared with sinus rhythm, with increased rates of both mortality and disability.8

**POSTULATED MECHANISMS BY WHICH ATRIAL FIBRILLATION CAUSES THROMBOEMBOLISM**

The precise mechanisms by which AF causes thromboembolism and subsequent cerebrovascular events have yet to be fully elucidated, but are postulated to be a consequence of altered hemodynamics in the left atrium, (and possibly also in the general circulation) which could be responsible for generation of a prothrombotic or hypercoagulable state in AF.

For thrombus formation to occur there needs to be fulfillment of Virchow’s triad, that is, abnormalities in blood flow, circulating blood constituents, and in the vessel wall. Certainly, the presence of thrombus in the left atrial appendage (LAA) has been demonstrated in patients with acute AF presenting with stroke, which supports this hypothesis. However, LAA thrombus can only be seen in approximately 15% of this population,9 and so we are left with the question as to the source of thrombus in the other AF patients who presented with stroke. Stasis in the left atrium of patients with AF is visually demonstrated by the presence of spontaneous echo contrast (SEC) on transesophageal echocardiography.

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<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gustafsson et al,13 1990</td>
<td>Atrial fibrillation with or without</td>
<td>Looking at the nonstroke population, those markers found to be significantly higher in NVAF when compared with healthy controls included:</td>
</tr>
<tr>
<td></td>
<td>a history of stroke versus sinus rhythm, with or without a history of stroke</td>
<td>• Factor VIII:C coagulation factor ($P&lt;0.001$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fibrinogen ($P&lt;0.01$)</td>
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<tr>
<td></td>
<td></td>
<td>• D-Dimer ($P&lt;0.05$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fibrinogen/antithrombin ratio ($P&lt;0.01$)</td>
</tr>
<tr>
<td>Kumagai et al,14 1990</td>
<td>Atrial fibrillation with or without organic (eg, valvular) heart disease compared with control group with or without heart disease</td>
<td>D-Dimer higher in AF than controls ($P&lt;0.001$)</td>
</tr>
<tr>
<td>Lip et al,15 1995</td>
<td>Chronic atrial fibrillation versus sinus rhythm controls</td>
<td>Comparing AF patients on no antithrombotic treatment with controls, the following were significantly raised:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fibrinogen ($P&lt;0.0001$)</td>
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<tr>
<td></td>
<td></td>
<td>• D-Dimer ($P&lt;0.0001$)</td>
</tr>
<tr>
<td>Yamamoto et al,16 1995</td>
<td>Mitral stenosis with AF versus sinus rhythm healthy controls, atrial, and peripheral sampling</td>
<td>Looking at peripheral sampling, fibrinopeptide A was significantly raised in comparison to controls ($P&lt;0.01$). D-Dimer, TAT, and PIC showed trends towards increased levels in AF, but not significant</td>
</tr>
<tr>
<td>Li-Saw-Hee et al,17 1999</td>
<td>Mitral stenosis with AF versus sinus rhythm healthy controls, atrial, and peripheral sampling</td>
<td>Looking at peripheral sampling, markers of coagulation were significantly increased in AF compared with controls:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fibrinogen ($P&lt;0.005$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• D-Dimer ($P&lt;0.011$)</td>
</tr>
<tr>
<td>Mondillo et al,18 2000</td>
<td>Nonvalvular chronic AF versus healthy controls,</td>
<td>Fibrinogen and D-dimer levels are significantly raised in AF:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fibrinogen ($P&lt;0.01$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• D-Dimer ($P&lt;0.01$). Antithrombin III and protein C. Levels were not found to be significantly different between groups</td>
</tr>
<tr>
<td>Feng et al,19 2001</td>
<td>Framingham Offspring study, 47 AF patients versus rest of study population, then analyzed in comparison with age, sex, and risk factor–matched group</td>
<td>Fibrinogen levels found to be increased in AF vs rest of study population ($P=0.004$). Significance is lost when compared with matched control group ($P=0.62$)</td>
</tr>
</tbody>
</table>

**Table 1. Examples of studies examining the hypercoagulable state in atrial fibrillation.**

**Abbreviations:** AF, atrial fibrillation; NVAF, nonvalvular atrial fibrillation; PIC, plasmin-alpha 2–plasmin inhibitor complex; TAT, thromboplastin activation test.
Echocardiography, seen as “smoke” in the left atrium and reduced LAA Doppler flow velocities, however, neither the presence of SEC or LAA thrombus have yet been correlated with outcomes in AF patients, although both are predictive of thromboembolism. It has been suggested that left atrial stasis and subsequent thrombus formation is not the only source of thrombus in AF, although it is of course one possible source.

It is now well established that AF is associated with abnormal blood constituents, leading to a prothrombotic state, generation of which appears to be multifactorial. Certainly, there is coagulation cascade activation and increased fibrinolytic activity in AF, as indicated by several studies (see Table I for examples). For example, Gustafsson et al first demonstrated the presence of hemostatic abnormalities in the plasma of patients with atrial fibrillation when compared with sinus rhythm controls, and associated these abnormalities with stroke. Kumagai et al also indicated that hemostatic abnormalities were present in AF compared with controls who were in sinus rhythm, and that the presence of associated organic heart disease was not associated with any significant difference in thrombogenesis, therefore suggesting the hypercoagulable state was associated with AF rather than its risk factors.

The study by Heppel et al reported that patients with AF who had spontaneous echo contrast on transesophageal echocardiography also had higher concentrations of certain markers of hemostasis, and importantly, peripheral plasma markers could be associated with the presence of LAA thrombus. A study by Mondillo et al also showed a positive linear correlation between left atrial volume and plasma fibrinogen and the endothelial markers soluble thrombomodulin and von Willebrand factor (vWF), supporting the hypothesis that the atria may be the origin of the hemostatic abnormalities observed in AF.

Platelet activation has been suggested to contribute to the prothrombotic state in AF. This hypothesis has been explored in studies examining platelet aggregation and indices of platelet function in AF patients. However, evidence is not consistent, and although markers of platelet activation such as β-thromboglobulin and platelet factor 4 have been noted by some groups to be increased with the onset of AF, other platelet markers measured in the plasma such as soluble P-selectin have not, as recently reviewed by Kamath et al. Endothelial damage/dysfunction in AF has also been explored, and some plasma endothelial markers are abnormal in AF compared with healthy controls. There also seems to be an increase in inflammatory markers in AF, as demonstrated by raised C-reactive protein and interleukin-6 in comparison with healthy controls, which could be either contributory to, or a consequence of, the hypercoagulable state seen in AF. Markers such as vWF can be related to risk stratification of stroke and thromboembolism, with the highest vWF levels seen in high-risk patients, and indeed, plasma vWF levels are also an independent predictor of mortality at follow-up.

It is possible that all of these hemostatic abnormalities are simply due to coexisting disease often seen in patients with AF, such as hypertension or ischemic heart disease. This was suggested in the Framingham population by Feng et al, who found that the significant difference in hemostatic variables seen between 47 people with atrial fibrillation and the rest of the Framingham subjects (n=3515) became nonsignificant when compared with a non-AF group matched on the basis of age, sex, and cardiovascular risk factors. If this is the case, AF could be considered an independent marker rather than a cause of thromboembolic risk. However, the analysis of the influence of confounding factors in a population of only 47 patients compared with controls is unlikely to be sufficiently powered to say that the hemostatic state in AF is purely a result of the presence of other cardiovascular risk factors. Neither does it explain fully how AF could be an independent risk factor for stroke or seems to have an independent association with hemostatic variables. In an effort to exclude confounding factors from the equation, we can look at lone AF, and even in a small lone AF population compared with patients in sinus rhythm, markers such as soluble P-selectin and vWF were increased, suggesting that it is probably AF itself that influences the prothrombotic state in this arrhythmia.

STROKE PREVENTION IN ATRIAL FIBRILLATION

An estimated 15% of strokes occur in the setting of AF. AF has also been associated with increased risk of silent cerebral infarction. As stroke is associated with substantial health care costs and morbidity, the treatment of patients with AF to prevent stroke is an increasingly important problem. However, the risk of stroke in association with AF is not uniform, and risk stratification is necessary to identify those patients who would benefit most from treatment.

Oral anticoagulation

In prospective randomized control trials, warfarin consistently reduces the risk of stroke in patients.
with AF. In the most recent meta-analysis by Hart et al examining the evidence for stroke prevention in atrial fibrillation, adjusted-dose warfarin, when compared with placebo (in 6 trials, 2900 patients), reduces stroke by 62% (95% CI, 48-72%) (Figure 1). Absolute risk reductions were 2.7% per year for primary prevention (number needed to treat [NNT] for 1 year to prevent 1 stroke = 37) and 8.4% per year for secondary prevention (NNT = 12), with an absolute risk for extracranial bleeding of 0.3% per year. All-cause mortality was also decreased in AF patients on warfarin (relative risk reduction 26%, 95% CI 4%-43%).

**Aspirin and other antiplatelet agents**

The efficacy of aspirin for stroke prevention in AF is less consistent. Again, in the meta-analysis by Hart et al, a total of 6 trials, involving a total of 3119 participants, looked at aspirin versus placebo in stroke prevention (Figure 2). AFASAK (Atrial Fibrillation, Aspirin AntiCoagulation), SPAF (Stroke Prevention in Atrial Fibrillation), EAFT (European Atrial Fibrillation Trial), and LASAF (Low-dose Aspirin, Stroke and Atrial Fibrillation study) were randomized clinical trials for atrial fibrillation, whereas ESPS II (Second European Stroke Prevention Study) and UK-TIA (United Kingdom–Transient Ischaemic Attack aspirin trial) were secondary prevention trials for stroke/TIA that included subgroups of patients with atrial fibrillation.

All trials showed a trend towards benefit in the aspirin-treated group, but this only reached significance in the SPAF trial. In combined analysis of these trials, Hart et al concluded there was a reduction in stroke of 22% when comparing aspirin with placebo for stroke prevention in AF (95% CI, 2%-38%). Absolute risk reductions of 1.5% per year for primary prevention and 2.5% per year for secondary prevention were calculated. However, all-cause mortality was not significantly reduced by aspirin (relative risk reduction 16%, 95% CI 5% to 33%).

Dipyridamole and dipyridamole/aspirin combination were also compared with placebo in secondary prevention for stroke in the (ESPS II), although the data are insufficient to assess the individual efficacy of dipyridamole for stroke prevention in AF patients. In the Studio Italiano Fibrilazione Atriale (SIFA) study, patients with a recent nondisabling stroke or TIA were randomized to receive indobufen or warfarin. There was no significant difference in primary event outcome rates between the groups (12% in the indobufen group vs 10% in the warfarin group, P=0.47), suggesting noninferiority of this antiplatelet agent when compared with warfarin.

**Figure 1. Adjusted-dose warfarin compared with placebo.**

Key to studies: BAAFAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation; SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation. Other trials, see Selected abbreviations and acronyms box.


**Figure 2. Aspirin compared with placebo.**

Key to studies: see Selected abbreviations and acronyms box.


**Adjusted-dose warfarin versus aspirin**

Five nonblinded randomized control trials have compared the efficacy of adjusted-dose warfarin with aspirin for stroke prevention in AF. On meta-analysis (5 trials, total 2837 patients, mean follow up 2.2 years),...
warfarin was more efficacious than aspirin, with an overall relative risk reduction for all strokes of 36% (95% CI, 14% to 52%) (Figure 3).35

Adjusted-dose warfarin versus low-dose warfarin or low-dose warfarin/aspirin combination

Two trials have compared adjusted dose warfarin to aspirin plus low fixed-dose warfarin,40,41 SPAF III, which only included high-risk patients, was stopped at interim analysis because of large reductions in relative and absolute risk reported for dose-adjusted warfarin. Other trials were stopped early as a result of the publication of SPAF III.

