Management Of Atrial Fibrillation

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Summary

Atrial fibrillation is the most commonly encountered sustained arrhythmia. The spectrum of symptomatology and presentation are broad. The goals of treatment should include (1) identification of any underlying cause(s) and/or precipitating factor(s), (2) control of ventricular rate, (3) restoration and maintenance of sinus rhythm and (4) prevention of thromboembolism. The characteristics of the arrhythmia differ among patients; hence, some goals will apply in some cases and a different combination in other cases. A thoughtful, individualized approach is essential. (*HK Pract* 1997;19:601-613)

Keywords: Inflammatory arthritis, rheumatoid arthritis

摘要

心房顫動是日常診治中最常見的心律失常，臨床表現多種多樣。治療目標包括：(1)鑒別出潛在疾病或誘發因素，(2)控制心室律，(3)恢復及維持竇性心律，(4)預防血栓栓塞。由於心律失常的患者有著不同的特質，因此治療目標因情況而異，必須悉心安排個體化的治療方案。

Background

Atrial fibrillation (AF) is certainly the most common of all the arrhythmia requiring treatment interventions. In the United States, the prevalence of both chronic and paroxysmal AF increases dramatically with age, from 0.2% to 0.3% in individuals less than 40 years of age, to 5% to 9% in those between 60-90 years old.[1] In Hong Kong, an incidence of 1.3% was documented in a recent survey.[2] AF affects men and women approximately equally. In an ageing population, AF will become an increasing burden to the health care system. The development of AF carries an ominous prognosis, since it is followed by a nearly doubled overall mortality rate and a greater than two-fold cardiovascular mortality compared with subjects who did not have AF.[3] The clinical manifestation of AF are highly variable, ranging from complete absence of symptoms to haemodynamic collapse. The rapid and irregular rhythm and the loss of synchronized atrial activity both contribute to decreased cardiac performance and symptomatology (**Table 1**).

Classification of AF

(A) New onset AF – first presentation of AF in which a proper classification is pending.
(B) Paroxysmal AF – AF that terminates spontaneously, usually within 48 hours.
(C) Persistent AF – sinus rhythm is restored either by medical or electrical means.

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CURRENT THERAPEUTICS

(D) Permanent AF – AF in which restoration of sinus rhythm either fails or is considered clinically inappropriate because of low success rate.

It is noteworthy that all cases of AF belonging to (B)–(D) are chronic in the sense that they are either recurrent or long-standing. Depending on the vigor of the patient and/or physician in restoring sinus rhythm, some cases of permanent AF may be classified as persistent under different scenario.

Basic principles of management

The management of AF should address five key clinical concerns:

1. Identify any underlying cause(s) and/or precipitating factor(s).
2. Control rapid ventricular rate, if present, with atrioventricular (AV) blocking drugs.
3. Decide whether restoration of sinus rhythm is a possible or desirable goal.
4. Decide how best to maintain sinus rhythm, should sinus rhythm be restored.
5. Initiate long-term anticoagulation or antiplatelet therapy for prevention of thromboembolism.

Identification of the underlying cause(s)

In every patient presenting with AF, it is important to consider the possible underlying cause(s) and/or precipitating factor(s) (**Table 2**).

Table 1: Presentation of atrial fibrillation

Asymptomatic

Rate-related symptoms

- palpitation
- ischaemia
- haemodynamic

Symptoms related to loss of atrial contraction / AV synchrony

- palpitation
- haemodynamic
- malaise, fatigue, reduced exercise tolerance

Complications

- emboli
- syncope
- tachycardia-related cardiomyopathy

Table 2: Causes and/or precipitating factors for atrial fibrillation

Structural Heart Diseases

- Hypertensive heart disease
- Coronary artery disease: Acute infarction, chronic ventricular dysfunction
- Valvular heart disease, especially mitral valve disease
- Cardiomyopathies: Dilated, hypertrophic, and restrictive
- Post-operative, especially open heart surgery
- Pericarditis
- Congential heart disease

