

Atrial fibrillation: advances and perspectives

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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 Cardiovasc 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, Engelman 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

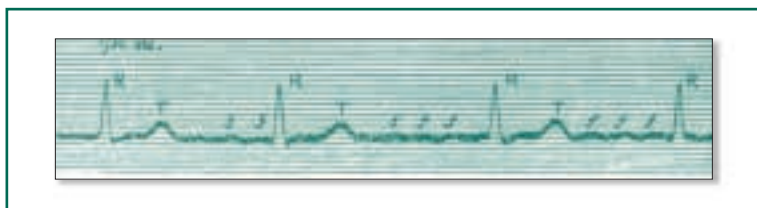


Figure 1. An electrocardiogram of a patient with atrial fibrillation recorded by Lewis depicting f waves “derived for the fibrillating auricle.”

Reprinted from reference 4: Lewis T. Evidences of auricular fibrillation, treated historically. *BMJ*. 1912;13:59. Copyright © 1912, BMJ Publishing Group Ltd.

SELECTED ABBREVIATIONS AND ACRONYMS

ACTIVE	Atrial fibrillation Clopidogrel Trial with Irbesartan for the prevention of Vascular Events
ACUTE	Assessment of Cardioversion Using Transesophageal Echocardiography
AF	atrial fibrillation
AFASAK	Atrial Fibrillation, ASpirin AntiKoagulation
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
ATRIA	AnTicoagulation and Risk factors In Atrial fibrillation
BAATAF	Boston Area Anticoagulation Trial for Atrial Fibrillation
CAFA	Canadian Atrial Fibrillation Anticoagulation
CHS	Cardiovascular Health Study
DIG	Digitalis Investigation Group
HOT CAFE	How to Treat patients with Chronic Atrial Fibrillation (Polish Study)
PIAF	Pharmacological Intervention in Atrial Fibrillation
PIPAF	Pacing In Prevention of Atrial Fibrillation
PLAATO	percutaneous left atrial appendage transcatheter occlusion
RACE	RAte Control versus Electrical cardioversion for persistent atrial fibrillation
SOLVD	Studies Of Left Ventricular Dysfunction
SPAF	Stroke Prevention in Atrial Fibrillation
SPINAF	Stroke Prevention In Nonrheumatic Atrial Fibrillation
SPORTIF	Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation
STAF	Strategies of Treatment in Atrial Fibrillation
TEE	transesophageal echocardiography
TRACE	TRAndolapril Cardiac Evaluation

of the arrhythmia (multiple wavelet hypothesis). Moe’s hypothesis has been further explored and substantiated by Allesie and colleagues; the first results were published in 1977.⁹

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,¹⁰ 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 1961¹¹ 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.¹²

EPIDEMIOLOGY OF ATRIAL FIBRILLATION

Twenty years ago, the prevalence of AF was said to be 0.4% of the general population.¹² Now AF has become more common and it is present in about 1.5% of the population.¹³ 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.¹⁴ 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

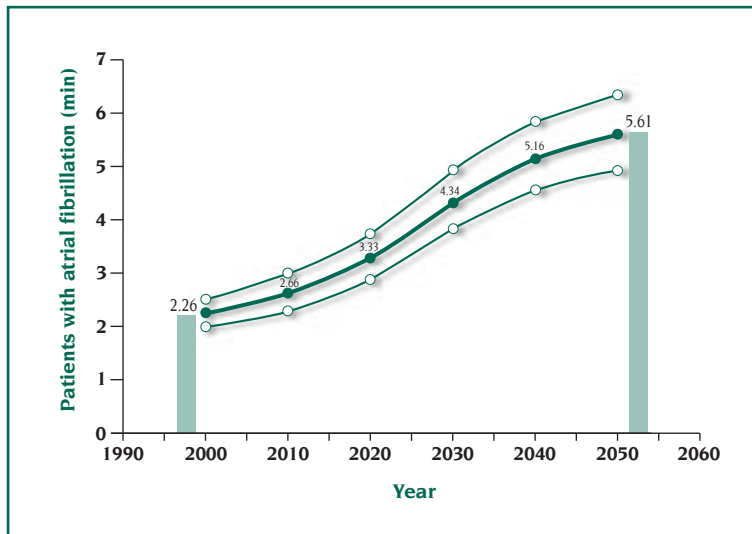


Figure 2. Projected number of patients with atrial fibrillation in the United States between 2000 and 2050. Data from the ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study. Upper and lower curves represent the upper and lower numbers based on sensitivity analysis.

