Reviews

Atrial Fibrillation in the Elderly

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Summary: The prevalence of atrial fibrillation is 11% in persons older than 70 years and rises to 17% in those aged 84 years or more. One-year mortality ranges from 0.2 to 16%, being highest in elderly patients, and is associated with a 4.8-fold increased risk of stroke. Atrial fibrillation can be cardioverted to normal sinus rhythm electrically or pharmacologically and rapid ventricular rate can be controlled with drugs. While anticoagulation prevents embolic events in those with atrial fibrillation, the decision to anticoagulate should be based on an assessment of the risk/benefit ratio.

Key words: atrial fibrillation, aged, epidemiology, electrophysiology, prognosis, management, anticoagulation

Introduction

Atrial fibrillation (AF) occurs in 0.4% of the adult population and in 2–4% of those > 60 years of age.[1,2] The prevalence of AF in healthy elderly persons > 70 years is 11% and rises to 17% by the age of 84 years.[3]

There are many different causes of AF (Table I), and the increased prevalence in the elderly is contributed to by the higher prevalence of these diseases. However normal aging of the heart also increases the risk of AF. Davies *et al.*[4] noted that the factors involved in the production of AF were atrial dilatation, sinoatrial nodal disease with muscle loss and fibrosis, and disruption of atrial muscle. Age-related changes include a gradu-

al loss of nodal fibers and an increase of fibrous and adipose tissue in the sinoatrial node. Other changes are focal myocardial fibrosis which is unrelated to coronary disease[5] and affects the ventricles. Decreased ventricular compliance due to fibrosis may contribute to the atrial enlargement which occurs with age[6,7] and predisposes to AF.[8] Focal deposits of amyloid are laid down in the atria with an increase in fat and fibrous tissue, and these also predispose to AF. Fatty metamorphosis probably contributes to the dilatation of the atria. Other changes such as mitral annular calcification predispose to the development of AF[9] and systemic emboli even without AF.[10] Atrial natriuretic peptide, which is released in increased amounts from the atria during AF[11] has reduced end-organ responsiveness in the elderly.[12] Its role in the presence of AF has still to be elucidated.

Epidemiology

The prevalence of AF is reported to be 2–3 per 1,000 at age 25 to 35 years, 30–40 per 1,000 at ages 55 to 64 years, and 50–90 per 1,000 at ages 62–90 years (Fig. 1). In the Framingham study, the occurrence, precursors, and prognosis of AF were examined in a 22–30 year follow-up of a cohort of 5,209 men and women aged 30–62 years at entry.[13–18] The incidence of AF was observed to increase with age, with a male predominance. The chance of developing AF over two decades was 2%.

The majority of cases of AF were related to a cardiovascular abnormality, and any cardiovascular disease increased the risk of AF by 3–5-fold. Coronary heart disease which is responsible for 8% of AF in men doubles the risk of developing AF in men, but no increased risk was shown in women. Atrial fibrillation is an uncommon presenting feature of myocardial infarction, but is a complication that occurs in 6–23% of cases of myocardial infarction. It is a marker of a more extensive myocardial infarct with ventricular dysfunction. Congestive heart failure, atrial infarction, and mitral regurgitation secondary to papillary dysfunction are other causes of AF in patients with ischemic heart disease. Rheumatic heart disease increases the risk of AF 8-fold in men and 27-fold in women. Hypertensive heart disease (responsible for 14% of AF) increases the risk of developing AF 4 times, and cardiac failure increases the risk 8 times in men and 14 times in women.

TABLE I   Causes of atrial fibrillation

Age-induced atrial changes
High atrial pressure, e.g., mitral valve disease, ventricular
    hypertrophy
Atrial ischemia
Inflammatory or infiltrative disease of the atria, e.g., pericarditis
Toxic effects, e.g., alcohol
Increased sympathetic activity, e.g., hyperthyroidism
Increased parasympathetic activity
Cardiac trauma, e.g., cardiac surgery
Congenital heart disease, e.g., atrial septal defect
Accessory pathways, e.g., Wolff-Parkinson-White syndrome
Idiopathic

FIG. 1   Prevalence of atrial fibrillation per thousand population. Data from Ref. 134.

There is a strong association between AF and pulmonary disease. In a series of patients presenting with AF, approximately 2–3% had underlying pulmonary disease.[19, 20] Hypoxia, respiratory acidosis, increased circulating catecholamines, involvement of the pericardium by the infective process, use of sympathomimetic drugs, and development of cor pulmonale predispose to AF. In the National Cooperation Study of Urokinase for Pulmonary Embolus,[21] only 3% of patients with pulmonary embolism had AF despite the fact that some had severe hemodynamic compromise.