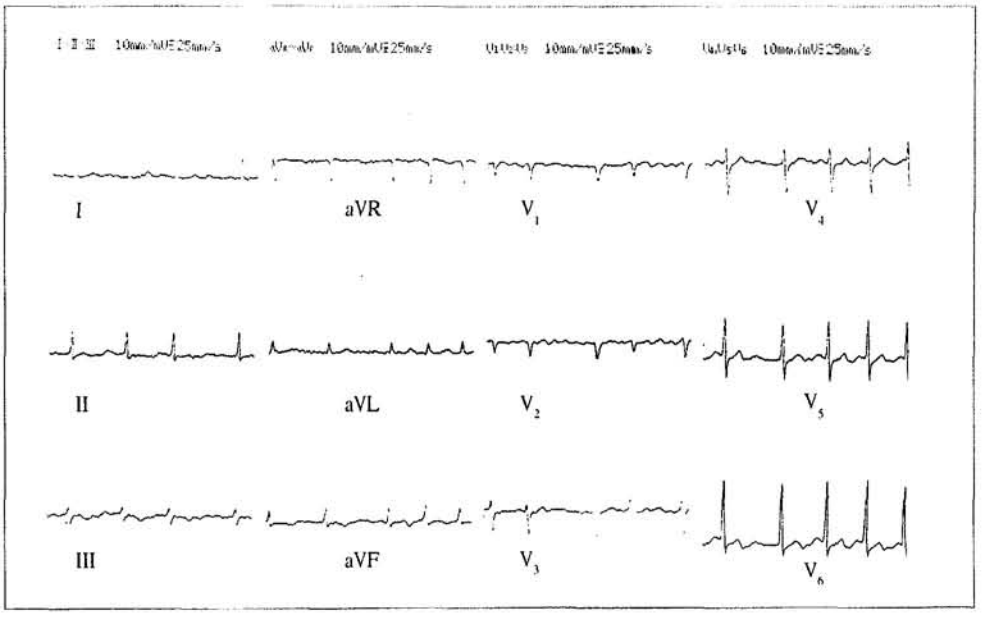
Systemic Conditions

- Systemic infection(s)
- Thyroid disease: Hyperthyroidism, hypothyroidism
- Electrolyte imbalance, especially hypokalaemia
- Malignancy, especially lung and mediastinal
- Alcoholism