Three trials comparing adjusted-dose warfarin (international normalized ratio [INR] 2-3.5) with low fixed-dose warfarin (mean INR 1.1-1.4),41-43 and, when analyzed together, showed a 38% reduction in stroke for adjusted-dose warfarin, but this was not statistically significant.35

It should be mentioned that in the above anticoagulation trials, the mean age of patients was only 69 years, which is considerably lower than the average age of patients with AF, and so these results should be applied to an elderly population with caution, but equally warfarin should not be withheld from the sector of the population which is most likely to benefit. However, in a recent systematic review comparing the results of anticoagulant treatment in the community (3 trials, 410 patients) with the pooled results of previous randomized controlled trials, patients undergoing anticoagulation in clinical practice are likely to be older and have more comorbidities than people enrolled in randomized controlled trials. However, the rates of stroke and major bleeding were similar between groups in the comparison, although the risk of minor bleeding was increased in the community group.44

RISK STRATIFICATION

As alluded to earlier, the risk of thromboembolism in AF is dependent on the presence of additional risk factors for stroke. In all risk stratification schemes for stroke in AF patients, those with a prior history of stroke or transient ischemic attack are considered high risk for a further event. By analysis of the pooled data from 5 of the prospective trials of anticoagulation in AF, the AF Investigators identified additional risk factors for stroke in AF patients, as: hypertension; age >65; and diabetes mellitus.45 The SPAF study, (included in the above analysis) identified patients with a recent history of congestive heart failure, systolic blood pressure >160 mm Hg, and women >75 years old as high risk.30

The American College of Chest Physicians Consensus similarly used age >75 years, hypertension, and left ventricular dysfunction to categorize a patient with AF as at high risk for stroke, but in their risk stratification included an intermediate risk group in which patients aged 65 to 75 years, or with a history of ischemic heart disease, diabetes mellitus, or hyperthyroidism were included.46 Application of these data should allow us to identify the patients who would most benefit from anticoagulation, and not expose those patients who are low risk to a risk of bleeding and the inconvenience of anticoagulation monitoring.

Criteria of risk from these 3 schemes have been applied to a cohort of atrial fibrillation patients with no prior history of stroke, to assess their...
Why does thromboembolism occur in AF and how can it best be prevented? - Freestone and Lip

successfully predict those patients at low risk of stroke, but are less successful at predicting those at high risk of stroke.

Identification of risk factors in patients with AF is nevertheless used for risk stratification for thromboembolism—this can be done mainly on clinical grounds (as outlined in Table II), and used to guide anti-thrombotic therapy in our everyday practice. However, some uncertainty still remains for certain AF patient groups.

In patients with AF complicated by stroke, the optimal timing for commencement of anticoagulation after a stroke is unclear. Furthermore, in acute AF, commencement of anticoagulation has not been studied in randomized control trials, but immediate risk of thromboembolism is considered low. For anticoagulation prior to cardioversion of AF, again randomized studies are also lacking. However, the risk of thromboembolism was between 1% and 5% in case-control series.

Current recommendations for treatment are anticoagulation for 3 to 4 weeks prior to and after cardioversion for patients with AF of unknown duration or that has lasted >48 hours. For patients with AF of a shorter duration, current guidelines recommend intravenous or low-molecular-weight heparin for immediate cardioversion if it cannot be delayed due to hemodynamic instability, as left atrial thrombus has been identified even in patients with AF of a short duration. A recent multicenter study (n=1222) has suggested that transesophageal echocardiography (TEE) may be used to guide cardioversion in AF, as patients who underwent immediate cardioversion followed by 4 weeks’ anticoagulation after a TEE that was negative for thrombus in the left atrium or LAA had a comparably low risk of stroke (0.8%) to those on conventional treatment (0.5%).

FROM TRIALS TO CLINICAL PRACTICE

The decision to anticoagulate, as well as based on risk stratification, is also dependent upon excluding any contraindication to treatment, which would include frequent falls in the elderly, cognitive impairment that would make reliable administration of warfarin and monitoring difficult, and any bleeding problems.

In a recent observational study, comparing the opinions of patients at high risk of developing AF to those of physicians who treat AF, it was found that patients placed more value on the avoidance of stroke and less value on the avoidance of bleeding than the physicians. The views of the individual being treated should therefore also be taken into account in the decision-making process, as they may prefer a “higher than average” risk of bleeding to a “higher than average” risk of stroke.

Table II. Risk stratification scheme (A) for thromboprophylaxis (B) in patients with atrial fibrillation. (Adapted from reference 48.)

Abbreviations: CVA, cerebrovascular accident; INR, international normalized ratio; LV, left ventricular; NVAF, nonvalvular atrial fibrillation; TIA, transient ischemic attack.

A. RISK

High risk (annual risk of CVA = 8%-12%)
- All patients with NVAF and previous TIA or CVA
- All patients aged 75 and over with NVAF and diabetes +/- hypertension
- All patients with clinical evidence of valve disease, heart failure, thyroid disease, and/or impaired LV function on echocardiography

Moderate risk (annual risk of CVA = 4%)
- All patients under 65 with NVAF and clinical risk factors: diabetes, hypertension, peripheral vascular disease, ischemic heart disease
- All patients over 65 who have not been identified in the high-risk group

Low risk (annual risk of CVA = 1%)
- All other patients under 65 with NVAF and no history of embolism, hypertension, diabetes, or other clinical risk factors

B. TREATMENT

Using the above criteria for risk stratification, patients with atrial fibrillation should be considered for anticoagulation as follows:

High risk
- Use warfarin (target INR 2-3) if no contraindications and possible in practice

Moderate risk
- Either warfarin or aspirin. In view of insufficient clear-cut evidence, treatment may be decided on individual cases. Echocardiography may help

Low risk
- Use aspirin 75-300 mg daily

*Echocardiography not needed for routine risk assessment, but refines clinical risk stratification in cases of impaired LV function and valve disease. A large left atrium per se is not an independent risk factor on multivariate analysis.
larly in the ethnic minorities), and indeed, increased education is probably required from the medical team in order to involve patients in their choice of antithrombotic therapy.

**SUMMARY**

The increased risk of thromboembolism associated with AF is proven. Whether AF is simply an indicator of a prothrombotic state associated with other risk factors or itself causes the prothrombotic state is not clear, but evidence so far is suggestive of the latter. Whichever is the case, in groups at risk of thromboembolism, anticoagulation is important for effective stroke prevention.

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**Why does thromboembolism occur in AF and how can it best be prevented? - Freestone and Lip**
What are the potential and proven advantages for rate or rhythm control of atrial fibrillation?

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Atrial fibrillation is not benign: all patients, even without underlying heart disease, ultimately develop left ventricular dysfunction. Despite theoretical advantages for rhythm control over rate control, of the four recent randomized trials, one showed a trend for lower mortality with rate control while the other three found no difference. However, the trials excluded the highly symptomatic arrhythmic patients who are typically younger and, in half the cases, have no associated cardiovascular condition. The trials also omitted to show how sinus rhythm would have influenced morbidity and mortality had it been maintained in more patients. Restoration of sinus rhythm with cardioversion and antiarrhythmic prophylaxis or other nonpharmacologic interventions remains mandatory in such patients. Safer and more effective rhythm control methods would cover an important unmet need.

Keywords: atrial fibrillation; treatment; clinical study; cardioversion; antiarrhythmic drug; nonpharmacologic intervention

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Dialogues Cardiacease Med. 2003;8:214-219

AF - atrial fibrillation
AFFIRM - Atrial Fibrillation Follow-up Investigation of Rhythm Management
CTAF - Canadian Trial of Atrial Fibrillation
ECV - electrical cardioversion
PIAF - Pharmacological Intervention in Atrial Fibrillation
RACE - RAte Control versus Electrical cardioversion for persistent atrial fibrillation
STAF - Strategies of Treatment of Atrial Fibrillation

Atrial fibrillation (AF) is not a benign condition. It causes symptoms like palpitations, chest pain, dyspnea, and fatigue. Some patients experience presyncope at arrhythmia onset or termination. All patients with longer-lasting AF develop left ventricular dysfunction, even those without underlying heart disease, and some incur a tachycardiomypathy. Apart from the above, AF is associated with excess thromboembolic complications. Finally, due to treatment of AF with oral anticoagulation and antiarrhythmic drugs, bleeding and severe adverse effects, respectively, may occur.

The optimal treatment regimen remains unclear. For years, maintenance of sinus rhythm has been the main therapeutic goal, using repeated electrical cardioversion (ECV) and prophylactic antiarrhythmic drugs (rhythm-control strategy). The rationale for this approach was that it was expected to reduce symptoms, reduce the incidence of heart failure, improve exercise tolerance, reduce the risk of thromboembolic complications and bleeding (after eventual discontinuation of oral anticoagulation), improve quality of life, and improve survival. However, frequent recurrences of AF and (life-threatening) side effects of antiarrhythmic drugs decrease the potential benefits of ECV. An alternative approach is acceptance of AF, with therapy aimed at adequate control of the ventricular rate during AF using negative chronotropic drugs and prevention of thromboembolic complications with oral anticoagulation (rate-control strategy). Recently, four studies, the North American AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and the European PIAF (Pharmacological Intervention in Atrial Fibrillation), RACE (RAte Control versus Electrical cardioversion for persistent atrial fibrillation), and STAF (Strategies of Treatment of Atrial Fibrillation) studies investigated whether rate control was equivalent, or not inferior, respectively, to rhythm con-
trol. The primary end point was mortality in AFFIRM, improvement in AF-related symptoms in PIAF, a composite of morbidity (heart failure, thromboembolic complications, bleeding, adverse events related to antiarrhythmic drugs, and pacemaker implantation) and mortality in RACE, and a composite of death, ischemic stroke, and major embolism in STAF.

In this article, we discuss the beneficial effects of both rate control and rhythm control in terms of prevention of morbidity and mortality due to (treatment of) AF.

REDUCTION OF SYMPTOMS AND IMPROVEMENT IN QUALITY OF LIFE

Symptoms during AF differ from patient to patient. The clinical basis of AF-related symptoms is not completely established. It is believed that they are related to the severity of the underlying heart disease and the hemodynamic deterioration associated with the high and irregular ventricular rate and loss of atrial contribution to cardiac output. Younger patients with paroxysmal AF often report more complaints. Depending on the patient groups investigated, different data on symptoms and impairment of quality of life are reported. Savelieva and Camm showed that, in at least one third of AF patients, no obvious symptoms were observed, which is in accordance with our RACE data in patients with persistent AF. Hamer, in contrast, reported that symptoms related to paroxysmal supraventricular tachycardia without underlying heart disease (38% of the patients had AF) were troublesome in 68% of patients.

Quality of life using the Short Form–36 (SF-36) health survey questionnaire (which may a better method to assess symptoms) was significantly worse in patients with paroxysmal and persistent AF, compared with healthy controls. Most information about changes in quality of life in patients with AF comes from highly symptomatic patients who are resistant to drug therapy and undergo pacemaker implantation and subsequently atrioventricular node ablation. In these patients, quality of life improved significantly after the procedure. Recently, the effects of either rhythm-control or rate-control therapy (using negative chronotropic drugs and not atrioventricular node ablation) were investigated. The CTAF (Canadian Trial of Atrial Fibrillation) showed that in patients with symptomatic AF (40% had persistent AF), quality of life improved after 12 months of follow-up with either amiodarone, sotalol, or propafenone, especially for those who kept sinus rhythm after conversion. In the AFFIRM, RACE, and STAF studies, quality of life did not change significantly during long-term follow up, neither with rate control nor with rhythm control. Patients in the rhythm-control group who maintained sinus rhythm, however, showed a minor improvement in quality of life. In contrast, the PIAF investigators showed a significant improvement in quality of life at 12 months’ follow-up for almost all SF-36 subscales in both the rate- and rhythm-control groups. Accordingly, 60% and 56% of patients in the rate- versus rhythm-control group, respectively, reported improvement in clinical symptoms (ie, primary end point of PIAF). Importantly, in that study, only symptomatic patients were included, whereas in the RACE study, 70% of patients were symptomatic. Taken together, improvement in quality of life can be expected especially in the highly symptomatic patients, irrespective of treatment regimen. Even so, some data suggest that quality of life may improve after restoration of permanent sinus rhythm. In general, however, both rate- and rhythm-control treatment strategies do not seem to affect quality of life importantly. This relates to the fact that long-term maintenance of sinus rhythm is achieved only in the minority of patients and symptoms related to the associated cardiovascular condition may be vast and may even nullify the potential beneficial effects of permanent sinus rhythm.