Modified from reference 13: Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults. National implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) Study. JAMA. 2001;285:2370-2375. Copyright © 2001, American Medical Association.

examinations and electrocardiograms (pre-operative checks, insurance examinations, screening medicals, etc).¹⁵ 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).¹³

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).^{12,14} The prevalence of AF associated with left ventricular dysfunction and con-

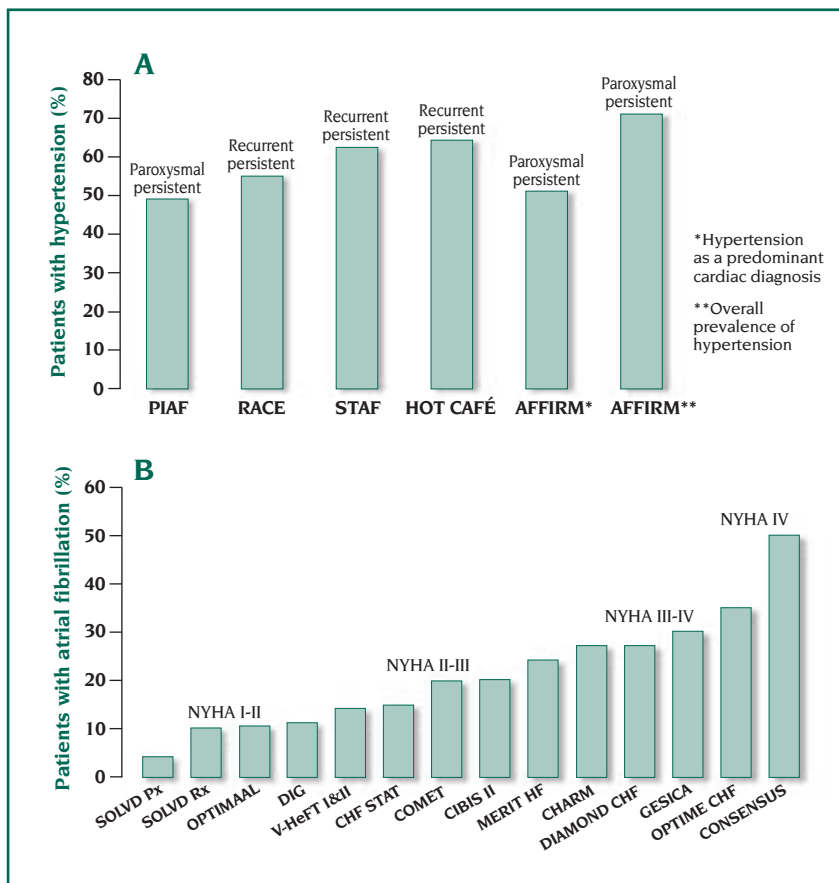


Figure 3. (A) Prevalence of hypertension as underlying cardiovascular disorder in patients with atrial fibrillation. (B) Prevalence of atrial fibrillation in heart failure studies.