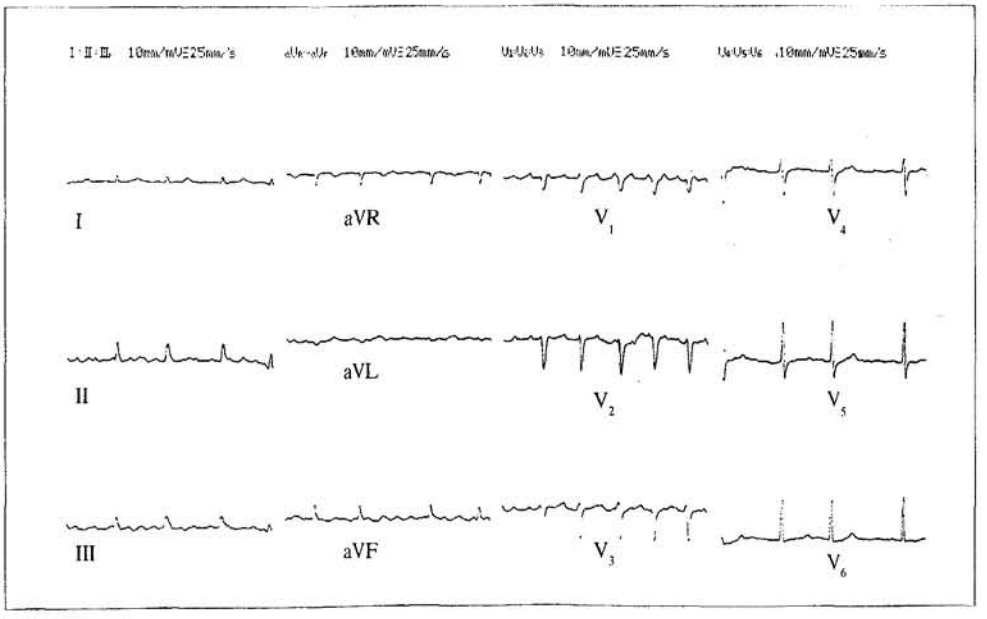
CURRENT THERAPEUTICS

Treatment of the underlying cause or reversal of a precipitating factor may control the ventricular rate or restore sinus rhythm. A careful history and physical examination should be performed to find out these potentially reversible cause(s). The diagnosis of AF can be made easily on the basis of a 12-lead electrocardiogram (ECG) (**Figure 1**). However, any additional ECG features e.g. left ventricular hypertrophy or presence of Wolff-Parkinson-White (WPW) syndrome, that are suggestive of the underlying causes should be noted. Curative therapy for the underlying diseases may prevent AF, e.g. radiofrequency ablation of the accessory pathway in patients with WPW syndrome (**Figure 2**). All patients presenting with new onset AF should have their thyroid status measured and transthoracic echocardiography performed. Echocardio-

Figure 1: Electrocardiographic appearances of atrial fibrillation



(a) Fine atrial fibrillation



(b) Coarse atrial fibrillation

graphy provides a valuable assessment of the left ventricular function and to detect the presence of any structural heart disease, such as hypertensive heart disease or mitral stenosis. Echocardiography is usually underused in both general and hospital practice.[4]

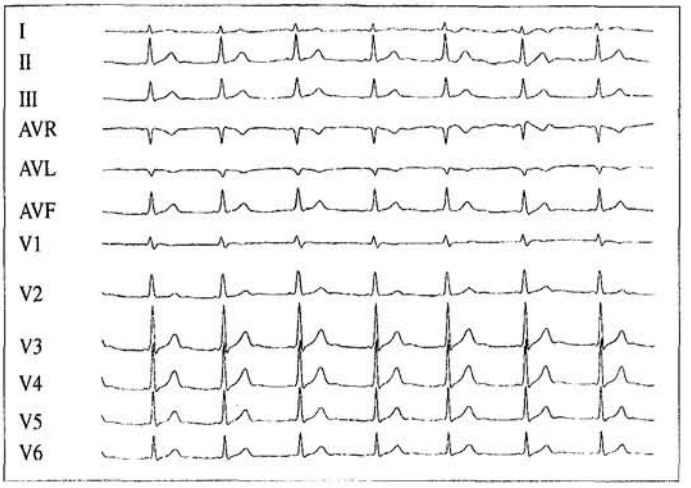
Control of ventricular rate

In patients with normal AV conduction, the ventricular response during AF is typically between 70-120 beats per minute (bpm) at rest, and higher during sympathetic activation e.g. exercise. Patients with AF often present with signs and symptoms of circulatory insufficiency owing to an inappropriately rapid ventricular rate. Considerable symptomatic relief can be obtained by administering drugs that slow AV conduction and ventricular rate. Furthermore, control of ventricular rate may prevent the development of left ventricular dysfunction due to tachycardiomyopathy.[5,6] It is important to consider in every patient with AF

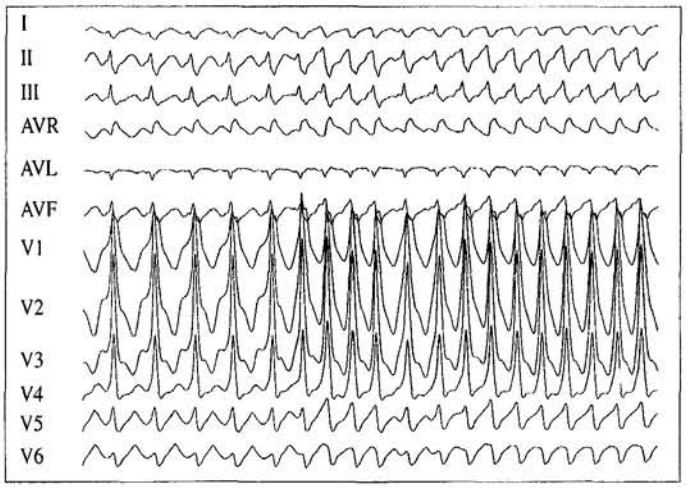
(1) whether ventricular rate control is necessary;
(2) how quickly control needs to be achieved; and
(3) which drug is to be used.