IMPROVEMENT OR REVERSAL OF HEART FAILURE

AF may cause heart failure by reducing cardiac output due to loss of atrial kick, excessive rate response, rhythm irregularity, progression of the underlying heart disease, and development of tachycardia-related cardiomyopathy. Small-scale studies have demonstrated that, in case of an inadequate control of the ventricular rate during AF (>100 bpm), a tachycardia-related cardiomyopathy may develop, which is reversible after adequate rate control or rhythm control (ie, restoration of sinus rhythm). Heart failure has, however, also been reported to occur in patients with AF and a normal heart rate. After regularization of the rhythm by His bundle ablation, a significant improvement in the left ventricular ejection fraction could be demonstrated, which suggests that the irregularity per se may contribute to the development of left ventricular dysfunction. Thus, either with rate or rhythm control, improvement or reversal of heart failure may be obtained, but data come from individual patients. RACE revealed that admittance for heart failure was similar in patients treated by rate control versus rhythm control, 3.5% (9/256) versus 4.5% (12/266), respectively, during a fol-
low up of 2.3 years. The latter data are probably not an adequate representation of rhythm control since only 39% of patients were in sinus rhythm at the end of follow-up. Also, data on the occurrence of heart failure during rate control may depend on the degree of rate control. In RACE, acceptable rate control was defined as a resting heart rate <100 bpm. The question remains whether rigid rate control (resting heart rate, eg, <80 bpm) may be associated with an improved prognosis, especially in terms of prevention of deterioration of heart failure, compared with the approach used in RACE. The data available now indicate that, during both rate and rhythm control, heart failure may develop or deteriorate either due to progression of the underlying disease or an inadequate control of the ventricular rate, eg, during a recurrent episode of AF, or adverse effects of (antiarrhythmic) drugs.

**IMPROVEMENT IN EXERCISE TOLERANCE**

Exercise capacity varies considerably in patients with AF and also depends on the severity of the underlying heart disease and patients’ age. Nevertheless, patients with lone AF may have a reduced maximal oxygen consumption compared with age-matched controls without AF. Several small-scale studies investigated exercise tolerance measured as maximal oxygen consumption before and after restoration of sinus rhythm or long-term acceptance of AF (Table I). Gosselink et al demonstrated in a nonrandomized study that patients who maintained sinus rhythm during a follow-up of 2 years showed an improvement in exercise tolerance. In contrast, patients who were in AF again at that time after an initial successful cardioversion demonstrated a small, but significant, decrease (Table II). In the randomized PIAF study, patients treated by rhythm control had better exercise tolerance compared with those treated by rate control (Table II) though, in that study, the improved exercise tolerance did not translate into a significant improvement in quality of life.

**REDUCTION OF THROMBOEMBOLIC COMPLICATIONS**

AF is associated with thromboembolic complications, usually stroke. Studies of secondary prevention recently demonstrated that heart rhythm is not an independent risk factor for stroke in patients with nonvalvular AF. Instead, other factors, including age >65 years, history of stroke and hypertension, diabetes mellitus, congestive heart failure, impaired left ventricular function, coronary artery disease,
Rate control (N=256) | Rhythm control (N=266)
--- | ---
Death from cardiovascular causes | 18 (7.0%) | 18 (6.8%)
Cerebral/retroperitoneal bleeding | 6 | 3
Heart failure | 4 | 1
Thromboembolism (stroke) | 0 | 6
Sudden cardiac death | 8 | 8

**Table III. Incidence of cardiovascular death in the RACE study (Rate Control versus Electrical cardioversion for persistent atrial fibrillation).**

and enlarged left atrium, are important. This may relate to the fact that, in addition to the development and subsequent migration of atrial thrombi, emboli originating in the thoracic aorta and the carotid arteries also contribute to stroke. Therefore, it was not surprising that, both in RACE and AFFIRM, rhythm control did not reduce the thromboembolic complication rate. In AFFIRM, all patients had risk factors for thromboembolic complications, in RACE 90% of the patients. The majority occurred either after discontinuation of oral anticoagulation after restoration of sinus rhythm or while receiving inadequate anticoagulant therapy (international normalized ratio [INR] below 2). Therefore, if risk factors are present, lifelong oral anticoagulation is necessary, independently of the chosen treatment strategy and the actual rhythm.

**REDUCTION OF BLEEDING**

The efficacy of warfarin for prevention of thromboembolic complications must be balanced against the risk of major bleeding. The risk of major bleeding is related to the intensity of anticoagulation. It was believed that rhythm control might reduce the risk of bleeding since, after long-term maintenance of sinus rhythm, oral anticoagulation may be eventually discontinued. However, since it has now been recognized that lifelong oral anticoagulation is necessary in patients with a history of AF and risk factors for thromboembolic complications independent of the actual rhythm, the risk of bleeding will not be lowered by rhythm control.

**REDUCTION OF MORTALITY**

Several cohort studies have demonstrated that the risk of death in subjects with AF is roughly twice that found in subjects with sinus rhythm. However, it is a matter of debate whether AF itself results in excess mortality or whether it reflects increased mortality of associated conditions. Patients with lone paroxysmal AF (ie, without underlying heart disease) do not have an impaired prognosis. The AFFIRM study investigated whether rhythm control therapy reduced mortality. In that study, there was a trend toward an increased overall mortality in patients treated by rhythm control (25.9% versus 26.7%, *P*=0.08 in the rate- versus rhythm-control group during a mean follow-up of 3.5 years). Rhythm control was associated with excess mortality among older patients, those with congestive heart failure, and those with coronary artery disease. After adjustment for these covariates, the trends towards an increased mortality in rhythm-control compared with the rate-control group persisted. Also, in this study the majority of patients (87.6%) had underlying heart disease. No data on cause of mortality and differences between both treatment strategies are yet available. In RACE, cardiovascular mortality was comparable between both groups, but the cause of death was different. The above indicates that mortality seems to be comparable with either treatment strategy.

**CONCLUSION**

As described above, theoretically, rhythm control would have advantages above rate control. Remarkably, there was a trend for a lower mortality in the rate-control treated patients in AFFIRM. Similarly, in the other studies, rhythm control did not differ from rate control. At first glance, this may seem to imply that the attempt to restore sinus rhythm is no longer justified. However, the randomized studies did not deal with the highly symptomatic arrhythmic patient. Typically, this patient is relatively young and does not have associated cardiovascular conditions in half of the cases. In these patients, restoration of sinus rhythm with cardioversion and prophylactic antiarrhythmic drugs or other nonpharmacological interventions remains essential. The development of new, safer and more effective, rhythm-control methods, would cover an unmet need. In this respect it is also important to note that the randomized studies cannot answer the question of how morbidity or mortality would have been influenced if sinus rhythm had been maintained in a significant number of patients. Indeed, long-term maintenance of sinus rhythm could be achieved in only a minority of patients. 56% maintenance of sinus rhythm after 1 year in PIAF, 63% after 5 years in AFFIRM, 39% after 2 3 years in RACE, and 40% after 1 year in STAF.
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The poor efficacy of new as well as previously established antiarrhythmic drugs in the suppression of atrial fibrillation has been disappointing to patients and physicians alike. Moreover, the adverse effects of antiarrhythmic agents, including the risk of sudden death from proarrhythmia, have been increasingly recognized over the last 15 years. The ongoing requirement for concomitant anticoagulant therapy while taking antiarrhythmic drugs further reduces the patient’s quality of life and conveys additional risks including a 0.3% risk per annum of intracranial hemorrhage. Thus, for patients with symptomatic atrial fibrillation who may be faced with the prospect of decades of antiarrhythmic drug therapy, the option over recent years of a potentially curative catheter ablation procedure for atrial fibrillation has been of considerable interest.

**EVOLUTION OF PULMONARY VEIN ISOLATION**

The success of catheter ablation in the elimination of other atrial arrhythmias such as atrial flutter and atrial tachycardia and the success of the surgical maze procedure in treating chronic atrial fibrillation stimulated the exploration of catheter ablative techniques for the treatment of atrial fibrillation in the early 1990s. Up until that point, the mechanism of atrial fibrillation had been regarded as being too chaotic to be approached by catheter ablation. The primary nonpharmacological procedure under clinical research for the curative treatment of atrial fibrillation at that time was the surgical atrial maze procedure, which sought to interrupt the spread of multiple reentrant wavefronts.

Swartz, in his pioneering work on the catheter maze procedure in patients with chronic atrial fibrillation in the early 1990s, attempted to replicate the surgical atrial maze procedure by the creation of lines of conduction block using a transvenous “drag and burn” radiofrequency catheter ablation technique. Unfortunately, the extent of radiofrequency applications in the era before temperature control resulted in a high risk of thromboembolism. Furthermore, the “drag and burn” approach guided by fluoroscopy alone before the advent of electroanatomical mapping technology frequently resulted in iatrogenic reentrant circuits around incomplete lines of conduction block requiring multiple repeat procedures in some patients. However, Swartz did demonstrate proof of the concept that atrial fibrillation could be cured by catheter ablation, albeit at the expense of a relatively high complication rate and prolonged procedure times. Furthermore, his experience and that of others demonstrated...
the relative importance of the left atrium in the maintenance of atrial fibrillation and his work stimulated extensive experimental studies examining the efficacy and safety of new catheter ablation technologies including linear radiofrequency, linear cryotherapy, linear diode laser, and irrigated radiofrequency ablation for the treatment of atrial fibrillation.3-9

When the catheter maze procedure is limited to the right atrium it is a safer procedure, but is associated with a lower probability of success.3-5 Overall, clinical results for the right atrial catheter maze procedure show a significant reduction in the number of symptomatic episodes of atrial fibrillation, but few patients are cured and most patients continue to have some episodes of atrial fibrillation and require long-term antiarrhythmic drug therapy.

