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CONTINUING EDUCATION

ATRIAL FIBRILLATION: CURRENT TRENDS IN MANAGEMENT

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Abstract
Quite a number of dramatic interventional advances in the treatment of cardiac arrhythmias such as catheter ablation and implantable cardiac defibrillators for serious ventricular arrhythmias have held the limelight over the last few years. The treatment of atrial fibrillation (AF), which remains the commonest arrhythmia affecting 0.5% of people aged 50-59 years increasing to 12% at age above 74years, has received relatively little attention. There is however, a recent resurgence of interest following some important experimental and therapeutic advances. This article reviews the current understanding of the nature of atrial fibrillation (AF) and some recent developments in the pharmacological and alternative therapeutic approaches.

Key words: Atrial fibrillation, treatment

Introduction

"When the pulse is irregular and tremulous and the beats occur at intervals, then the impulse of life fades; when the pulse is slender (smaller than feeble but still perceptible, then like a silk thread), then the impulse of life is small" Huang Ti Nei Ching su Wen. The atrial are far from being a single pair of spherical surfaces with uniform electrophysiological characteristics. They are anatomically and functionally complex structures that can provide a substrate for various arrhythmias (atrial fibrillation inclusive), and pose a diagnostic and therapeutic challenge to the clinicians.

Atrial fibrillation (AF) is by far the commonest sustained cardiac arrhythmia, with an overall prevalence of 0.5% - 1% in people aged < 50 years, rising to about 12% in those over 74 years.[1] Atrial fibrillation, is slightly more in men than women and, the arrhythmia may either be chronic or paroxysmal. Up to a third of patients with atrial fibrillation may have idiopathic or "lone" atrial fibrillation, when no precipitating cause can be identified and no evidence of structural heart disease exists.[2, 3] In most patients with chronic AF, the arrhythmia can be attributed to organic heart disease or a metabolic disorder. Ischaemic heart disease, coronary arterial disease, pulmonary thromboembolism, pre- excitation syndromes are numerically more important causes of AF in the Western countries while rheumatic heart disease, acute infections, thyrotoxicosis and hypertension usually constitute the important causes of AF in developing countries.[3, 4] Overall, AF is associated with an increased mortality, its presence reflecting the severity of the underlying cardiac disease, and greatly increasing the risk of stroke.[4] Non- rheumatic AF increases the risk of stroke by a factor of five.[1] This risk increases by about 5% per year especially in the elderly, the presence of high blood pressure or other evidence of heart disease, e.g., myocardial infarction.[3,5] Table 1 shows some of the common causes of AF.

Aetiopathophysiology

Pathogenesis

The mechanism of atrial fibrillation has recently become clearer and is understood in terms of multiple irregular wavelets of excitation. This understanding allows a single model to be proposed which unites the various etiologies and treatment of atrial fibrillation (Figure 1).