Those patients who are haemodynamically unstable or who have acute pulmonary edema due to a rapid AF requires urgent synchronized DC cardioversion. However, most stable AF patients with persistent tachycardia (> 100 bpm) at rest should be treated with AV nodal blocking agents (see below) to slow ventricular rate. However, in patients with aberrant and wide QRS complex

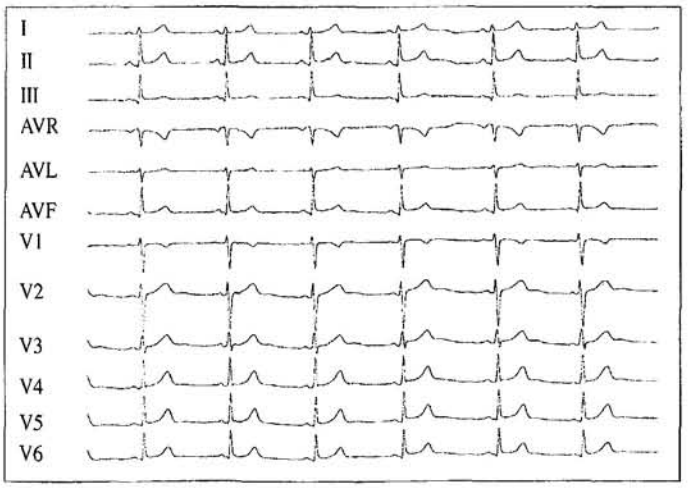
Figure 2: Electrocardiographic appearance of Wolff-Parkinson-White syndrome during



(a) Sinus rhythm



(b) Atrial fibrillation



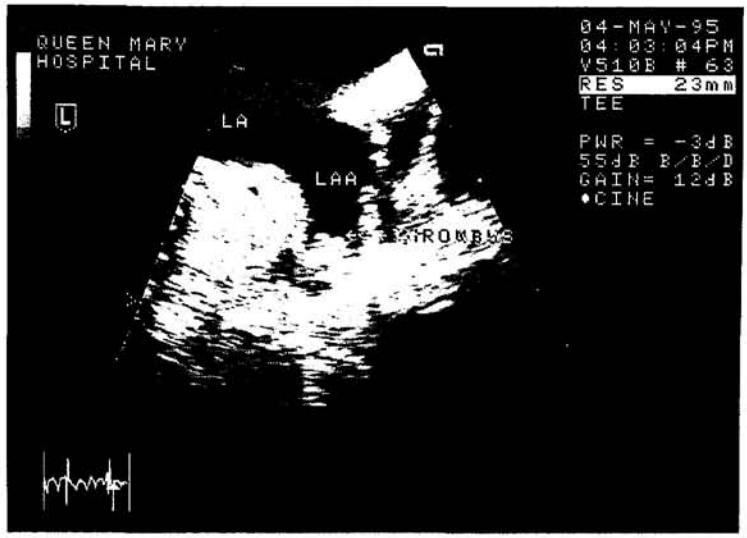
(c) After successful radiofrequency ablation

(Continued on page 607)

CURRENT THERAPEUTICS

that are suggestive of the presence of accessory pathway with pre-excitation, AV nodal blocking agents are contraindicated (**Figure 3**).