Thus, up until the late 1990s, catheter ablation approaches to atrial fibrillation were limited to the concept of interrupting the multiple wavelets maintaining atrial fibrillation.5 Haissaguerre and colleagues subsequently discovered that catheter ablation of underlying ectopic foci, which initiate episodes of atrial fibrillation, could prevent further recurrences and successfully cure selected patients with paroxysmal atrial fibrillation (Figure 1). They found that such ectopic foci are predominantly located within the myocardial sleeves of the pulmonary veins. These focal triggers within the myocardial sleeves of the pulmonary veins presented a discrete and finite target for catheter ablation and their discovery represented a major advancement in our understanding of the mechanism of paroxysmal atrial fibrillation and opened new avenues for research. It had long been recognized that in utero, as the pulmonary veins bud out from the atrium to the lungs, they retain an investiture of atrial myocardium in their proximal portions. The role of such myocardium, however, had been felt to be limited to a sphincter function to reduce reverse venous flow during atrial systole. The effective refractory period of pulmonary vein myocardium has recently been shown to be significantly shorter than that of the left atrium in patients with atrial fibrillation.11 This allows both rapid discharge from ectopic foci as well as favoring reentry within the pulmonary venous myocardium, which may contribute to the maintenance of atrial fibrillation.12 The myocardial extensions vary significantly in their length (0.5 to 4.0 cm) and in some patients are asymmetric. Histologic studies have found that the further out from the pulmonary vein ostium, the poorer the myocyte-to-myocyte cell coupling, which, through a mechanism of reduced electrotonic inhibition, may contribute to their arrhythmogenicity.13 The connections to the myocardium of the left atrium vary from fully circumferential (360 degrees) around the pulmonary vein ostium to one or two myocardial bridges at the superior and inferior poles of the pulmonary vein ostium. Originally, Haissaguerre and Jais demonstrated the clinical efficacy of catheter ablation of pulmonary vein ectopic foci in patients with lone paroxysmal atrial fibrillation who had a high burden of spontaneous ectopic activity on ambulatory monitoring (Figure 1). While the procedure was remarkably successful in a minority of patients, most patients had recurrences of atrial fibrillation on longer-term follow-up. These recurrences were most often due to ectopic activity from additional sites within other pulmonary veins as well as within previously targeted pulmonary veins. The focal ablation approach was limited by difficulty in the induction of sufficiently frequent spontaneous ectopic activity during the procedure despite the administration of high doses of isoproterenol and difficulty in accurately mapping the more distal branches as well as proximal sites of the myocardial sleeves. Ablation
at sites distal to the pulmonary vein ostium was also found to induce an inflammatory response in some veins with a subsequent risk of pulmonary vein stenosis. Despite the high requirement for repeat procedures and the difficulty encountered in patients who developed pulmonary vein stenosis, proof of concept had again been demonstrated for a curative procedure in selected patients with atrial fibrillation. The further refinement of the procedure by Haissaguerre et al\(^\text{10}\) from catheter ablation of individual foci within the pulmonary veins to empiric isolation of all four pulmonary veins not only significantly increased the efficacy of the procedure, but also greatly reduced the risk of pulmonary vein stenosis.

**Efficacy and Safety**

**Efficacy**

At centers where all pulmonary veins are empirically isolated (as opposed to isolation of only those veins that appear to be active at the time of study) the success in eliminating recurrences of atrial fibrillation ranges from 50% to 85% for patients with paroxysmal atrial fibrillation and 22% to 75% for patients with persistent atrial fibrillation.\(^\text{10,14-18}\) Factors contributing to the wide range of reported success rates include method of patient follow-up (symptoms versus systematic ambulatory recordings), remote versus personal local follow-up, inclusion or exclusion of repeat procedures as a component of the primary treatment strategy, reporting of early transient recurrences within the first 6 weeks post procedure, or the use of a blanking period, case mix (proportion of paroxysmal lone atrial fibrillation versus persistent atrial fibrillation with structural heart disease), procedural technique (eg, segmental ostial ablation versus periostial atrial encirclements and energy settings), and operator experience. Elimination of atrial fibrillation has been achieved with both the catheter maze procedure\(^\text{3}\) as well as the pulmonary vein isolation.\(^\text{11}\) While the results of long-term follow-up will not be available for another decade, catheter ablation has eliminated atrial fibrillation for up to 5 years of follow-up in selected patients. The probability of long-term success seems favorable, although this may be better for patients with lone atrial fibrillation compared with patients with advanced cardiomyopathy in whom the intermediate-term efficacy of the pulmonary vein isolation has yet to be adequately studied. It is encouraging to note that the majority of patients who underwent catheter ablation of atrial flutter a decade ago have not had late recurrences of atrial flutter.

**Figure 2.** In the upper panel, the first beat is sinus followed by an ectopic beat within the pulmonary vein with exit block to the left atrium. The third beat is again sinus, followed by an ectopic beat, which starts fibrillatory reentry within the pulmonary vein, which then conducts to the atrium. The atrial rhythm is initially a regular flutter, but it subsequently degenerates into atrial fibrillation (lower panel). Such findings are consistent with the hypothesis that in some patients the pulmonary veins themselves may play a role in the maintenance as well as the initiation of atrial fibrillation.

**Abbreviations:** LA-CS, left atrium–coronary sinus electrogram; PV, pulmonary vein electrogram; RA, right atrial electrogram; Surface, surface ECG lead.
Safety

Potential complications of pulmonary vein isolation include cardiac tamponade, thromboembolic stroke, phrenic nerve injury, peripheral vascular injury, and the development of pulmonary vein stenosis. The risk of pulmonary vein stenosis was highest when catheter ablation involved direct ablation of active foci within the pulmonary vein itself. However, following the change in approach to pulmonary vein isolation, the risk of pulmonary vein stenosis has not been eliminated. This most likely arises from an inability to prevent the ablating catheter tip from moving into the vein itself during respiration and atrial systole and the limitations of 2-dimensional echo in imaging the 3-dimensional course of the ablation catheter and the mismatch between the electrical junction of the atrial and venous myocardium and the anatomical ostium. The incidence of pulmonary vein stenosis reported varies from 0% to 42%. Factors contributing to such a wide range of reported stenosis include: (i) the method of pulmonary vein assessment; (ii) routine magnetic resonance imaging (MRI) of lumen diameter at 6 months versus transesophageal Doppler assessment of venous blood flow versus imaging only upon the reporting of symptoms; (iii) definition of stenosis (>20% versus >50% diameter stenosis); (iv) ablation technique (eg, segmental ostial ablation versus periostial atrial encirclements); (v) use of electroanatomical mapping ± intracardiac echo guidance instead of reliance upon fluoroscopy alone to determine the excursion of the electrode at the pulmonary vein ostium; and (vi) operator experience. However, if both are available, selection of MRI avoids exposing the patient to additional ionizing radiation. A chest CT scan can expose the patient to a radiation dose equivalent to 40 chest x-rays. Although the risk associated with such exposure is low in absolute terms, it is accumulative and the patient may elect to undergo MRI instead, particularly if routine follow-up imaging is planned at 3 or 6 months post procedure to screen for asymptomatic pulmonary vein stenosis. The issue of radiation exposure is of greater concern at centers where pulmonary vein isolation is performed under fluoroscopic guidance alone without the use of an electroanatomical mapping system or intracardiac echo and the fluoroscopy time is therefore prolonged. A fluoroscopy rate of 7.5 frames per second (fps) provides excellent imaging for the guidance of catheter ablation and should be routinely selected (rather than 15 or 30 fps) for pulmonary vein isolation procedures.

CURRENT APPROACH TO CATHETER ISOLATION OF PULMONARY VEINS

Preprocedural imaging

Prior to the procedure, patients undergo MRI or spiral computerized tomography (CT) to provide a 3-dimensional anatomical road map of the proximal pulmonary veins (Figure 3). The resolution of the two imaging techniques is comparable.
lenging, while it facilitates the approach of peristomal left atrial encirclement. The presence of a separate ostium for the right middle pulmonary vein typically results in an ostium of small caliber, which is therefore more prone to stenosis, and care should be taken to avoid phrenic nerve palsy. Advance knowledge of the size of pulmonary veins facilitates selection of ablation and mapping catheters of appropriate diameter. It can also reveal in advance the presence of anomalous venous anatomy, such as a persistent left superior vena cava from which ectopic foci can arise.

Upon arrival in the electrophysiology laboratory (EP Lab), patients undergo transesophageal echocardiography to exclude a left atrial appendage thrombus. For patients with lone paroxysmal atrial fibrillation who have been transitioned from warfarin to subcutaneous low-molecular-weight heparin at home immediately prior to the procedure, the need for transesophageal screening for thrombus at the time of the procedure is not established. However, transesophageal echo may also reveal a patent foramen ovale or lipomatous hypertrophy or aneurysm of the septum, and, for patients undergoing a repeat procedure, transesophageal echo provides another opportunity to detect any evidence of pulmonary vein stenosis.

**Intracardiac echocardiography**

Intracardiac echocardiography is used at some centers to guide transseptal punctures (Figure 4) and can also be used to confirm positioning of the ablating catheter at the pulmonary vein ostium (Figure 5). During ablation, intracardiac echo can be used to detect excess bubble formation, which in animal studies has been found to correlate with

**Figure 4.** Guidance of transseptal puncture by phased array intracardiac echocardiography in a patient undergoing pulmonary vein isolation for paroxysmal atrial fibrillation. In this patient, the fossa is seen to be floppy and accommodates marked excursion into the left atrium (B & C), before the needle punctures (D).

**Figure 5.** Phased array intracardiac echo showing a mobile thrombus attached to the shaft material of a catheter in the right atrium prior to ablation.

**Abbreviations:** RA, right atrium; RV, right ventricle.

**Figure 6.** Intracardiac echo guidance of pulmonary vein isolation. This image shows that the catheter has advanced into the pulmonary vein ostium and therefore needs to be withdrawn back to the left atrium before energy is applied. The color Doppler function can be used to detect any increased flow or turbulence that would be expected in the case of acute pulmonary vein stenosis.
risk of endocardial disruption. Intracardiac echo also can reveal formation of thrombus on catheters or transeptal sheaths despite weight-adjusted heparin administration (Figure 6). Intracardiac echo is particularly useful in the guidance of studies of balloon isolation catheters and can confirm when occlusion of blood flow has been achieved. The limitations of intracardiac echo include the inadequacy of 2-dimensional echo to guide manipulation of the 3-dimensionally curved ablating catheter and mapping catheter. Furthermore, maintaining stable deflection and torque of the ablating catheter, the mapping catheter and intracardiac echo catheter by a single operator to ensure that the ablating electrode continues to be imaged throughout manipulation and delivery of energy can be a challenge.

Anticoagulation

Anticoagulant regimens vary significantly from center to center. In addition to intravenous heparin, inhibitors of platelet aggregation are also used at most centers. Agents used include aspirin, clopidogrel, and short-acting intravenous glycoprotein IIa/IIIb inhibitors. The incidence of thromboembolism is so low that a clinical trial to demonstrate superiority of one anticoagulant regimen over another would require approximately 4000 patients, and thus a lack of standardization in this regard is likely to continue, particularly while different centers continue to use different ablation techniques (irrigated versus nonirrigated radiofrequency ablation, cryothermy, and ultrasound).19

Repeat procedures

The rate of repeat pulmonary vein isolation procedures relates not only to the power used,20 but also to the timing of repeat procedures. Centers that waited for more than a month before deciding to bring a patient back to the EP Lab found that recurrences in the first weeks after ablation often settled over time and that in one third of patients such recurrences would resolve spontaneously.18 Such resolution over time is felt to be secondary to a transient inflammatory state or subclinical pericarditis post ablation. Patients who develop an early recurrence post pulmonary vein isolation can be managed by resumption of their antiarrhythmic drug therapy for 2 to 3 months. Another advantage of waiting 3 months before deciding to bring a patient with atrial fibrillation recurrence back for a repeat procedure is that most patients who develop pulmonary vein stenosis will already have evidence of this process on repeat MRI by 3 months.

Findings at repeat procedure in patients with ongoing atrial fibrillation recurrences include recovery of conduction from the previously isolated pulmonary veins in the majority of cases and cuffs of surviving muscle proximal to the site of previous pulmonary vein isolation. In addition to pulmonary vein sites at both initial and repeat procedures, ectopic foci may also be found to emanate from the right and left atria, the coronary sinus, superior vena cava, the inferior vena cava, the coronary sinus and ligament of Marshall, persistent left superior vena cava, and other anomalous veins (Figures 7 and 8, page 226).21,22

The superior vena cava can be easily isolated at its junction with the high right atrium by the use a circumferential mapping catheter and segmental ablation and is now practiced routinely in patients who present with recurrence of atrial fibrillation after previous pulmonary vein isolation (Figure 7).