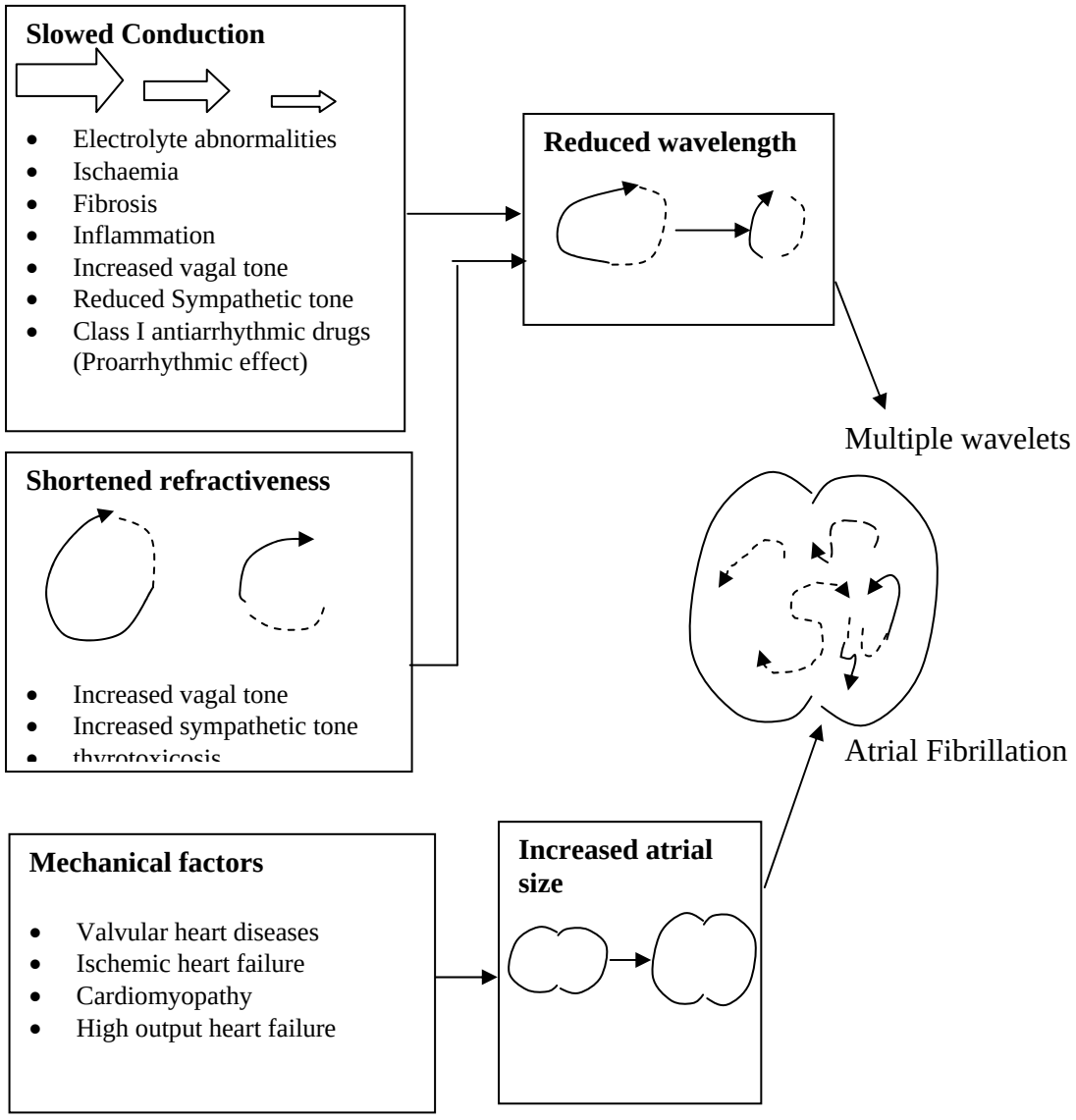
Cardiac arrhythmia is caused by an abnormality in the rate regularity or site of the cardiac impulse or by certain disturbances in the conduction of the impulse such that the normal sequence of activation of the atria and ventricles is disturbed. This may be explained in terms of abnormalities of impulse initiation (i.e. abnormal automaticity), impulse conduction (re-entry) and/ or both.[6 - 12] Abnormal automaticity arises from the ability of all cardiac tissue in the right circumstances to generate its own impulse. A rapidly firing automatic focus can compete with the sinus node to dominate the cardiac rhythm, e.g. tachycardia due to drug toxicity. However, re-entry occurs when the cardiac impulse circulates in a closed loop with excitatory waves spreading out

to the rest of the heart on each circuit, e.g., junctional tachycardia and most ventricular tachycardias.[8] Earlier experiments establish that AF cannot arise from ectopic automatic foci, either singular or multiple, [7,8] until Moe's observation in 1962.[7]

Table 1: Some causes of atrial fibrillation

Cardiac causes	Non – cardiac causes
Common	
Rheumatic heart disease	Acute infections e.g. pneumonias
Hypertension	Thyrotoxicosis
Cardiomyopathy or heart muscle disease	Excess alcohol intake
Ischaemic heart disease	Pleural effusion
Pericardial disease e.g. pericarditis	Pulmonary thromboembolism
Sick sinus syndrome	Pre – excitation syndrome e.g. wpw
Less common	
Atrial septal defect	Lung carcinoma
Atrial myxoma	Thoracotomy

Figure 1: Proposed model for the pathogenesis of atrial fibrillation (Adapted from Murgatroyd FD et al. Lancet 1993; 341: 1317 – 1322)



In 1962, Moe proposed that AF consisted of several co- existing re- entrant wave fronts of activation within the atria. Moe's model was refined and given an electrophysiological basis by experimental studies in the 1970s to 1990s.[7, 8, 9] These studies also showed that most wave fronts do not in fact re- enter but rather sweep around the atria continually invading excitable tissues and being extinguished or divide around obstacles.[10] Sustained AF is dependent on these multiple wave fronts continually encountering excitable tissue. This process is favored by three factors (Shortening of atrial refractoriness, Slow conduction (allowing time for the tissue to regain excitability between each wave front) and Increased atrial size (and therefore surface area). [11] Mechanical stimuli (valvular, hypertensive heart disease and failure) give rise to AF by causing atrial dilatation and slow conduction, whereas functional factors (atria ischaemia, biochemical abnormalities, and autonomic tone) exert various influences on conduction and repolarisation.[10, 11]