Key to studies: AFFIRM; Atrial Fibrillation Follow-up Investigation of Rhythm Management; CHARM, Candesartan in Heart failure Assessment in Reduction of Mortality; CHF-STAT, Congestive Heart Failure—Survival Trial of Antiarrhythmic Therapy; CIBIS II, Second Cardiac Insufficiency Bisoprolol Study; COMET, Carvedilol Or Metoprolol Evaluation Trial; CONSENSUS, COoperative North Scandinavian ENalapril SURvival Study; DIAMOND CHF, Danish Investigation of Arrhythmia and Mortality ON Dofetilide in Congestive Heart Failure; DIG, Digitalis Investigation Group; GESICA, Grupo de Estudio de la Sobrvida en la Insuficiencia Cardiaca en Argentina; HOT CAFÉ, How to Treat patients with Chronic Atrial Fibrillation (Polish Study); MERIT HF, METoprolol controlled release Randomised Intervention Trial in Heart Failure; OPTIMAAL, OPTimal Trial In Myocardial infarction with Angiotensin II Antagonist Losartan; OPTIME CHF, Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure; PIAF, Pharmacological Intervention in Atrial Fibrillation; RACE, RAtE Control versus Electrical cardioversion for persistent atrial fibrillation; SOLVD Px, Studies Of Left Ventricular Dysfunction, Prevention arm; SOLVD Rx, Studies Of Left Ventricular Dysfunction, Treatment arm; STAF, Strategies of Treatment in Atrial Fibrillation; V-HeFT I & II, Veterans Administration Heart Failure Trial I & II.

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

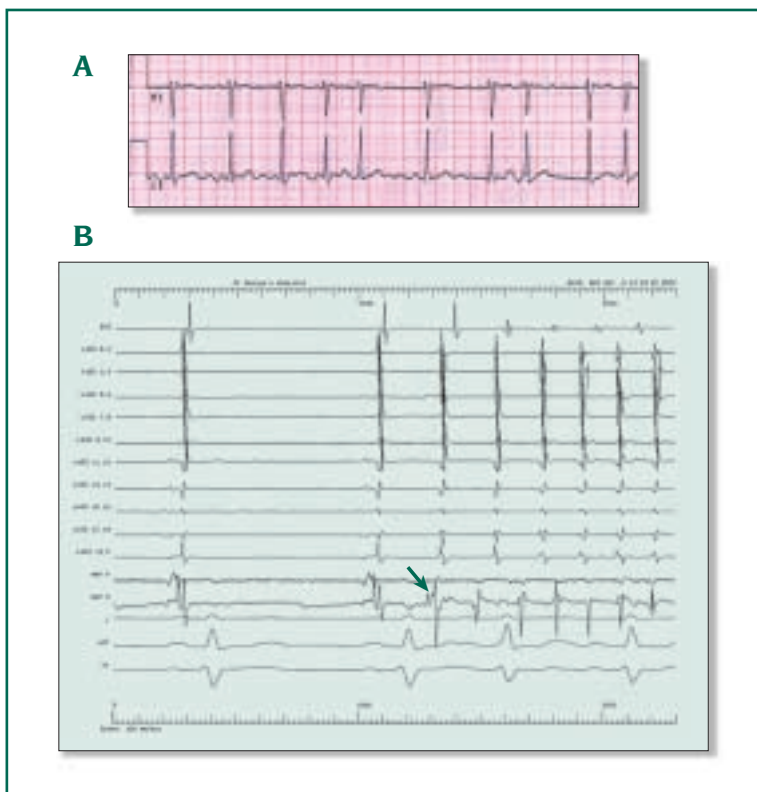
PATHOPHYSIOLOGY OF ATRIAL FIBRILLATION

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 intra-atrial conduction block (type II), or by multiple slowly conducting wavelets separated by multiple lines of functional conduction

Figure 4. (A) Coarse atrial fibrillation with discrete atrial f waves in a patient with suspected "focal" atrial fibrillation. (B) Pulmonary vein tachycardia originating from the left upper pulmonary vein with conduction to the atria that initiates atrial fibrillation. Shown are leads I, aVF, VI, proximal and distal electrode pairs of a mapping catheter positioned within the left upper pulmonary vein (MAP P, MAP D), a decapolar Lasso™ catheter positioned in the left atrium (LASS D, 2 ... LASS 19, P), and a distal electrode pair of a coronary sinus catheter (DCS). A premature pulmonary vein depolarization (arrow) initiates pulmonary vein tachycardia, which triggers atrial fibrillation.





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 AF^{36,37} 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}



Figure 5. Light microscopy of atrial myocardium showing accumulation of glycogen and fat in vacuolated, oversized myocytes (trichrome stain) in a patient with sustained atrial fibrillation. Courtesy of M. N. Sheppard, Royal Brompton Hospital, London, UK.