CURRENT AND FUTURE RESEARCH

Periostial circumferential encirclement in the left atrium versus segmental ablation at the pulmonary vein ostium

It remains to be determined whether periostial circumferential encirclement of the pulmonary veins by ablation exclusively in the left atrium as described by Pappone et al14 confers greater efficacy than segmental ostial ablation guided by pulmonary vein mapping as described by Haissaguerre et al.10 The periostial left atrial approach is less prone to miss any proximal myoccardium with enhanced automaticity and should further reduce the risk of pulmonary vein stenosis. Another proposed advantage of this left atrial periostial approach is that not only it may prevent ectopic beats from initiating atrial fibrillation recurrences, but it may also affect the substrate involved in the maintenance of atrial fibrillation. Optical mapping studies in isolated Langendorff sheep atria have found evidence for periodicity in the atrial tissue adjacent to the pulmonary veins.23,24 In some patients with atrial fibrillation, such periodicity can also be observed by direct recording of the electrogram intervals at different atrial sites (Figure 9, page 227). Occasional termination of atrial fibrillation during periostial ablation also provides encouragement for this approach. Using this approach, Pappone et al14 have not only reported a higher success rate (85%) for this procedure than most series of segmental ablation in patients with paroxysmal atrial fibrillation, but they have also found that patients with chronic atrial fibrillation are also successfully treated with this procedure with a success rate of 75%, which is significantly greater than that reported for the segment-
tal ostial ablation approach. Based on the above, we routinely encircle all pulmonary veins using a left atrial circumferential approach and create a single circle for each pair of ipsilateral veins (Figure 10). Given that the different approaches are performed at different centers, a multicenter randomized clinical trial is currently under consideration to compare the relative merits, efficacy, and safety of periostial circumferential ablation in the left atrium versus segmental ablation at the pulmonary vein ostium. Furthermore, a number of new technologies are currently in clinical trials to simplify the process of circumferential ablation, including balloon-based ultrasound systems ultrasound and coil-based cryothermal systems.

**Linear ablation**

For patients with persistent atrial fibrillation who remain in atrial fibrillation at the end of the procedure after circumferential ablation of the pulmonary veins, supplemental linear lesions are created under electroanatomical guidance. The lesions that are most frequently created are a line of conduction block from the lower pole of the left inferior pulmonary vein to the posterolateral mitral annulus and a right atrial isthmus lesion from the eustachian ridge to the tricuspid annulus. To date, no randomized trial has been completed to demonstrate the efficacy of these and other linear lesions as an adjunct to pulmonary vein isolation.

**Relative role of pulmonary vein isolation with respect to antiarrhythmic drug therapy**

It is anticipated that the role of pulmonary vein isolation will evolve in a similar direction to that of atrial flutter ablation. Conventionally, catheter ablation has been considered second-line therapy after a pa-
tient had failed antiarrhythmic drug therapy. However, as awareness of the risks of antiarrhythmic drug therapy and anticoagulation gained increasing recognition, the role of catheter ablation in the management of recurrent atrial flutter has become an acceptable option for first-line management. Early catheter ablation of recurrent atrial flutter has also been shown to be more cost effective than long-term medical management. The current accepted indication for pulmonary vein isolation is for patients with symptomatic recurrent atrial fibrillation who have failed antiarrhythmic drug therapy. After initial treatment of any condition that may be contributing to the etiology of atrial fibrillation and initiation of a β-blocker, most patients under 65 years of age presenting with symptomatic recurrent atrial fibrillation are currently offered antiarrhythmic drug therapy as the next step in therapy. For young patients with recurrent symptomatic atrial fibrillation who may be faced with decades of pharmacological therapy with significant accumulative risk, and particularly where their condition may have career or occupational implications, the option of proceeding directly with pulmonary vein isolation after being fully informed of all risks should not be excluded.

An ongoing multicenter study will address the question of whether pulmonary vein isolation procedure versus antiarrhythmic drug therapy offers the greatest efficacy and safety profile in patients who have previously failed one antiarrhythmic drug. Given the growing appreciation for the risk of sudden death associated with antiarrhythmic drug therapy, and the significantly improved efficacy and safety profile of pulmonary vein isolation, a second trial comparing pulmonary vein isolation with antiarrhythmic drug therapy as primary therapy for patients with recurrent atrial fibrillation is envisaged.

The Atrial Fibrillation Research Program at the Massachusetts General Hospital is funded in part by: The Blum Family, Newton, MA; The Robert Maloney Family, NH, and The Atrial Fibrillation Foundation.
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Veratrum is the generic name of 45 species of plant, for example, *Veratrum viride* (American green hellebore; false hellebore; Indian poke) (Figures 1, and 2 [next page]), and *Veratrum album* the white hellebore of Europe where it grows on alpine meadows. The name hellebore is misleading because the genus *Helleborus*, as for example the Christmas rose *H. niger*, the black hellebore, is in the family Ranunculaceae. The genus veratrum is in the lily family (Liliaceae) and the species are mostly found in North America. For centuries it had been well known as a poisonous plant producing very unpleasant symptoms, especially purging, vomiting, and fainting, while sometimes severe prostration and death resulted from eating the rhizome. In 1819, William Brande of London wrote “Although it has been prescribed in some cases of mania and of epilepsy modern practitioners reject it.” Likewise, in the United States it was said in 1840 that “*Veratrum viride* has seen its day, that its glory has departed.”

However, the preparation and sale of a tincture of *V. viride* by Dr Norwood of South Carolina in 1852 led to renewed interest in the medicine, which was found to “reduce the heart’s action” and slow the pulse. It became widely used to control the circulation in inflammatory diseases such as typhoid fever.

However, the really important use of this plant was discovered in the small town of Eufala in Alabama by Dr Paul DeLacy Baker in 1859, and this was for the treatment of eclampsia of pregnancy. In his paper “Veratrum Viride in chorea and other convulsive disorders,” Dr Baker tells in graphic language how he had to manage a desperately ill woman who was having a succession of convulsions before and after the birth of her stillborn child. He told how he treated a severe convulsion, her seventh, after delivery:

> I immediately gave her fifteen drops of *Veratrum Viride* and directed that she should take ten more in two hours. There occurred no more convulsions and the woman recovered perfectly, she was not even nauseated though the medicine was given at regular intervals during the whole night.

He refrained from giving it before delivery for fear of harming the fetus. One might ask why did he use this remedy? The answer is given in his paper in which he tells of using it with success a year previously in a man who was clearly having an attack of grand mal epilepsy. In both cases he was treating a convulsion and he had no way of knowing that they had totally different causes. Dr Baker declared that “it is eminently a nervine.” At that time the term eclampsia was used for any type of fit or convulsion, and was not restricted to pregnancy.

Quite remarkably, that single report was the beginning of the use for nearly 100 years of veratrum in eclampsia and later in preeclampsia of pregnancy. It was known then that it “softened the pulse,” but it would be another 48 years before the blood pressure could be accurately measured and certainly there was no concept of hypertension in pregnancy. Dr Norwood spoke of it as “a controller of vascular and arterial excitement” and Dr Baker wrote, “...by its influence, the heart’s action is simply held in check, and the force of the circulation reduced to nature’s standard.” It was much better, said Dr Baker, than venesection—which was at the time the preferred treatment, usually in large and repeated amounts, for almost any serious disease.

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*Dialogues Cardiovasc Med.* 2003;8:229-233
Experience in the United States with veratrum led to its use in Europe, and in fact the first large series and one in which the blood pressure was reported for the first time came from Professor Mangiagalli in Milan in 1907. He noted that not only was the systolic blood pressure always very high in eclampsia, but that a fit was preceded by a strong increase, up to 280 mm Hg. In his clinic, an extract of *Veratrum viride* was given in preeclampsia whenever the pressure exceeded 150 mm Hg and in 94 women there was a mortality of only 6.3% over a 10-year period compared with 23% of his own patients in the 10 previous years. He wrote that its efficacy was most probably due to its hypotensive action. In passing we can note that it was an Italian physician, Scipione Riva-Rocci, whose invention of the pneumatic cuff in 1896 led to reliable blood pressure measurement.

Nevertheless, it was in the United States that the banner for veratrum therapy was kept aloft by the obstetricians at Cincinnati General Hospital, where it became established as the treatment of first choice for eclampsia of pregnancy, and, in 1935, it was said to have been the basis of treatment there for many years. In 1940, Bryant and Fleming reported 120 cases treated at that hospital with a regimen consisting of a preparation of *Veratrum viride*, “Veratrone,” by injection, repeated every 15 minutes, until the pulse rate was below 60 mm Hg or the systolic blood pressure below 120 mm Hg. They wrote,

The effect of an injection is startling and may cause undue alarm to those not accustomed to seeing it. The blood pressure falls sometimes to as low as 50 systolic and the heart beat to 40 per minute. Vomiting is copious.

It was combined with injections of magnesium sulfate, so the total effect of treatment is difficult to apportion to either drug, but it was remarkably effective in an era when the mortality rate could be as high as 20%. Only 2 of their patients died (1.67%), both from late sepsis, but 28% of the babies were stillborn. The methods at Cincinnati were adopted in 1947 by Frederick Irving at the Boston Lying-In Hospital. He gave Veratrone subcutaneously, together with magnesium sulfate, to all of his patients who had convulsions, if necessary at 20-minute intervals, to keep the systolic blood pressure below 150 mm Hg. As a result, the death rate was reduced from a previous 30% to 5%.

**CHEMISTRY OF VERATRUM**

Steroidal alkaloids are compounds with a fairly complex nitrogen-containing nucleus, and they are divided into two main classes: (i) the veratrum type with over 50 alkaloids and divided into two main subtypes, jerveratrum and ceveratrum—to give one example, the chemical formula for protoveratrine is C32 H51 O9 N; (ii) the solanum type, found in the Solanaceae family. The steroidal alkaloids are found most often in the plant families Liliaceae, Solanaceae, and Apocynaceae. This is interesting because these last two families also contain medically important drugs. Species of Solanaceae yield atropine and hyoscine, while from Apocynaceae are derived the vinca alkaloids, reserpine, and the cardiac glycoside ouabain.

**ISOLATION OF THE VERATRUM ALKALOIDS AND MODE OF ACTION**

Veratrum was at first used clinically without knowledge of its constituent alkaloids or indeed of their mechanism of action. The active principles are contained in the rhizome and when a pure alkaloid was isolated in 1944, it stimulated interest in using veratrum for non–pregnancy-related hypertension. *Veratrum album* L. contains, among others, the active alkaloids germine and protoveratrine. *Veratrum viride* Aiton yields a potent stable extract containing a mixture of amorphous alkaloids, which was market-
ed under the trade name of Veriloid. A related species from Mexico called *Schoenocaulon officinalis* A. Gray, known as Sabadilla, contains veratrine and cedrine and an extract of the plant is known as Veratrine. Like the other two it is also a species of Liliaceae.

The three major effects of the veratrum alkaloids are hypotension, bradycardia, and vomiting. As long ago as 1597, the London surgeon John Gerard wrote in his famous herbal, "The root of white hellebor procureth vomite mightily wherein consisteth his chiefe vertue" (Figure 3). However, it was Albert von Bezold, in 1867, who made the first scientific study, and his conclusion that the hypotension is due to afferent impulses from the heart producing a reflex fall of blood pressure has stood the test of time. Later work gave more detail. Veratrum causes the afferent impulses from the heart (the von Bezold reflex) and also from the lungs to discharge continuously, leading to arteriolar dilatation in skeletal muscle and the splanchnic area, with no fall in cardiac output. The decrease in peripheral resistance is caused through the sympathetic nervous system, as the drug does not increase blood flow in a sympathectomized limb. It is mediated through reflex inhibition of central vasoconstrictor impulses. Importantly, the alkaloids are not sympatholytic, and as a result the pressor reflexes such as the Valsalva maneuver are maintained and postural hypotension does not occur.