Pathophysiology

The haemodynamic disturbance of atrial fibrillation results essentially from the absence of atrial systole ("atrial kick") and from the rapidity and irregularity of the ventricular response, with a consequent loss of cardiac output (a loss of about 10% in normal individuals with a greater loss of ventricular rate). A rapid heart rate reduces the diastolic filling interval, and the additional loss of the sequential atrioventricular contraction mechanism in AF may lead to a dramatic reduction in cardiac output and to other haemodynamic disturbances. Atrial dilatation and loss of atrial systole leads to intra- atrial stasis favoring the formation of thrombus.[12] Also, with the onset of a rapid ventricular rate or response, some incompetence of the mitral valve may occur leading to further reduction of forward flow.[3, 5, 12]

Clinical subsets of atrial fibrillation

For practical purposes, three distinct forms of AF according to their pattern of occurrence are being suggested here.[3]

1. Paroxysmal atrial fibrillation

This term is used to describe at least one episode of self-terminating AF. The duration of the episodes may vary from seconds to days and the interval between successive episodes is unpredictable. The natural history of the condition is a progression towards more prolonged episodes of AF and ultimately to persistent or permanent AF, a process which may take many years. The goal of therapy for paroxysmal AF is to prevent recurrences.

2. Persistent atrial fibrillation

This term may be used to describe the clinical situation where an episode of AF has not spontaneously reverted to sinus rhythm, although chemical or direct current cardioversion is capable of restoring it. The probability of restoring sinus rhythm is dependent on a variety of factors, in particular, duration of the episode of AF (Less than one year) and the degree of left atrial enlargement. Usually, the probability to restore and maintain sinus rhythm is very low if left atrial diameter is > 6cm as measured by echocardiography.[12] In contrast, if left atrial diameter is < 5cm, the result of cardioversion and reduction of the relapse risk by treatment with antiarrhythmics is generally better. The patients with left atrial diameter of 5 to 6cm generally comprise the subset with intermediate probability for successful cardioversion.

3. Permanent atrial fibrillation

This term may be used when attempts at restoration of sinus rhythm have failed or here the probability of successful cardioversion is considered so low that no attempt has been made. Once the permanence of AF has been determined, the objectives of therapy become those of adequate rate control and prophylaxis against thromboembolism.

Therapeutic options in atrial fibrillation

The therapeutic goals that should be considered for each patient are: restoration of sinus rhythm, maintenance of sinus rhythm, rate control and prevention of thromboembolism.

A) Pharmacologic methods

1. Restoration of sinus rhythm

Electrical cardioversion is the method routinely used to restore sinus rhythm especially in haemodynamically unstable patients.[3] The best predictors of a successful cardioversion are (Short duration of the AF, Age, Absence of underlying disease (especially rheumatic), Heart failure (low New York Heart Association Function Class I/ II, high left ventricular ejection fraction) and small left atria.[12] However, pharmacologic conversion of AF is often preferred and may have the particular benefit of preventing early recurrences.[13 - 16] Overall, it appears that moderate to good efficacy in chemical cardioversion is achieved with the use of class IA, IC agents and amiodarone [17, 18] Sotalol is less effective[22] while, digoxin, beta- blockers and calcium channel blockers (CCB) are essentially ineffective in cardioversion, although they slow ventricular rate. [18 - 20] The use of class I anti- arrhythmic drugs to terminate AF or prevent recurrence in acutely ill patients runs the risk of provoking serious ventricular arrhythmia, or acute heart failure, and should therefore be avoided.[3] The efficacy of the newer class III agents such as Ibutilide and Defetilide, appears to be very promising, but they are still awaiting clinical use approval.[15]

Amiodarone is considered by some, the most effective agent for refractory, symptomatic, recurrent AF. Although minimal prospective comparative drug data are available, nearly two thirds of patients treated remained in sinus rhythm for up to one year follow up.[12, 21] Frequent use of amiodarone for AF is limited due to its potentially severe and life threatening side-effects. These however can be minimized with low daily dosing.[13] As recurrence of AF is common, successful drug therapy should be evaluated by the decrease in number and duration of AF episodes and not its mere recurrence. Usually, patients with long standing AF, large left atrial size, or those with previous multiple drug failures, will experience the highest recurrence rates.[3, 12, 22, 23] In such patients, concomitant ventricular rate control therapy with oral digoxin, verapamil, diltiazem or a beta- blocker should be considered.[15, 20, 22 - 28]