Of men and women developing AF, 16.6% and 6%, respectively, had no underlying cardiovascular disease;[18] however, some had preexisting nonspecific abnormalities or intraventricular conduction delays. Important noncardiac causes of AF in the elderly are alcohol and hyperthyroidism. Both acute alcohol binges and long-term alcohol abuse predispose to the development of AF. Patchy inflammatory lesions are noted in the hearts of chronic drinkers,[22] and high doses of alcohol can prolong intra-atrial conduction, shorten the refractory period of atrial conduction, and therefore predispose the heart to AF.[23] The incidence of AF in patients with overt hyperthyroidism is approximately 10–20%,[24, 25] occurring more frequently in the elderly.[26, 27] Of ambulatory individuals over 75 years with hyperthyroidism, 11% have AF.[28] In the elderly, hyperthyroidism may be masked and not suspected and AF may be the presenting feature of this disease. Even though hyperthyroid-induced AF is uncommon (2–3% of cases of AF),[29–31] it is important to consider it as a cause as conversion and long-term maintenance of sinus rhythm can be expected if antithyroid treatment is started early.[25, 27, 32] Atrial fibrillation can occur secondary to various infections (pneumonia, empyema), toxic exposure, anesthetic agents, and metabolic abnormalities such as hypokalemia, hypocalcemia, hypomagnesemia, hypothermia, hypoxia, and hypoglycemia. Drugs such as beta₂ agonists,[33, 34] cold remedies, antihistamines, local anesthetics, and coffee can precipitate AF.[35]

Atrial fibrillation is a frequent complication of coronary artery bypass surgery and other types of cardiac surgery, especially valvular surgery. It occurs in 5–40% of patients and is more common in the elderly age groups.[36, 37] It is also seen quite commonly pos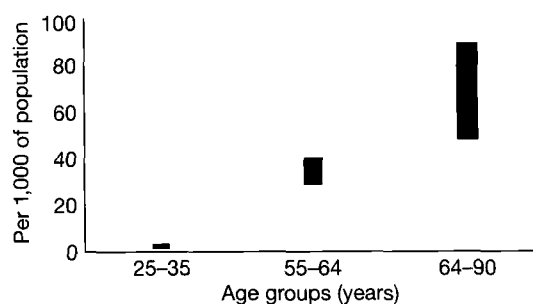t thoracotomy for lung operations, and in one recent study it occurred in up to 15% of patients post thoracic surgery for lung cancer.[38]

Prognosis

In a large series of 4,600 cases of AF, the 1-year mortality ranged from 0.2 to 16% and is highest in the elderly hospitalized patients with chronic AF.[2] In the Framingham study, AF was found to be associated with a doubled cardiovascular and all-cause mortality (Table II). Atrial fibrillation has been identified as the rhythm disturbance responsible for more than 85% of systemic thromboembolism from the heart.[39] The brain is the target in more than two thirds of all clinical embolic events.[40, 41] Aberg demonstrated a 7.5% incidence of right atrial thrombus at necroscopy in patients with nonrheumatic AF compared with a 1% incidence in those not in AF.[40] The role of AF as a cause of pulmonary embolus has still to be elucidated.

Atrial fibrillation is associated with a 4.8-fold increased risk of stroke (Fig. 2),[15] and this effect is independent of other cardiovascular abnormalities.[14] While other cardiovascular contributors have decreasing influence on the development of stroke with advancing age, AF has a constant influence into the ninth decade (Fig. 3).[14] Since the prevalence of AF is much greater in the elderly, the proportion of strokes associated with

TABLE II   Mortality among male and female participants who developed atrial fibrillation during a 22-year follow-up period in the Framingham study

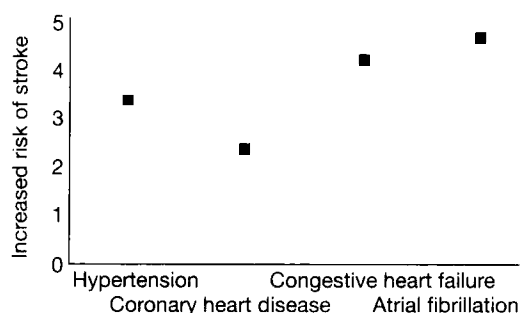| Mortality	Male		Female	
	Cases	Controls	Cases	Controls
Total deaths	59.2%	34.3%	44.9%	25.3%
Deaths from cardiocascular causes	43%	21%	40.8%	15.1%

Source: Ref. 13.