Figure 3: Left atrial appendage (LAA) thrombi revealed by transoesphageal echocardiography in a patient with atrial fibrillation (LA = left atrium)



Acute rate control

Digoxin, beta-blockers and calcium channel blockers with AV nodal blocking properties (verapamil or diltiazem) singly or in combination are effective in reducing the ventricular rate in AF patients. The agent and route of administration used are determined by the clinical characteristics and presentation (**Table 3**). Intravenous therapy is indicated for control of rapid

Table 3: Therapies for acute control of the ventricular rate in atrial fibrillation

Clinical Setting	Drug	Dose	Efficacy	Comments
Rapid rate, hypotensive	None			Urgent DC cardioversion
Rapid rate, symptomatic	Diltiazem	IV bolus 20 mg or 0.25 mg/kg over 2 min followed if necessary by IV 25 mg or 0.35 mg/kg 15 min later. Maintenance infusion of 5-15 mg/h.	Rapid rate control	Well tolerated. May be synergistic with digoxin with no effect on digoxin levels.
	Verapamil	IV 5-10 mg over 2-3 min. Repeat 5-10 mg 30 min later if required. Maintenance infusion rate is not well documented.	Good rate control	Hypotension may occur. May be synergistic with digoxin but also increases digoxin levels.
	Metoprolol	IV 5 mg every 5 min, total 15 mg.	Rapid rate control	Useful in post-operative setting, caution in patients with congestive heart failure.
	Propranolol	IV 1-5 mg (1 mg every 2 min)	Rapid rate control	Useful in post-operative setting, caution in patients with congestive heart failure.
	Esmolol	IV 0.5 mg/kg over 1 min. Repeat if necessary. Maintenance infusion 0.05 mg/kg/min.	Short-acting	Useful in post-operative setting, hypotension is common. Delayed onset of AV node slowing (hours)
	Digoxin	IV 0.25 - 0.5 mg (total 1 mg/24 hr)	Moderate to low efficacy	
Slow rate, stable	None			No therapy

symptomatic ventricular rates. Intravenous digoxin does not provide immediate heart rate control, onset occurs anywhere from 1 to 6 hours, while maximum efficacy may not be seen for up to 24 hours. However, it is particularly desirable in patients whose AF is a complication of, or is associated with congestive heart failure. Intravenous beta-blocker, may be used to control the ventricular rate especially in situation with high sympathetic drive e.g. post-operative. Both intravenous diltiazem and intravenous verapamil are very effective with rapid onset of action. In general, both drugs are well tolerated but should be avoided in patients with hypotension and severe left ventricular dysfunction.

Long term rate control

In the majority of AF patients, long term oral therapy is appropriate (**Table 4**). Digoxin therapy remains the mainstay of monotherapy for sustained AF in most sedentary patients or in those requiring inotropic support. Calcium channel blockers with AV nodal properties (verapamil or diltiazem) may have some advantage over beta-blocker for control of ventricular rate in AF because they have vasodilator properties that partially offset their negative inotropic effects. Beta-blockers and calcium channel blockers and AV nodal blocking properties (verapamil or diltiazem) either used alone or in combination with digoxin, may provide better overall control of ventricular rate in chronic AF especially during exercise.[7,8] For those patients with persistent rapid AF despite adequate drug therapy with AV nodal blocking agents, they may benefit from radiofrequency ablation of AV node and implantation of a ventricular or dual-chamber rate adaptive pacemaker.[9]

Table 4: Therapies for chronic control of the ventricular rate in atrial fibrillation

Clinical Setting	Drug	Dose	Efficacy	Comments
Rapid rate and/or exercise	Diltiazem	90 - 360 mg daily	Good	Reduce rest and exercise rate, may cause ankle edema
	Verapamil	120 - 480 mg daily	Good	Reduce rest and exercise rate.
	Atenolol	25 - 100 mg daily	Especially effective to reduce exercise rate	Any beta-blocker may be used
	Propranolol	10 - 120 mg 3 times daily	Especially effective to reduce exercise rate	
	Digoxin	0.1-0.75 mg daily	Reduces resting rate	Delayed onset of AV node slowing (hours). Minimally effective during exercise, fever, and other high cate-cholamine status. Caution in elderly patients or those with renal impairment
Rapid symptomatic ventricular rate despite medical therapy.				AV junction ablation and permanent pacemaker

CURRENT THERAPEUTICS

Restoration of sinus rhythm

The two most compelling reasons to consider eliminating AF and restoring sinus rhythm are:

(1) restitution of organized and effective atrial mechanical function and
(2) prevention of thromboembolism. Only 30-50% of patients with recent onset of AF will revert spontaneously to sinus rhythm within 48 hours. Elective cardioversion is probably indicated for all patients with a first episode of AF unless relative contraindications exist such that the benefits of restoring and/or the chance of maintaining sinus rhythm are minimal (**Table 5**). Either synchronized electrical shock or pharmacologic therapy can achieve cardioversion of AF. Unless AF occurred within 48 hours, medical or electrical cardioversion should be preceded by a period of anticoagulation for 3-4 weeks.[10] Alternative strategy is to perform a transoesphageal echocardiography to exclude left atrial thrombi (**Figure 3**) together with intravenous heparin before cardioversion.[11] It is also imperative to continue anticoagulation for 3-4 weeks after return of sinus rhythm, as most of the thromboembolic events occur after restoration of sinus rhythm when effective atrial contraction resumes. The general efficacy of external defibrillation is about 70%. Recently, low energy biphasic shocks delivered via catheters between the right and left atria are associated with significantly higher successful rate of cardioversion compared with external defibrillation without any increase in complication.[12]

Table 5: Relative contraindication for elective cardioversion

- Poor prognosis (i.e. advanced malignancy)
- High risk from anaesthesia (i.e. severe respiratory disease)
- Other severe functional limitations
- Long standing AF (years)
- Left atrial dimension >6 cm
- Minimal or no symptom with a well-controlled ventricular rate

Pharmacological cardioversion

Class IA, Class IC, and Class III antiarrhythmic drugs are all modestly effective in restoring and maintaining sinus rhythm (**Table 6**). For all agents, the successful rate (30-80%) of cardioversion is related to the duration of AF and conversion of long standing AF is unlikely. All these agents have a risk of proarrhythmia especially in patients with structural heart disease.[13,14] Thus, these agents should preferably be administrated in the hospital under careful monitoring. If the chosen pharmacological agent has not achieved conversion in 24 hours, direct DC synchronized shock is usually required for cardioversion. Concomitant antiarrhythmic agent increases the chance that sinus rhythm will be maintained after cardioversion. All patients on antiarrhythmic agent should be monitored for proarrhythmia for up to 24 hours following restoration of sinus rhythm.[15]

Electrical cardioversion

DC synchronized shock may be the first line therapy or may be used in combination with antiarrhythmic drug therapy with a successful rate up to 90%. The procedure is performed after fasting and under general anaesthesia or deep sedation. Cardiac monitoring and full resuscitation equipment should be available. DC synchronized shocks are delivered via defibrillation patches placed in apex-anterior or anterior-posterior position. Initially, 100 J will be used, and if unsuccessful, followed with up to 3 additional shocks of 360 J each, usually with different patch positions.

Maintenance of sinus rhythm

Patients with reversible underlying cause or precipitating factor should be corrected. Infrequent episodes of AF can be managed with repeated pharmacological or electrical cardioversion. However, when occurrences are more frequent and very likely, consideration must be given to long term maintenance with antiarrhythmic agents (**Table 6**). While there seems to be little agreement regarding the