2. Maintenance of sinus rhythm

Without medical treatment, most studies indicate persistence of sinus rhythm in only about 20-40% of patients after 1 year.[21, 29] This result can be improved by treatment with anti- arrhythmic agents. Class IA drugs (quinidine, disopyramide, procainamide) may present some desirable effects on electrophysiology, but accelerate atrioventricular conduction. Quinidine has been the mainstay for AF prophylaxis, however a meta- analysis of six placebo controlled trials [25, 30, 31] and observations from the SPAF (Stroke Prevention in Atrial Fibrillation) trial, [26] have shown a significantly greater mortality in patients receiving quinidine. This has led to the reappraisal of the class IA agents in the management of AF. By contrast, class IC drugs such as Flecainide and Propaferone, have been well investigated.[15] They have potent effects on conduction within cardiac cell membranes and lengthen the PR interval and QRS complex in the ECG. Flecainide has been shown to be effective in preventing recurrences of atrial fibrillation in up to 60% of patients but does not limit the ventricular response. Adverse effects with flecainide have been reported in up to 74% of patients, but these effects were mostly tolerable. Nevertheless, doubts about the safety of flecainide have been raised by the CAST (Cardiac Arrhythmia Suppression Trial). [24] Recent studies [15, 25] however supported the use of Propafenone and Flecainide as safe and effective choices for the pharmacological treatment of AF, supraventricular tachycardia or premature ventricular complexes in properly selected patients (particularly in terms of preserved left ventricular function and without history of myocardial infarction or congestive heart failure). In patients with recurrent episodes of AF, class IC agents are usually more effective than class IA drugs in maintaining sinus rhythm, and are also better tolerated. [15]

The role of amiodarone (a class III drug) in the maintenance of sinus rhythm is of considerable interest. Direct comparisons suggest that amiodarone is superior to quinidine [22, 23, 25 – 27] in efficacy and is not responsible for an excess of deaths due to proarrhythmic effect in patients with structural heart disease (myocardial infarction and congestive heart failure). However, the non- cardiac side effects of amiodarone i.e. abnormal thyroid function, lung fibrosis and corneal deposits may lead to drug in continuance. But this can be curtailed with lower dose of 100mg/day. [28]

3. Rate control in atrial fibrillation

Pharmacological agents that depress conduction and prolong refractoriness in the atrioventricular node are frequently required for control of symptoms and improvement of haemodynamic during AF. [3, 19, 26] These includes digoxin, beta-adrenergic antagonists and calcium channel blockers.[3] Optimal rate control includes reducing resting heart rate to < 90 beats/ minute and preventing excessive rate response on minimal exercise.[14, 27]

The physician attempting to slow the ventricular rate during AF must consider two phases of treatment: an acute phase that involves rapid control of ventricular rate and a long- term phase that involves drugs given orally to patients that develop rapid ventricular rates and symptomatic. [3] In the presence of important clinical symptoms, such as chest pain or exacerbation of congestive heart failure, that are related to a rapid ventricular response, intravenous drug therapy to slow the heart rate relatively quickly is often required. [20] Although, intravenous digoxin may effectively slow the ventricular rate- at rest, there is delay in its onset of effect of at least 60 minutes in most patients, with the full effect delayed for up to 6 hours.[3, 28]

Adenosine is a naturally occurring substance with a half life of approximately 10 seconds, which produces marked inhibition of AV nodal conduction. Although it is very effective for terminating re- entrant arrhythmias using the AV node, this agent has no role in the management of AF because of its transient duration of action.[3] For patients with severe symptoms relating to a rapid ventricular rate, intravenous Diltiazem, Verapamil, Esmolol, Propranolol, or Metoprolol provides rapid control of heart rate as reported from various studies. [3, 15, 23] These agents can result in lower heart rates during exercise than digoxin alone but significant side effects of bradycardia and atrioventricular block should be taken into account. This is particularly a problem in the elderly and those with sick sinus syndrome.

Figure 2a: Algorithms for the management of atrial fibrillation; applicable to patients other than those with recent stroke (AF less than 48 hours' duration) (Adopted from Golzari H et al. Ann Intern Med 1996, 125; 311 – 323)