**TREATMENT OF HYPERTENSION**

Sixty years ago, there was little that could be done to lower the blood pressure in patients with essential or renal hypertension. Potassium thiocyanate, introduced in 1901, was of minor value and the enthusiasm for lumbar sympatheticotomy in the 1940s mirrored therapeutic desperation. The introduction of the ganglion-blocking drugs pentamethonium halide and hexamethonium halide in 1948 was an important advance, and at much the same time, physicians such as Edward Freis in Boston, USA, were attracted to the veratrum alkaloids, often in the form of Veriloid. When given orally, their hypotensive effect reached a maximum in 4 hours and had disappeared by 14 hours. Freis and Stanton treated 40 patients with Veriloid for up to 13 months and found that the development of side effects and changing sensitivity to a given dose limited its usefulness. However, short-term treatment for a hypertensive crisis was very effective.

Kauntze and Trounce, in 1951, reported 10 patients at Guy's Hospital all with a diastolic pressure over 120 mm Hg. Blood pressure control with oral Veriloid was good in 8, but its short-lived effect made control variable. Nausea was invariable, but usually mild (Figures 4 and 5, page 232).

One of the best studies came from Doyle and Smirk in New Zealand in 1953, using the pure alkaloids neogermitrine and protoveratrine, and also mixed alkaloidal preparations. They achieved good blood pressure control in 15 out of 65 hypertensive patients. They found that although control was initially good in a majority, the margin between therapeutic and toxic doses narrowed as treatment is continued. The toxic manifestations were burning sensation in the mouth, hiccough, salivation, nausea, and vomiting. This study made it clear that the veratrum alkaloids, whatever the preparation used, were never going to be a satisfactory method of treating hypertension.

At the time this was a disappointment because the mode of action with preservation of pressor reflexes and no postural hypotension was in marked contrast to the inhibition of these reflexes with ganglion-blocking agents.

**SEVERE TOXICITY AND POISONING**

The poisonous nature of veratrum had been known for centuries, and early settlers in North America used it as an insecticide and to poison crows. In Germany, it was used as an ointment to treat scabies, hence the name "Kratzwurzel," itch-root. Toxicity was an especial problem in earlier times when the potency of a plant extract would be unknown, a problem referred to by William Withering when he investigated the use of foxglove in cardiac failure in 1775. Dr Baker had found this, "soon after entering upon the practice of medicine." He was treating a lady with a high fever when she suddenly collapsed, "with an icy coldness which simulated the chill of death itself. Friends and relatives were hurried for to see her die." Yet she recovered, with a soft, slow, and regular pulse. The use of the pure alkaloids or standardized extracts after 1944 helped to reduce severe side effects.
A different problem, that of plant identification, led in 1985 to a report of accidental poisoning in France, when five men were taken ill after making wine from what they thought was yellow gentian, *Gentiana lutea* L. It was in fact *Veratrum album*. They all had vomiting, abdominal pain, hypotension, and bradycardia and in one there was complete atrioventricular block with idioventricular rhythm, which recovered without pacing. When not in flower these two species can be readily confused. It is known to be a strong teratogen, and it has been reported that ewes who eat it may have a lamb with a central eye.  

**COMMENT**

The veratrum alkaloids have a very attractive mode of action in hypertension and were it not for their inevitable side effects they might constitute a good form of treatment today. Variable response is also a problem, not apparently to tachyphylaxis. Unfortunately, the toxicity, especially the vomiting, seems to be linked directly to their mode of action via the von Bezold reflex and this almost rules them out for long-term therapy. This problem does not, however, apply to short-term treatment, as in preeclampsia and eclampsia, but modern drugs such as methyldopa and labetalol have overaken veratrum for this condition. However, it is clear that Dr Paul DeLacy Baker initiated a major advance in the treatment of eclampsia of pregnancy when, no doubt at his wit’s ends to know what to do, he treated that woman in 1859. The large series of preeclampsia and eclampsia reported in the first half of the 20th century leave one in no doubt that veratrum was a life-saving drug and furthermore that it could be administered with safety, especially now that blood pressure measurement had become readily available.

As one might expect, the distribution of effective medicines within the plant kingdom is not predictable because plant medicines are secondary compounds within plants, which have evolved chiefly to protect them from predators. However, it so happens that the Liliaceae family does have another genus with medicinal properties. This is the Mediterranean sea onion or squill, *Drimia maritima*, used in former times to treat heart failure. It contains cardiac glycosides, and oxymel of squill was invented by Pythagorus as an expectorant.

The veratrum alkaloids have such an interesting and seemingly good mode of action that it seems a pity that side effects have limited their use for chronic administration. Perhaps an enterprising pharmaceutical company could either synthesize a derivative without the side effects, or else investigate some of the 40 or so alkaloids that may not so far have been studied pharmacologically.

I thank Dr Walter Sneader of the University of Strathclyde for his valued advice.
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Auricular fibrillation and its relationship to clinical irregularity of the heart

T. Lewis

Br Heart J. 1910;1:306-372

The first electrocardiographic recording of atrial fibrillation was made by Einthoven in 1906, but a significant background noise precluded the identification of atrial activity, although normal ventricular complexes were seen. With an improvement of the method, the fibrillatory f waves became clearly visible, but were not linked to atrial fibrillation until 1909 when Sir Thomas Lewis, independently of two German investigators, Rothberger and Winterberg, described an electrocardiogram in a patient with arrhythmia perpetua, an absolute ventricular arrhythmia and the presence of irregular waves seen in diastole replacing the P waves. He believed that these waves could result only from fibrillation of the auricle.

The question, however, remained as to whether the irregularity of ventricular contractions was secondary to atrial fibrillatory activity. There was no sufficient experimental evidence as to the origin of atrial fibrillation. James MacKenzie suggested that, in the case of arrhythmia perpetua, the heart was driven by the impulses originating from the atrioventricular node.

This hypothesis had prevailed until 1910 when Lewis noted that the R waves were usually normal in the presence of arrhythmia perpetua. From the detailed study of the chest leads, Lewis concluded that the f waves present throughout the cardiac cycle could only originate from the atria and not from the atrioventricular node with simultaneous conduction to both the atria and the ventricles as it was earlier suggested by MacKenzie. Atrial fibrillation was finally identified with the irregularity of the heart rhythm.

Lewis was the first to acknowledge a high prevalence of atrial fibrillation, describing it as “the commonest persistent irregularity exhibited by the human heart, constituting... approximately 50 per cent of all... cases.” In the first part of his paper, he presented the results of his experiments in dogs with electrically induced atrial fibrillation, and showed that oscillations of the electrocardiogram occurring at a varying rate of 500 to 900 beats per minute that replaced the normal P waves were present through the entire cardiac cycle and were the result of the continual, fibrillatory activity of the atrium. In the second part of his work, Lewis presented 31 clinical cases of atrial fibrillation. He described a “ventricular” form of the venous pulse characterized by the absence of the atrial a wave, but the presence of rapid undulations of venous pressure during slower heart rates associated with atrial fibrillation, and suggested a complete electrocardiographic picture of atrial fibrillation.

It was Lewis who formulated the first, “multiple heterotopous centers” hypothesis, whereby atrial fibrillation “might be regarded as a state in which stimuli are generated, at many separate and uncertain points and the incoordination of the contracting fibers may be held to result from the impact of contraction waves and the production of localized areas of block.” Although his theory mixed electrical and mechanical phenomena, it was the best possible explanation of an increasing insight into atrial fibrillation. Eighty-five years prior to Allessie’s experiments demonstrating that “atrial fibrillation begets atrial fibrillation” (see summary in this section), based just on circumstantial evidence, Lewis concluded that “the fibrillation itself aggravates the irritability of the auricular tissue. It is perhaps a factor of this nature which accounts... for long continued auricular incoordination in patients who are affected with it.”

1910

Johannes Diderik van der Waals, who discovered the weak attractive forces between electrically neutral atoms and molecules, wins the Nobel Prize for Physics; Portugal becomes a republic, and King Manuel II flees to England; and the Cape of Good Hope becomes part of the Union of South Africa.
Atrial fibrillation was first described in the association with congestive heart failure, but it was less commonly appreciated that it could be a cause and not only a consequence of severe left ventricular dysfunction. By the mid-thirties of last century, there was increasing evidence for atrial fibrillation occurring in the absence of identifiable underlying heart disease, with a reported incidence between 6% and 15% of all cases. Although the prognosis of “lone” atrial fibrillation is generally benign, some patients may develop overt congestive heart failure. The cessation of the arrhythmia or mere achievement of adequate rate control with digitalis can be followed by a complete recovery from heart failure.

In this paper, Phillips and Levine reported on 84 patients (mean age 50 years) with atrial fibrillation with no evidence of organic heart disease. Of these, 47 underwent a detailed investigation during the arrhythmia and after reversion to sinus rhythm. Seven of these patients presented with overt congestive heart failure and the other 7 had asymptomatic left ventricular dysfunction determined as cardiomegaly on chest x-rays, a reduced vital lung capacity, and a slower velocity of blood flow. Seventy-three per cent of patients had sustained arrhythmia defined as one that lasted more than 7 days. None of the patients had a history of rheumatic heart disease, hypertension, angina, hyperthyroidism, or acute infection at the time of examination.

Oral quinidine restored sinus rhythm in 88.5% of patients. In patients with advanced heart failure, reversion to sinus rhythm was associated with a dramatic improvement in symptoms, a reduction in the diameter of the heart from 17.4 cm to 15.4 cm within 48 hours after the cessation of the arrhythmia, a nearly 50% increase in the vital lung capacity, a decrease in the venous pressure, and some acceleration of the velocity of blood flow. The same was true to a less dramatic degree in those with asymptomatic left ventricular dysfunction. The only patient, a 63-year old man, who showed no decrease in heart size had 73 prolonged attacks of atrial fibrillation and presented with left ventricular hypertrophy. The mean time to relapse back into atrial fibrillation was 26.9 months, significantly longer than was observed in patients with organic heart disease. In those under 50 years of age, sinus rhythm persisted for more than 5 years.

The authors concluded that “auricular fibrillation per se may produce cardiac dilatation and progressive congestive heart failure in patients with otherwise normal hearts. This is a truly reversible type of heart failure.” The development of irreversible heart failure and the subsequent disability can, therefore, be prevented by early restoration of sinus rhythm in essentially asymptomatic patients. Interestingly, the duration of the arrhythmia was not a significant factor determining the progression to heart failure in patients with essentially normal hearts, whereas the actual ventricular rates seemed to have a definite influence on the development of heart failure.

This work was one of the first systematic reviews to show that poorly controlled atrial fibrillation could lead to left ventricular dysfunction, which was later termed “tachycardia-induced cardiomyopathy.” It has been reported in as many as 25% of patients and was completely reversible after the institution of adequate rate control or restoration of sinus rhythm.

Auricular fibrillation without other evidence of heart disease: a cause of reversible heart failure

E. Phillips, S. A. Levine

Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge

G. K. Moe, J. A. Abildskov

Am Heart J. 1959;58:59-70

Since atrial fibrillatory activity on the electrocardiogram was linked to auricular fibrillation, there has always been a debate as to which mechanisms operate in sustaining atrial fibrillation: a single focus, multiple foci, or a fixed reentrant circuit. In 1959, Moe and Abildskov developed a cholinergic canine heart model of atrial fibrillation to find out at which frequencies atrial flutter, which was believed to be initiated by a single or multiple foci in the same way as fibrillation, would degenerate into fibrillation. The authors observed that atrial flutter induced either by electrical stimulation or by injection of aconitine terminated when the inciting agent was eliminated, but that atrial fibrillation could exist as “a stable state, self-sustained and independent of its initiating agency.”