CURRENT THERAPEUTICS

Table 6: Antiarrhythmic drug therapy in atrial fibrillation

Drug	Dose	Useful in	Avoid in	Comments
Class IA				
Quinidine gluconate	PO 1.2 - 1.6 g/day in divided dose	Renal failure	Liver failure Heart failure	Vagolytic. Many side effects including diarrhea, nausea, torsades de pointes and hypotension. Monitor QRS, QT, plasma K
Procainamide	PO 1 g, then up to 500 mg 3 hourly. IV 100 mg bolus over 2 min up to 25 mg/min to 1 g, then 2 - 6 mg/min.	Men, short term therapy	Renal failure Heart failure Joint disease	Torsades de pointes rare. Hypotension with IV dose. Limit oral use to 6 months to reduce the risk of drug-induced lupus
Disopyramide	PO 100-200 mg 6 hourly. Loading dose 300 mg	Women Vagally mediated AF	Renal failure Heart failure Glaucoma	Vagolytic (urinary retention, dry mouth) and negative inotropic effects. Hypotension and torsades de pointes.
Class IC				
Flecainide	PO 75-150 mg BD. IV 1-2 mg/kg over 10 min, then 0.15 - 0.25 mg/kg/h.	Patients without heart disease. Failure of Class IA drugs	Heart failure, IHD	Proarrhythmia. Negative inotropic. CNS effects. Increased incidence of sudden death postinfarct.
Propafenone	PO 150 - 300 mg TDS. IV 2 mg/kg then 2 mg/min.	Patients without heart disease. Failure of Class IA drugs	Heart failure	Proarrhythmia. Modest negative inotropic effect. Gastrointestinal side-effect.
Class III				
Sotalol	PO 80 - 240 mg BD	IHD Failure of Class IA or IC drug	Heart failure Where beta-blocker is contraindicated	Sinus bradycardia, AV block, negative inotropic, torsades if hypokalemic
Amiodarone	PO loading 1200 - 1600 mg daily, maintenance 200 - 400 mg QD	CHF. Failure of other drug. Renal failure	Young patients Pulmonary disease Thyroid dysfunction	Many side effects including pulmonary fibrosis, gastrointestinal upset, thyroid dysfunction, eye and skin changes. Torsades uncommon.

CURRENT THERAPEUTICS

efficacy of several antiarrhythmic agents to prevent recurrence of AF, great concerns have been raised relative to the long term safety of these agents and their possible negative impact on patient's survival. Patients with a history of congestive heart failure and underlying structural heart disease seem to be at greatest risk of adverse effects from antiarrhythmic agents (especially Class IA and IC agents).[13,14] If long term antiarrhythmic therapy is selected to maintain sinus rhythm, patients should be seen regularly and monitored for proarrhythmia. Class IA and III drugs prolong the QT interval and may give rise to a polymorphic ventricular tachycardia called Torsades de Pointes. ECG should be monitored during initiation of these drugs, and it is wise to avoid a greater than 25% to 30% increase in the QT interval or a corrected QT interval exceeding 500 msec. Although the proarrhythmic risk is lower with amiodarone, other potentially serious side effects that involve the thyroid, lungs, skin, and nervous system may occur, especially with long-term and higher-dose therapy. At follow-up patients should be questioned about possible side effects (**Table 6**).

Non-pharmacological methods have recently been explored to maintain sinus rhythm due to limitation of pharmacological therapy as described above. Surgical method with "Maze procedure" that involves breaking the potential re-entry circuits in the atria by making a series of incision in each atrium is associated with 95% cure rate for AF. However, it is a major operation that requires open-heart surgery and carries a 1% to 5% morbidity and mortality.[16] Recently, catheter-based procedures with radiofrequency energy application to focal source of AF or to atrial tissue to mimic surgical maze have been attempted with variable success.[17,18] Furthermore, a new form of pacing, biatrial pacing has been suggested to prevent AF in patients with drug refractory paroxysmal AF.[19] Finally, early data has suggested that implantable atrial defibrillators is a feasible, safe and effective method for cardioversion of AF, but its long term clinical efficacy is still unclear.[18] Although the preliminary results of these new therapies for AF seem promising, further clinical studies are required to prove their usefulness before any recommendations can be made.

Table 7: Summary of the randomized trial of anticoagulation in atrial fibrillation

Trial	Sample Size	INR	Embolic Event %/Year		% Risk Reduction	Comment
			Control	Warfarin		
BAATF[24]	420	1.5 - 2.7	3.0	0.4	86	
CAFA[25]	378	2.0 - 3.0	4.6	3.4	45	
SPINAF[26]	525	1.4 - 2.8	4.3	0.9	79	
AFASAK[27]	1007	2.8 - 4.2	5.5	2.0	58	Aspirin 75 mg, no benefit
SPAF[28]	1330	2.0 - 4.5	7.4	2.3	67	Aspirin 375 mg, associated with a 42% risk reduction
SPAF II[29]	1100	2.0 - 4.5	1.9 (aspirin)	1.3	67	