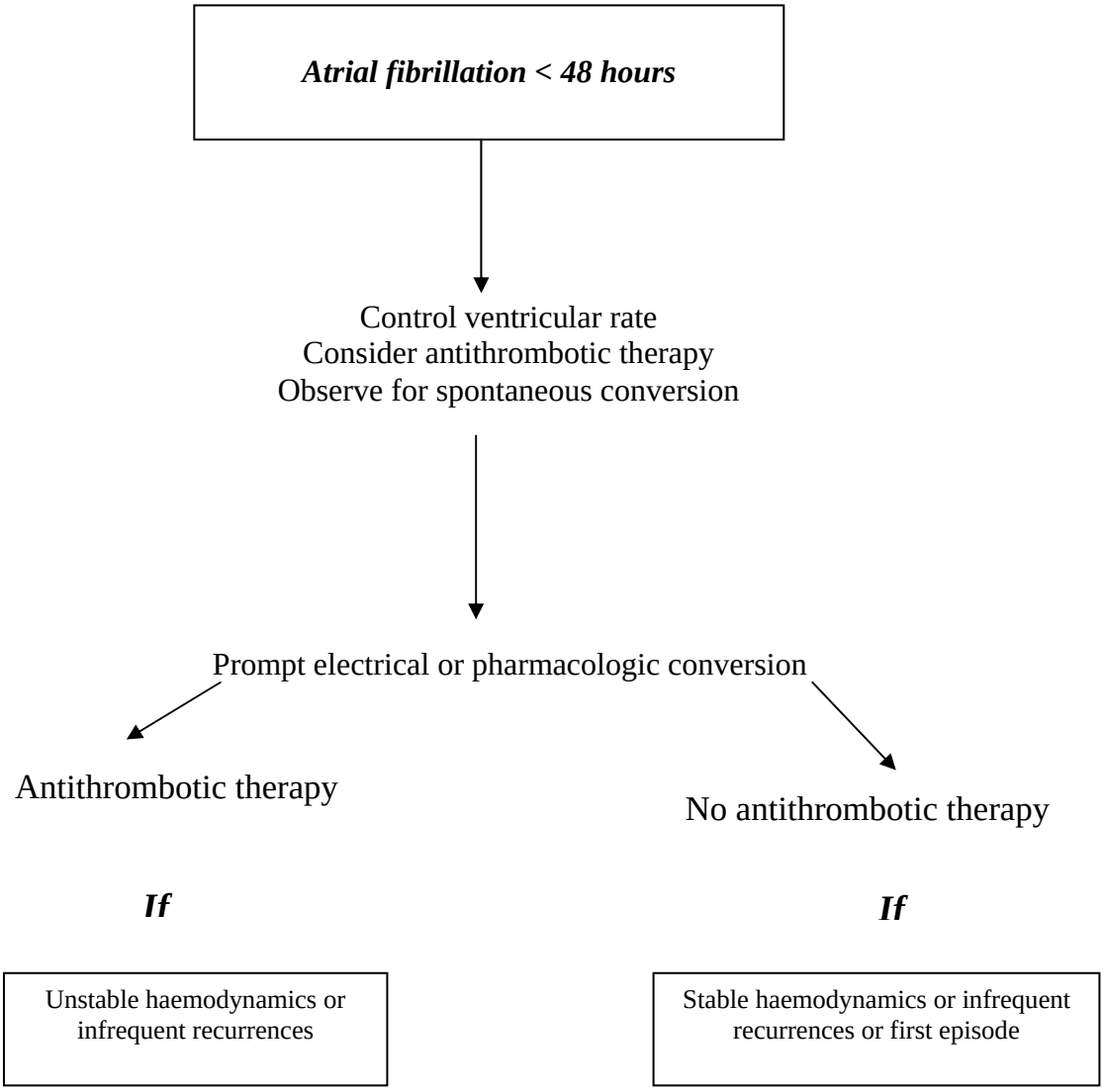


Figure 2b: Atrial fibrillation more than 48 hours' duration. (Adapted from Golzari H et al. Ann Intern Med 1996; 125: 311 - 3230