Moe explained this by differences in the atrial refractory periods, resulting in the presence of zones in the atrial myocardium in different states of excitability and recovery and characterized by different conduction velocities that made uniform propagation of the atrial impulse no longer possible. He was convinced that although atrial fibrillation could be initiated by a rapidly firing focus or even by a single atrial premature beat, the presence of such a focus was not sufficient, and in order to persist and propagate, fibrillation required multiple random reentrant circuits. In this paper, he described the formation of such multiple wavelets:

The grossly irregular wave front becomes fractionated as it divides about islets or strands of refractory tissue, and each of the daughter wavelets may now be considered an independent offspring. Such a wavelet may accelerate or decelerate as it encounters tissue in a more or less advanced state of recovery. Fully developed fibrillation would then be a state in which many such randomly wandering wavelets coexist.

Five years later, Moe, Rheinboldt, and Abildskov, using a computer model to reproduce animal experiments, showed that multiple chaotic circuits widely scattered in myocardium and constantly varying in number, size, and location are likely to be the mechanism of established arrhythmia. These circuits, or wavelets, travel in changing directions and are capable of extinguishing or reinitiating themselves or each other. Moe’s hypothesis was enriched by systematic animal experiments by Allessie’s group and, until recently, remained the most plausible hypothesis for understanding the mechanisms governing self-perpetuation of atrial fibrillation.

In his paper, Moe introduced what later was termed a “critical mass theory.” He noted that the likelihood of persistence of fibrillation depended upon the number of circulating wavelets. This in turn is determined by the atrial mass capable of accommodating the sufficient number of wavelets. He observed that when a clamp was applied across the base of the fibrillating atrium disconnecting the right atrial appendage that was the site of stimulation that initiated the arrhythmia, fibrillation persisted in the atrium but terminated in the appendage. He concluded that the size of the appendage was too small to accommodate the sufficient number of circulating wavelets necessary for maintaining the arrhythmia, while the much larger mass of the rest of the atrium supported an adequate number of wavelets. He postulated:

Large mass, short refractory period, and slow conduction will all favor perpetuation of the arrhythmia by permitting the coexistence of many independent, randomly wandering wavelets. The results of the present study may be interpreted in terms of this multiple wavelet hypothesis.

1959

General Charles de Gaulle becomes president of France’s 5th Republic; Alaska becomes the 49th state of the USA; and Billy Wilder’s film “Some Like it Hot,” starring Marilyn Monroe and Jack Lemmon, premiers.
It is now 40 years since the introduction of electrical cardioversion for cardiac tachyarrhythmias. Cardioversion was first employed in 1961, at the Peter Bent Brigham Hospital in Boston, for the treatment of refractory ventricular tachycardia in an elderly woman with acute myocardial infarction and left ventricular failure. A single 100 watt-seconds shock promptly reinstated sinus rhythm, resulting in almost immediate resolution of hypotension and pulmonary edema.

While cardioversion was introduced for ventricular tachycardia, by far the commonest arrhythmia treated in Lown’s series of patients was atrial fibrillation. He reported a remarkable 94% success rate in converting 456 episodes of the arrhythmia in 350 patients. Rheumatic valvular disease was the underlying pathology in 70% and coronary artery disease in 12% of patients, while 10% were considered to have lone atrial fibrillation. The first patient with atrial fibrillation was treated on November, 1961, and continued to maintain sinus rhythm after 6 years of follow-up.

Although there had been attempts to cardiovert atrial fibrillation for more than 20 years, understanding of the factors conducing to success were only beginning to emerge. The duration of the arrhythmia became a key determinant of success or failure of therapy. The likelihood of failure increased from 2% for atrial fibrillation of less than 3 months to 39% when it had been present for a decade. A wide stream of unselected patients with atrial fibrillation permitted impartial insight into causes of failure of cardioversion. In 1967, Lown provided a comprehensive list of electrocardiographic features at the time of cardioversion auguring early recurrence of the arrhythmia. These include, but are not limited to, atrioventricular block with the PR interval greater than 280 ms, depressed sinus node function with profound bradycardia and junctional escape rhythm, sinus tachycardia, and multiple persistent atrial premature beats and bursts of atrial tachycardia or flutter. Cardioversion was more readily achieved with lesser energy requirement and better chances of maintenance of sinus rhythm when high-amplitude and discernable fibrillatory f waves were present.

Chronic atrial flutter was the easiest arrhythmia to terminate by means of cardioversion and it generally responded to a single low-energy shock. This held true in patients with atrial flutter as essential arrhythmia and those with atrial fibrillation organized into flutter on an antiarrhythmic drug. Lown has also suggested employing a 5-10 watt-seconds shock to deliberately induce atrial fibrillation in patients with atrial flutter, as the former was easier to manage.

Of the first 100 patients reverted, 23% remained in sinus rhythm over the long term, but, with improvement in patient selection, 50% were expected to maintain sinus rhythm for at least 1 year. Of note, only quinidine, procainamide, and digitalis were available for prophylaxis of recurrence at that time. In conclusion, although Lown’s name is invariably associated with the introduction and the development of the cardioversion technique, he has never patented the cardioverter.

1967

Vivian Leigh, the British actress who played Scarlett O’Hara in “Gone With the Wind,” dies, aged 53; Billie Jean King completes a clean sweep of Wimbledon Tennis titles, winning the singles, doubles, and mixed championships; and the Beatles’ “Sgt. Peppers Lonely Hearts Club Band” album is released.
The Framingham Study was the landmark study to appreciate the epidemiological significance of atrial fibrillation and to introduce the concept of risk factors for the arrhythmia. It was set up in late 1940s when a representative population sample of 5209 men and women aged 30 to 62 years had their initial examination between 1948 and 1952. This report presented data of a 22-year follow-up during which the participants were examined biennially, including medical histories, physical examinations, and electrocardiograms. The presence of atrial fibrillation was also determined from hospital records and subjects' physicians. The overall incidence of atrial fibrillation in both genders was 2 per thousand in each biennium and rose sharply with age, doubling with each advancing decade. Atrial fibrillation was predominant among the men and those with a history of cardiovascular disease. After adjusting for age and other risk factors, men were 50% more likely than women to develop the arrhythmia. Hypertension, congestive heart failure, rheumatic valve disease, ischemic heart disease with myocardial infarction, and diabetes were commonly associated conditions. Heart failure and valve disease posed as the most powerful risk factors for atrial fibrillation, with relative risks in excess of 6-fold, whereas hypertension was the most common antecedent disease, largely because of a higher prevalence in the general population. Hypertension was present in half the patients who developed atrial fibrillation, but was a strong predictor of atrial fibrillation only if accompanied by cardiac enlargement on chest x-rays or electrocardiographic evidence of left ventricular hypertrophy. When these factors were not present, hypertension was only weakly related to the occurrence of the arrhythmia, suggesting that myocardial damage was a prerequisite. Approximately one third of the patients developed atrial fibrillation in the absence of underlying cardiovascular disease.

This study was the first to show that the development of atrial fibrillation was also associated with a doubling of overall as well as cardiovascular mortality, providing a clear impetus for restoration and maintenance of sinus rhythm that governed the physicians’ approach to the management of atrial fibrillation. The Framingham Study has also provided strong evidence for the association between atrial fibrillation and stroke, with a 3- to 5-fold increased risk in the presence of the arrhythmia. With increasing age, the effects of hypertension, heart failure, and ischemic heart disease on the incidence of stroke decreased, whereas the impact of atrial fibrillation remained equally important in both younger and older patients. In fact, the proportion of strokes attributed to atrial fibrillation tended to grow with age. In subsequent publications from the Framingham Study, new-onset atrial fibrillation has been reported to be associated with an imminent risk of stroke.

The study is remarkable in that, by defining the risk factors for atrial fibrillation, it introduced the concept of arrhythmia prevention by preventing myocardial damage, progression of congestive heart failure, and atrial dilatation. This “upstream therapy” approach has been confirmed by the accumulating evidence of the beneficial effects of angiotensin-converting enzyme inhibitors on the development of atrial fibrillation in patients with overt heart failure and asymptomatic left ventricular dysfunction.

Several thousand Argentinean troops seize the disputed Falkland (Malvinas) Islands; the Zimbabwean capital Salisbury is renamed Harare; and biologists discover a thriving ecosystem supported by geothermal energy 8600 feet beneath the sea off the Californian coast.
Absence of organized mechanical contraction of fibrillating atria with a consequent increase in atrial pressure and atrial stretch and dilation due to multiple pathophysiological mechanisms compensating for reduced cardiac output create conditions for blood stasis. The unique anatomical and physiological properties of the left atrial appendage render it the major site of thrombus formation, particularly in nonvalvular atrial fibrillation. The hypercoagulable state, including endothelial dysfunction and platelet hyperactivation, is additive to increased risk of thromboembolism.

Five large randomized trials (AFASAK, BAATAF, CAFA, SPAF, and SPINAF*) published between 1989 and 1992 evaluated oral anticoagulation, and two tested aspirin for primary prevention of thromboembolic events in patients with atrial fibrillation. There was also a sixth trial, EAFT,† which focused upon secondary prevention in patients who had survived stroke or transient ischemic attack and was not included in this meta-analysis. For warfarin therapy, the target intensity of anticoagulation ranged from a prothrombin time ratio of 1.2-1.5 to an international normalized ratio (INR) of 2.8-4.2. The dose of aspirin varied from 75 mg to 325 mg.

Meta-analysis of these five trials had an unsurpassed effect on physicians' attitude to anticoagulation in atrial fibrillation. It has shown that adjusted-dose warfarin is highly efficacious for prevention of stroke, with a 68% risk reduction (95% confidence interval [CI], 50% to 79%). The annual rate of stroke was 4.5% for the control group and 1.4% for the treatment group. The efficacy of warfarin was consistent across all studies and subgroups of patients. Aspirin showed less impressive results, with the risk reduction of 36% (95% CI, 4% to 57%).

The incidence of major bleeding was, however, higher with warfarin, and the investigators have expertly developed the conception of risk stratification for stroke, which is essential for decision making in favor of anticoagulation. The independent risk factors for stroke were age >75 years, previous stroke or transient ischemic attack, hypertension, and diabetes. For example, a 75-year-old patient with hypertension would theoretically have an 8% annual event rate, compared with a 1% rate in a 60-year-old with no risk factors. Anticoagulation would be expected to reduce the event rate to 1.2% in a high-risk individual, whereas a low-risk subject would not gain sufficient benefit from anticoagulation to outweigh the attendant risks and the inconvenience of close anticoagulation monitoring. For completeness, there was also excess of stroke if ischemic heart disease, myocardial infarction, or congestive heart failure were present, and left ventricular dysfunction was found to be a risk factor in subsequent analyses. It is also worth noting that the threshold risk of stroke warranting anticoagulation and the need for routine anticoagulation in patients with intermediate risk (eg, 2%-6%/year) are still controversial.

*AFASAK, Atrial Fibrillation, ASpirin AntiKoagulation; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation; SPAF, Stroke Prevention in Atrial Fibrillation; SPINAF, Stroke Prevention In Nonrheumatic Atrial Fibrillation.
†EAFT, European Atrial Fibrillation Trial.