AFASAK = The Copenhagen AFASAK Study
BAATF = Boston Area Anticoagulation Trial for Atrial Fibrillation
CAFA = Canadian Atrial Fibrillation Anticoagulation
INR = international normalized ratio
SPINAF = Stroke Prevention in Nonrheumatic Atrial Fibrillation
SPAF = Stroke Prevention in Atrial Fibrillation
SPAF II = Stroke Prevention in Atrial Fibrillation II

CURRENT THERAPEUTICS

Preventing thromboembolism with chronic anticoagulation and antiplatelet therapy

The most serious complication of AF is thromboembolism which is frequently cerebral (> 90%) and may result in a large stroke (> 50%). In fact, recent studies have shown that stroke related to AF is usually more severe and is associated with two-fold increase in mortality as compared with stroke due to other aetiologies.[21,22] Most ischaemic strokes associated with AF are probably due to embolism of stasis-induced thrombi forming in the left atrium and particularly its appendage. However, perhaps 25% of AF associated with stroke is due to associated intrinsic cerebrovascular disease, other cardiac sources of embolism, or aortic arch atheroma.[23]

The high risk of thromboembolism in AF associated with valvular heart disease is well known. However, AF even in the absence of valvular disorders still carries a substantial risk of thromboembolism. The rate of stroke among elderly people with AF averages 3% to 7% per year, about six times that of people without AF.[23] Thus, prevention of thromboembolism is one of the most important considerations regarding long-term management of patients with AF. Anticoagulation with warfarin is highly effective for reducing stroke in AF patients. Five large, multi-centre randomized trial[24-29] using international normalized ratio (INR) ranges of approximately 1.8 to 4.2 showed a mean reduction in stroke of nearly 70% in patients assigned to receiving anticoagulation (**Table 7**). The incremental risk of serious bleeding was less than 1% per year. The risk reduction significantly outweighed the slightly increased risk of serious bleeding, especially in patients with coexistent risk factors for stroke. In a more generalized outpatient population, risk of bleeding may be greater and low-intensity anticoagulation (INR 2.0 to 3.0) clearly confers benefit.

The absolute rate of stroke varies importantly with patient age and coexistent cardiovascular disease. Stratification of AF patients into those at high and low risk thromboembolism is a crucial determinant of optimal anticoagulation prophylaxis (**Table 8**). The decision to anticoagulate a patient with AF must be individualized, and assessment of bleeding risk from anticoagulation must always be considered. For high risk group, anticoagulation with warfarin is recommended to achieve an INR of 2.0 to 3.0. In patient with lower risk of thromboembolism, anticoagulation is not required. Higher dose aspirin (325 mg daily) also reduces the risk of stroke, its effects are more modest (approximately 20% reduction) and should be considered in patients in whom anticoagulation is contraindicated or in low risk population. ■

Table 8: Risk stratification for thromboembolism in atrial fibrillation

High Risk Variables

1. **Structural heart disease risk factors**
   - Left ventricular systolic dysfunction
   - Left atrial enlargement
   - Congestive heart failure
   - Valvular heart disease
   - Coronary artery disease
2. **Systemic risk factors**
   - Age > 65 years
   - Prior thromboembolic event
   - Hypertension
   - Diabetes

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CURRENT THERAPEUTICS

Key messages

1. Atrial fibrillation (AF) is a common arrhythmia which carries doubled overall mortality and twofold increase in cardiovascular mortality.
2. The spectrum of symptomatology and presentation are broad, a thoughtful and individualized approach of management is essential
3. In every patients with AF, it is important to consider the possible underlying causes and precipitating factors.
4. In the majority of patients with chronic AF, control of ventricular rate and prevention of thromboembolism are the main goal of therapy.
5. However, in suitable patients with recent onset of AF and no contraindication for cardioversion, restoration and maintenance of sinus rhythm should be the preferred goal.

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