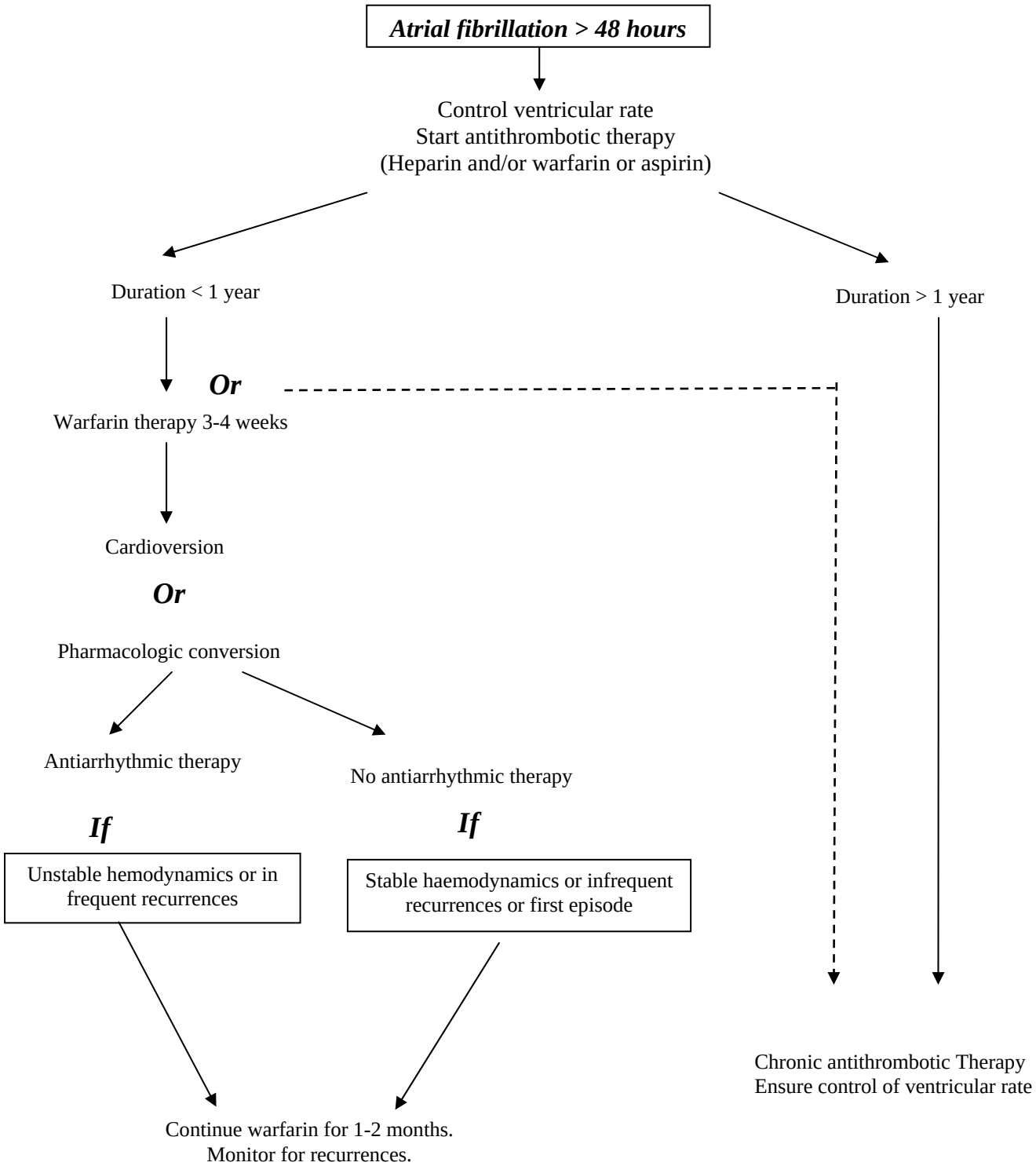
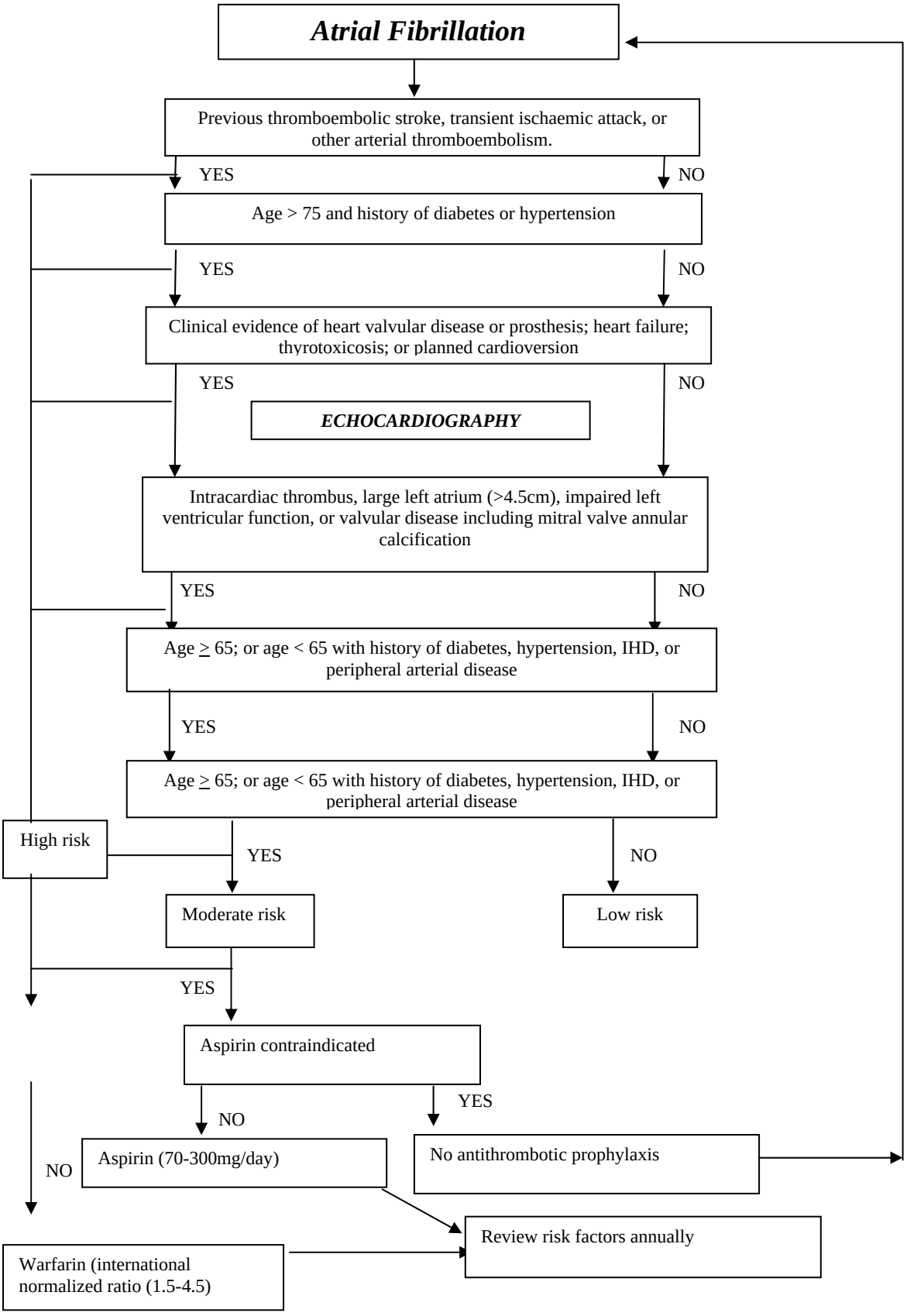