President Mitterrand of France becomes the first world leader to visit South Africa since the ending of apartheid; the Sumo Wrestling Association bans the use of silicon scalp implants to permit wrestlers to reach the minimum height requirement of 172.7 cm; and presidential elections in two of the former Soviet Union republics see Leonid Kuchma win in Ukraine and Alexander Lukashenko in Belarus.
Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats

M. C. Wijffels, C. J. Kirchhof, R. Dorland, M. A. Allessie


Paroxysmal atrial fibrillation is a recurring disease. The first attack will not be the last in over 90% of patients. It also tends to progress to a permanent form over time, the transition rate varying considerably with the etiology. The epidemiological studies have shown that even in the absence of cardiovascular disease almost one fifth of patients are bound to develop sustained arrhythmia. Even since electrical cardioversion for atrial fibrillation was introduced by Bernard Lown (his work is discussed above), the duration of atrial fibrillation has been recognized as an important predictor of successful restoration and maintenance of sinus rhythm. These intriguing epidemiological and clinical observations lacking a complete and satisfactory explanation have motivated Allessie and his team to pose the question of whether atrial fibrillation itself may produce electrophysiological and structural alterations in the atria that would make atrial fibrillation a self-perpetuating arrhythmia and explain its progressive nature.

The authors conducted a series of elegant experiments in a goat model of atrial fibrillation continuously induced by high frequency burst atrial pacing via an external pacemaker ("fibrillator"). In normal goat atria, electrically induced atrial fibrillation lasted only a few seconds and terminated spontaneously. The device detected spontaneous conversion by sensing an atrial electrogram, and delivered a burst of stimuli to promptly reinduce the arrhythmia. Multiple electrodes sutured to the epicardium enabled the researchers to map both atria and measure atrial effective refractory periods at baseline and after 6 and 24 hours, and then at regular intervals for a few days of sustained fibrillation. The reversibility of changes in effective refractory periods and the vulnerability of the atria were studied 1 day, and 1 and 2 weeks following restoration of sinus rhythm.

Already within the first 24 hours, both the duration and the rate of fibrillation increased significantly, accompanied by low-amplitude and fragmented atrial electrograms, suggesting a shift to a more complex activation of the atrium. The atrial effective refractory periods shortened by one third, but also displayed a reversion of the normal adaptation to increased pacing rates (ie, a lesser degree of shortening at higher pacing rates). The inducibility of fibrillation by a single premature stimulus increased from 24% to 76%. The atrial fibrillation cycle length shortened progressively at a rate of 1 to 2 ms per every hour and continued to decrease at a lower rate, until after about 4 to 6 days when a new steady state was reached. A critical fibrillation cycle length (120 ms in a goat model) was required for the arrhythmia to become sustained. Thus, it has been demonstrated that the most important electrophysiological changes leading to persistent fibrillation involve a progressive shortening and reversion of rate adaptation of the atrial effective refractory period resulting from prolonged exposure to rapid atrial rates. This phenomenon was termed “electrical remodeling.”

The same group continued their experiments to investigate the time course of metabolic, electrical, and structural remodeling of the atria during fibrillation. While structural changes may take months to develop, metabolic adaptation occurs virtually immediately and can rapidly reverse. Electrical remodeling develops later and persists longer than metabolic changes and is believed to arise from alterations in ion channel protein expression in atrial myocytes. It should, however, be acknowledged that the time course of electrical remodeling, its prevention by prompt cardioversion, and reversibility have not yet been studied in the human heart.

Quebec narrowly rejects independence from Canada; the Nobel Peace Prize is awarded to scientist and antinuclear campaigner Joseph Rotblat; and the United Nations celebrates its 50th anniversary with a major gathering of world leaders in New York
Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins


For the best part of the last century, Moe’s multiple wavelet reentry hypothesis prevailed in our understanding of the mechanism of sustained atrial fibrillation. But Moe’s hypothesis does not tell why atrial fibrillation occurs. Until recently, little attention has been paid to triggers of the arrhythmia because many landmark studies in humans have focused on atrial fibrillation induced in the electrophysiological laboratory and because spontaneous initiation of atrial fibrillation is rare in animal models. Of note, Moe himself considered that multiple wavelet reentry did not provide a satisfactory explanation for mechanisms of clinical arrhythmia and thought a single focus or multiple foci to be equally conceivable in the genesis of atrial fibrillation.

The French electrophysiologists who authored this paper have revived the old concept by Rothberger that a rapidly firing single focus may produce atrial fibrillation. Such a focus can drive the atria fast enough that atrial tissue fails to respond in a 1:1 fashion, resulting in fibrillatory conduction. The focus may also act as a trigger (an equivalent of burst pacing in a lab) and the arrhythmia may then become sustained due to multiple wavelets. However, their most important finding was that 80% to 95% of rapidly firing foci are clustered within the pulmonary veins, and this resulted in the development of a new curative ablation technique for atrial fibrillation: pulmonary vein isolation. Firstly applied in patients with lone paroxysmal atrial fibrillation where no identifiable substrate often can be seen, this method has been extended to cure more persistent forms by preventing the initiation instead of modifying the substrate of the arrhythmia. Thus, this paper opened up a new field of research in the management of atrial fibrillation.

Haissaguerre and coworkers mapped the left atrium during spontaneous initiation of atrial fibrillation in 45 patients with frequent recurrence of the arrhythmia and identified 69 sites with the earliest electrical activity preceding the atrial ectopic beat that initiated atrial fibrillation. Ninety-four percent of these foci were located 2 to 4 cm inside the pulmonary veins, and the application of radiofrequency energy at these sites resulted in interrupting conduction to the rest of the atria and abolishing atrial fibrillation. The reasons why pulmonary veins become arrhythmogenic are unknown. The ability to accommodate various electrophysiological mechanisms, notably automaticity, thanks to their architectural topography augmented by modifying factors such as dilatation and stretch, has been implicated, but this hypothesis not completely satisfactory.

Limitations of pulmonary vein ablation have been immediately recognized as this approach supposes initiation of atrial fibrillation during atrial mapping and the elimination of one focus does not necessarily cure atrial fibrillation because it may be induced by another focus in the same or spared veins. However, the solution has been found for both problems: firstly, the earliest local depolarization can be seen during sinus rhythm and isolation of all four pulmonary veins may achieve the curable goal. Additional maneuvers, such as pacing from the coronary sinus, can help to differentiate between far field atrial potentials and left pulmonary vein spikes.

The UN International criminal tribunal for Rwanda finds Jean-Paul Akayesu guilty of genocide and crimes against humanity; death of the celebrated Japanese film director Akira Kurosawa; and Mark McGuire of the St Louis Cardinals scores his 62nd home run of the baseball season to break the all-time record
The demand for effective therapeutic strategies for atrial fibrillation has always been high and is anticipated to further increase. Until recently, anticoagulation and pharmacological anti-arrhythmic therapy or radiofrequency catheter ablation with permanent ventricular pacing remained the mainstay of treatment for atrial fibrillation. The considerable limitations of existing therapeutic options and promising results with internal low-energy cardioversion have prompted interest in implantable devices capable of restoring sinus rhythm expeditiously in patients with recurrent symptomatic arrhythmia failing on conventional therapies.

A stand-alone atrial defibrillator (Metrix Atrioverter system) was the first in a series of such devices to enter the clinical investigation. The device, with a weight of 79 g and a volume of 53 cc, is implanted in the pectoral region. The system consists of a pulse generator connected to the right atrial and coronary sinus defibrillation leads and a bipolar ventricular pacing lead. The device detects and converts atrial fibrillation with a synchronized low-energy (up to 6 J) atrial shock. It may be either programmed in an automatic mode with a preset delay of shock delivery from onset of the arrhythmia, or it can be activated by the patient or a physician.

The first atrial defibrillator was implanted on October 30, 1995. As of May 1997, a total of 51 systems had been implanted as a part of the phase 1 Metrix multicenter clinical trial in patients with drug-refractory atrial fibrillation and no or little underlying heart disease. Wellens and Metrix coinvestigators have reported prompt and safe restoration of sinus rhythm with the atrial defibrillator. In this study, shock was administered in-hospital under physician observation. The device terminated 96% episodes of atrial fibrillation.

However, the primary efficacy of the defibrillator was marred by frequent early recurrence of the arrhythmia, which occurred in 27% of all episodes in half the patients and required repeat shock. The median number of shocks was 3 per episode. Thus, after adjustment for early recurrence, the clinical efficacy of defibrillation therapy was reduced to 86%. For completeness, the clinical efficacy of ambulatory cardioversion, either executed automatically or initiated by the patient, was approximately 80%. Of importance is the fact that the frequency of atrial fibrillation tends to subside over time, probably because prompt restoration of sinus rhythm prevents advanced electrical and structural remodeling.

This paper is significant as it was the first to show that atrial fibrillation can be successfully and safely treated by implantable devices. It must, however, be emphasized that the use of solely atrial defibrillators is limited to patients with minor heart disease and infrequent, but highly symptomatic recurrence of atrial fibrillation. Dual-chamber cardioverter-defibrillators with capacity to prevent and interrupt atrial fibrillation, including painless antitachycardia pacing, may offer more comprehensive and successful treatment for patients with advanced heart disease, frequent recurrence of the arrhythmia, concomitant ventricular tachycardia, and the risk of drug- or shock-induced proarrhythmia.

Former Chilean ruler Augusto Pinochet is arrested in a London hospital and charged with the murder of Spanish citizens during his 17-year rule; the Japanese government passes bank reform legislation, associated with a $513 billion aid package to help economic recovery; and British Poet Laureate Ted Hughes dies, aged 68.
A comparison of rate control and rhythm control in patients with atrial fibrillation


There are two main approaches to the management of atrial fibrillation: the first, most often pursued in patients with new-onset and persistent atrial fibrillation, is rhythm control aimed at restoration and maintenance of sinus rhythm; the second is to minimize symptoms by merely administering agents blocking the atrioventricular node. Rhythm control has generally been accepted as theoretically preferable, but there has been no direct evidence for the superiority of this strategy in terms of improved survival and reduced thromboembolic events.

Among the recent studies comparing the two strategies, the AFFIRM trial (Atrial Fibrillation Follow-up Investigation of Rhythm Management) was the largest and was powered to detect the mortality benefit. Its population of over 4000 patients 65 years of age and older or with a risk factor for stroke was representative of the majority of patients with atrial fibrillation, and the antiarrhythmic drug was chosen by the treating physician. The investigators hypothesized that rhythm control would decrease the risk of stroke and the need for lifelong anticoagulation, improve symptoms, functional status, and quality of life, and ultimately reduce mortality. The results of the trial proved the opposite. There was a trend to excess mortality and more strokes, hospital admissions, and torsades de pointes in the group assigned to rhythm control. There was no difference in generic and cardiac-specific quality of life measures between rhythm and rate control.

Given the strength of this evidence, an important consideration is whether the conclusions drawn form the AFFIRM trial can be applied to all patients with atrial fibrillation. The trial pertained to older patients who are likely to have modest symptoms and in whom rate control has generally been presumed (but not proven) preferable. The results cannot be readily extrapolated to younger individuals who are more likely to be symptomatic and have impaired quality of life, even if good rate control is achieved. In the subgroup analysis, the point estimate of the hazard ratio was shifted toward benefits of rhythm control in patients under 65 years. Furthermore, the mere fact that more than one third of patients in the rate control arm had sinus rhythm at the end of follow-up made the comparisons ambiguous. A significant proportion of patients presented with paroxysmal or recent-onset atrial fibrillation, suggesting that the benefits of being in sinus rhythm can be offered to many more patients than participated in the trial.

Finally, it must be recognized that the AFFIRM trial and other studies compared predominantly pharmacological therapies. Greater use of nonpharmacological therapies, resulting in more effective rhythm control and less side effects compared with traditional antiarrhythmic drugs, might shift the balance in favor of the rhythm control strategy.

Iraq delivers a 12 000-page document to the United Nations stating that the country possesses neither weapons of mass destruction (WMD) nor programs to create them; South Korea elects Roh Moo-hyun as its new president; and the first comparison of the complete mouse and human genomes reveals striking similarities.
## Bibliography of One Hundred Key Papers

selected by **A. John Camm, MD; Irina Savelieva, MD**

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Am Heart J. 1953;189-194.


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Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. 


# Bibliography of One Hundred Key Papers

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