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,⁴⁶ even when "asymptomatic."⁴⁷ It is clear that AF is associated with an increased morbidity and mortality⁴⁸ related to thromboembolic complications such as cerebrovascular accident^{49,50} and to aggravation of heart failure (Table I).^{51,52} Lone AF, not linked with any apparent underlying heart disease, may also have an adverse prognosis.⁵³ 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.⁵⁴

Atrial fibrillation numbers

- 5- to 7-fold increased risk for stroke
- 10-fold increased risk for stroke in hypertrophic cardiomyopathy
- 1.65-fold increased risk for developing heart failure
- 3-fold increased risk for worsening heart failure
- 2- to 3-fold increased risk for hospitalizations
- Half of all hospitalizations for arrhythmias
- 1.5- to 1.9-fold increased risk for mortality in the general population
- 4.2-fold increased risk for cardiovascular mortality in lone atrial fibrillation
- 2.5-fold increased risk for mortality in heart failure
- 4.5-fold increased risk for mortality in acute coronary syndromes
- 2-fold increase in the number of publications in 1993-2003 compared with 1973-1982

SOURCES:

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Table I.

Risk of stroke

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.⁴⁹ 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%.⁵⁰ The risk is considerably higher (about 12%/year) for recurrent stroke in patients with a previous cerebrovascular accident.⁵⁵

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 years⁵¹ and a 3-fold risk of worsening heart failure.⁵⁶ 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).⁵⁷ 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).⁵⁸ 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-

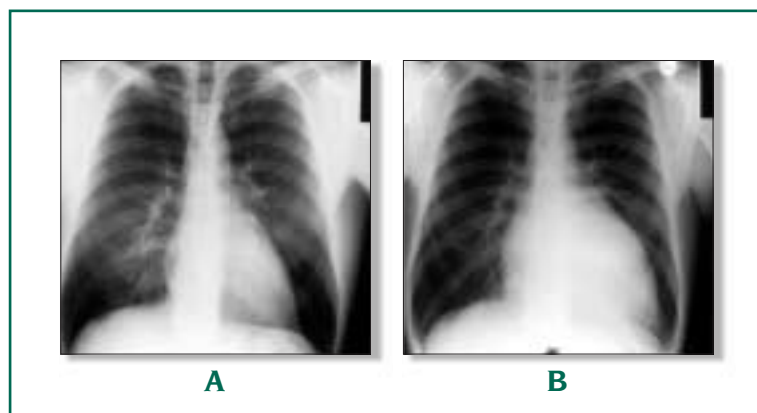


Figure 6. X-ray images of patients with: (A) tachycardia-induced cardiomyopathy: sinus rhythm; (B) persistent atrial fibrillation with rapid ventricular rates for 3 months.

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.⁵⁹ 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,⁶⁰⁻⁶² 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.^{63,64}

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.⁶⁵ 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.^{66,67} 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 far 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.⁶⁷ These complications are especially likely to occur when hy-

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pokalemia, 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.⁶⁸

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

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,⁷⁵ 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.⁷⁶

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

	PIAF	STAF	HOT CAFE	RACE	AFFIRM	Delhi	CHF STAT	DIAMOND
Mortality	N/A	No	No	No	No	Yes	Yes*	Yes*
Symptoms	Yes	No	Yes	No	No	Yes	N/A	N/A
Thromboembolic events	N/A	No	No	No	No	N/A	N/A	N/A
Heart failure	N/A	No	No	No	No	Yes	N/A	N/A
Hospitalizations	No	No	No	No	No	N/A	N/A	Yes*
Quality of life	No	No	N/A	No	No	Yes	N/A	Yes*
Patients in AF at the time of an end point	N/A	94.7%	N/A	73%	42.7%	N/A	N/A	N/A

*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.

persistent atrial fibrillation), and AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) have reported in full⁶⁹⁻⁷² and the HOT CAFE (How to Treat patients with Chronic Atrial Fibrillation - Polish Study) and Delhi trials have reported in abstract form.^{73,74} 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

largely 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



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.⁷⁷ 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