Figure 3: Stroke prevention in patients with atrial fibrillation (Adapted from Golzari et al. Ann Intern Med 1996; 125: 311 – 323)



Prevention of thromboembolism

Atrial fibrillation is the most common cardiac condition that predisposes to systemic embolism.[29 - 40] The high risks of thromboembolism stroke is the most devastating complication commonly associated with mitral stenosis and prosthetic mitral valves. [12, 41 - 42] AF even in the absence of any valvular disorder, carries a substantial increase risk of ischaemic stroke especially among the elderly, averaging about 5 percent per year. [5] But with transient ischaemic attacks, the rate of brain ischaemia accompanying non- valvular AF exceeds 7 percent per year.[42, 43] The absolute rate of stroke varies importantly with patient age and co- existing cardiovascular disease [44] (Table 2).

Most ischaemic strokes associated with AF are probably due to embolism or stasis; however, about 25 percent of AF associated stroke is due to intrinsic cerebrovascular diseases, other cardiac sources of embolism, or aortic arch atheroma. [35 - 41] Identification of subpopulation of AF patients with relatively high or low absolute rates of stroke and or other risk factors determine which patients will gain the greatest benefit from anticoagulation therapy [39, 40, 45]

Antithrombotic therapy

Long term warfarin therapy prevent stroke in patients who have atrial fibrillation associated with either rheumatic valvular disease or prosthetic heart valves.[46] However, in non- rheumatic atrial fibrillation, the value of anti- coagulation therapy was not established until the recent randomized, prospective clinical trials using INR (International Randomize Ratio) of between 1.8- 4.2.[47] Table 3. Combined analysis of these trials showed a reduction in the incidence of ischaemic stroke or embolus from 4.5 to 1.4 percent per year for a risk reduction of 69 percent. [46, 48]

Although aspirin appeared to be beneficial in the Stroke Prevention in Atrial Fibrillation (SPAF I) trial, [37] its efficacy relative to that of warfarin was only established after the completion of the SPAF II trial. [40] The study showed that the rates of ischaemic stroke and systemic emboli for patients on 325 mg/ day of aspirin and those of warfarin, did not differ significantly in patients 75 years or younger, in those older than 75 years or the two groups combined. The study also confirmed that a history of hypertension, thromboembolism or recent heart failure were important risk factor(s) for thromboembolism.

Anticoagulation for cardioversion

Systemic embolism is a complication of electrical and pharmacological cardioversion of AF to sinus rhythm.[15] Prior anticoagulation appears to decrease the embolic risk, [47] even though no randomized, controlled prospective trials evaluating the efficacy of prophylactic anticoagulation therapies in this setting have been performed. Current recommendations are to give anticoagulants to patients who have AF of unknown duration or more than 48 hours for approximately 3 weeks before and 4 weeks after cardioversion. [15] Alternatively, TEE (Transaesophageal Echocardiography) has been suggested as another approach for in hospital patients with AF lasting more than 2 days. [46, 48] The role of immediate anticoagulation therapy for atrial fibrillation of less than 48 hours duration remains unexplored. [27]

Anticoagulation therapy is substantially more effective than aspirin in the secondary prevention of stroke and vascular events. [41] The European Atrial Fibrillation Trial, [47] showed a 47 percent reduction in the overall risk for vascular events and a decrease in the rate of stroke from 12 to 4 percent per year. However, optimal time for initiating anticoagulation therapy in patients with recent onset stroke and atrial fibrillation is still controversial. The Cerebral Embolism Study Group, [48] proposed that, in patients with a small or moderate infarction, anticoagulation therapy should be initiated if no evidence of hemorrhage is shown on CT scan 24 to 48 hours after the stroke. In patients who have a large infarction, anticoagulation therapy should be started if after 7 days, CT excludes the possibility of delayed hemorrhage.