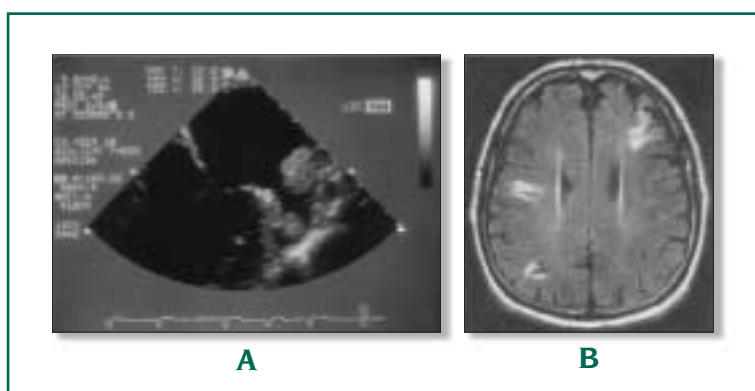


Figure 7. (A) Thrombi in the left atrial appendage. (B) Magnetic resonance image of multiple cerebral infarcts.

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.⁷⁸⁻⁸⁰

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.⁸¹ Abnormalities of hemostasis, endothelial function, and platelet activation

often associated with AF further increase the risk of thromboembolic events.⁸² With transesophageal echocardiography, left atrial thrombi can be found in about 14% of patients with AF,⁶⁵ and spontaneous echo contrast can be seen in 52% of patients (Figure 7).⁸³

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.⁸⁴

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.⁸⁵ 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,⁸⁶ 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)⁸⁷

and SPINAF (Stroke Prevention In Nonrheumatic Atrial Fibrillation)⁸⁸ studies exclusively enrolled patients with permanent AF, whereas the proportion of patients with intermittent AF was 7% in CAFA (Canadian Atrial Fibrillation Anticoagulation),⁸⁹ 16% in BAATAF (Boston Area Anticoagulation Trial for Atrial Fibrillation),⁹⁰ and 34% in SPAF.⁹¹ 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.⁵⁰

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.⁹² 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.^{65,83} 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 without contraindications for warfarin therapy receive this prophylactic treatment, probably due to physicians' 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 xime-

lagatran 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 AF⁹³ 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.⁹⁴ Left atrial appendectomy via thoracoscopy or limited sternotomy may also be considered for prevention or reduction of thromboembolism.

NONPHARMACOLOGICAL THERAPY

Nonpharmacological treatment alternatives for management of AF include atrioventricular 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 1982,⁹⁵ is now an established effective treatment in patients with symptomatic drug-refractory AF.⁹⁶ 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.⁹⁷ 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.

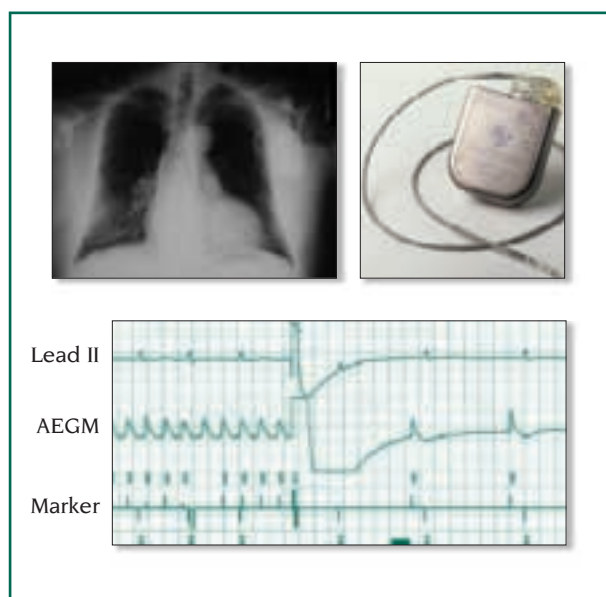


Figure 8. Internal cardioversion of atrial fibrillation with a 4 J shock via the implantable dual-chamber cardioverter-defibrillator. AEGM, atrial electrogram.

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.^{38,98-100} 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.¹⁰¹ 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%.¹⁰²

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.¹⁰³⁻¹⁰⁵ 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.¹⁰⁶⁻¹⁰⁹ *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

Presentation of AF		Case studies	Small studies	Medium studies (≈100 patients)	Large RCTs (250-000s)
Bradycardia with little AF		✓	✓	✓	✓+
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.⁷⁹ 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.⁶² 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 intra-atrial 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.¹¹¹ 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

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 IV.

of the arrhythmia substrate by atrial linear ablation in combination with antitachycardia and preventative pacing has also anecdotally proven an effective therapeutic approach.¹¹³ 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

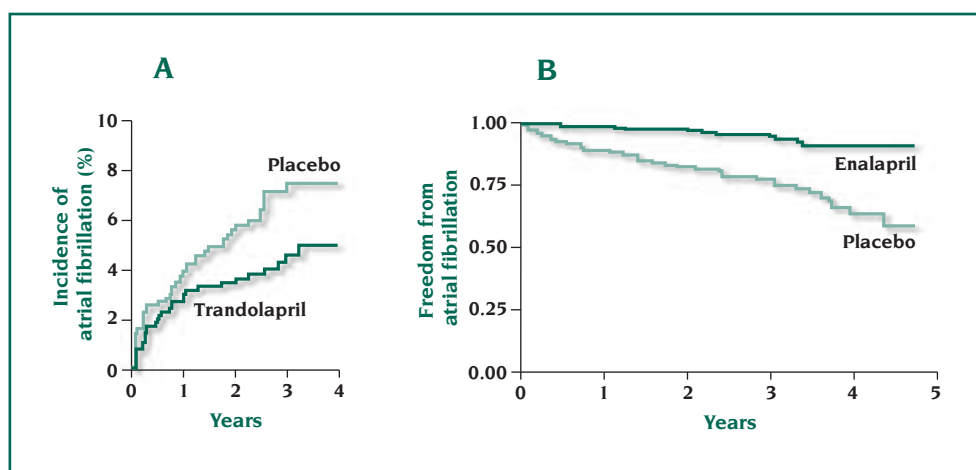


Figure 9. (A) Kaplan-Meier curves showing the incidence of atrial fibrillation with trandolapril versus placebo in the TRACE (TRAndolapril Cardiac Evaluation) trial. (B) The proportion of patients free from atrial fibrillation with enalapril versus placebo in the SOLVD (Studies Of Left Ventricular Dysfunction, 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 tachyarrhythmias 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}

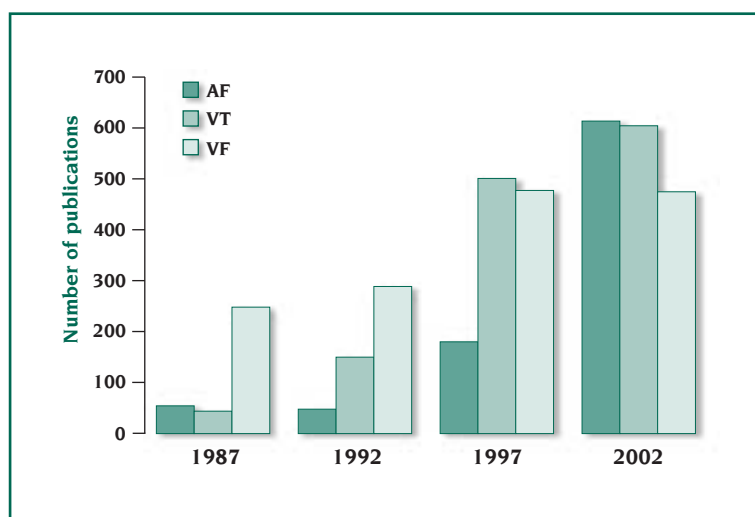


Figure 10. Increase in number of publications on atrial fibrillation (AF), ventricular tachycardia (VT), and ventricular fibrillation (VF).

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 reduc-

tion 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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