Table 2: Factors associated with high risk of stroke in patients with AF

Age > 65 years
Hypertension
Rheumatic heart disease
Prior stroke or transient ischaemia attacks (TIA)
Diabetes mellitus
Congestive heart failure
Left atrial dimension > 5 cm

Table 3: Recommendation(s) for long term anticoagulation in patients with chronic atrial fibrillation

Age (years)	Risk factors	Recommendations
< 65	Absent	Aspirin
	Present	Warfarin (target inr 2.5)
65 - 75	Absent	Aspirin or warfarin
	Present	Warfarin (target inr 2.5)
> 75	All present	Warfarin (target inr 2.5)

Risks factors: Prior transient ischaemic attack, systemic embolus, or stroke, hypertension, poor left ventricular function, rheumatic mitral valve disease, prosthetic heart valve Adapted from: A laupacis et al: chest 114: 579s, 1998.

B) Non- pharmacologic therapies

A variety of non – pharmacological techniques are being developed for use as alternatives and /or adjuncts to drug therapy. These include:

1. Atrial pacing
   The realization that episodes of AF often occur at times of sinus bradycardia or following sinus pauses, suggests that atrial pacing may have a preventive role in the treatment of AF.[3] Overdrive suppression is a common technique in the acute management of atrial and ventricular arrhythmias but has not been subjected to trials in long – term use.[3, 12] However, there is preliminary evidence that dual chamber pacing at a rate slightly higher than the mean sinus rate, reduces the incidence of atrial arrhythmias. [3]
2. Atrioventricular nodal ablation
   The established treatment for AF that is refractory to pharmacological therapy is ablation of the atrioventricular (AV) node. This was originally undertaken using ligation or cryo – surgery via right atriotomy, but that method has been supplanted in the last decade by catheter based techniques. [14, 49 - 53]
3. Direct current radiofrequency energy [50] delivered to a catheter tip positioned adjacent to the AV node can be reliably used to produce complete AV block. Furthermore, the procedure is generally painless and thus, can be done without general anesthesia. AV nodal ablation is not a cure for AF, it simply disconnects the ventricles from the atria and the sinus node and therefore, the patient will require a permanent ventricular pace maker. Although such patients no longer suffer symptoms due to an irregular or rapid pulse, atrial transport is not regained nor is the risk of thromboembolism lessened. Thus, the ideal candidate for this procedure is an elderly patient in whom paced cardiac rhythm is an acceptable alternative to chronic, expensive and often ineffective pharmacological therapy with frequent hospital attendance.[51]

C) Surgery for atrial fibrillation

A variety of surgical procedures have been developed for the treatment of refractory paroxysmal or chronic AF. These aim at restoring a regular ventricular rhythm driven by the sinus node and hence retain a normal rate response to exercise. The two most promising are: the “corridor” and “maze” procedures. The corridor procedure effectively isolates both the left and right atria, leaving a strip of myocardium connecting the sinus node to the AV. [52] This procedure does not prevent AF, but the AV node and hence the ventricles, are not affected by the AF.

The most radical operation devised the maze procedure, aims to completely prevent AF. [52, 53] A series of incisions divides the entire atrium into a labyrinth, the passages of which allow all parts to be excited by impulses arriving from the sino- atrial node but are of insufficient width to allow reentry. This is the only surgical procedure that restores coordinated atrial as well as ventricular electrical activity. [3] The relative merits of the corridor and maze procedures remain theoretical but should become clearer with increasing experience. Surgery is likely to remain an unusual treatment for AF, being reserved for younger patients with severe and refractory symptom who do not wish to be committed to life long artificial cardiac pacing.

Conclusion

AF in all forms is a common and challenging arrhythmia. The long term treatment cannot be defined after first consultation and the approach therefore, needs to be flexible. The “sinus rhythm restoration and maintenance” strategy whenever it is possible, is a better option than “good ventricular rate control” strategy. In general, prophylaxis against thromboembolism should be initiated at the first diagnosis of AF not be discontinued until stable sinus rhythm has been documented over a period of months. Class IC agents have demonstrated an overall better efficacy and fewer side- effects than class IA agents in properly selected patients, while amiodarone is especially effective in preventing AF on a short term basis. For cases that are refractory to conventional therapy, catheter ablation and pacemaker based and surgical treatments are becoming available, but their long term outcomes are unknown.

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Circus movements in rabbit atrial muscle as a mechanism of tachycardia III. The "leading circle" concept: a new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. Circ Res 1977; 41: 9-10
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