FIG. 2   Risk of stroke in women and men, aged 50–89 years, by cardiovascular abnormality. Data from Ref. 15.
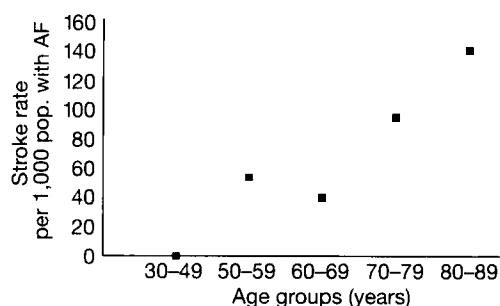

FIG. 3   Stroke incidence in patients with atrial fibrillation according to age. Data from Ref. 134.

AF increases from about 7% at ages 50–59 years to 36% at ages 80–89 years. Atrial fibrillation increases the risk of a recurrent stroke more than two-fold, most of these occurring within 6 months after the initial event.[17] The risk of peripheral embolism is also increased in AF, occurring at approximately 2% per year compared with 4–6% per year for strokes. The prognosis for patients with idiopathic AF appears to be excellent in the young, but there is an increased incidence of stroke and mortality in elderly patients.[18]

Electrophysiology of Atrial Fibrillation

Reentrant mechanisms are involved in the genesis and maintenance of AF.[42, 43] Reentry rhythm is facilitated by a conduction block and a depolarizing wave with a short wavelength. Wavelength is directly proportional to the conduction velocity and refractory period of the wave.[44] Short wavelengths require small areas of conduction block to establish a reentry circuit, and since conduction block is more likely to occur in the atria in small areas, short wavelengths are more likely to initiate and maintain AF. A critical number (between 4 and 6) of these small waves (known as wavelets) is required to maintain AF in dogs. Therefore, atrial waves with low conduction velocity and short refractory periods predispose to the development of AF. Indeed, studies have shown that persons with AF demonstrate reduced resting membrane potential and therefore slow conduction velocity,[45] and they also have shorter refractory periods[46] and increased dispersion of refractory periods.[47] These electrophysiologic abnormalities predispose to the development and maintenance of AF. Aging has been shown to prolong the refractory period[48–51] and also to increase the dispersion of refractoriness.[52]

Other studies have shown that patients with a history of AF have an abnormal increase in atrial conduction time when early cycle premature atrial beats are induced during the atrial relative refractory period.[53] The ability to induce AF with the early premature beat increases with age, left atrial size, P-wave duration, and excessively short refractory period.[53]

Programmed atrial stimulation can induce electrophysiologic changes such as fragmented atrial activity, interatrial conduction delay, and repetitive atrial firing. These phenome-

na may indicate a predisposition to AF.[54–63] However, studies comparing younger and older patients showed no increased prevalence of these factors in the older age groups.[64] They did show that the coupling interval to develop these electrophysiologic changes was increased in the elderly, suggesting that a wider range of premature beats might initiate AF.[64]

In paroxysmal AF, where there is no detectable cardiac disease, invasive studies have shown increased conduction delay and fragmentation in early stimulated atrial beats.[61, 65, 66] Noninvasive studies have also shown that signal-averaged P-wave duration is significantly increased in patients with paroxysmal AF.[67]

Stimulation of the vagus nerve shortens the refractory period and can initiate and maintain AF. Vagally mediated AF is more common in women than in men with a ratio of 4:1. It normally starts between the ages of 25 and 60 years, and there is a low tendency to develop chronic AF. The role of the autonomic nervous system in AF in the elderly is not clear, and studies have shown an exaggerated shift toward sympathetic activity and a reduction in parasympathetic activity with age.[68, 69] There is some evidence that the autonomic nervous system has a role to play in many cases of paroxysmal AF.

In one group of patients, paroxysmal AF occurs at times of high vagal tone, for example, after a meal or when at rest or asleep. One suggestion is that these patients have increased vagal tone and they do respond to antiarrhythmic drugs with anticholinergic properties. Exercise-induced AF is less common, but is responsive to beta blockade. There is also a group of patients who have a mixed picture of vagal and adrenergic AF and in this group autonomic imbalance probably is more important than vagal or sympathetic drive alone. Clinical trials are now underway to compare beta blockade with anticholinergic drugs in cases of paroxysmal AF.

Management of Atrial Fibrillation

Frequently, AF is diagnosed in the elderly as an irregular heart rate in an asymptomatic patient. All such patients should have a 12-lead electrocardiogram (ECG) to document the arrhythmia and biochemical blood tests including thyroid function tests. However, they may also present with symp-

toms of AF such as palpitations, lightheadedness, chest pain, fatigue, or more severe problems such as dyspnea, heart failure, angina, syncope, or confusion. The extent of the symptoms is dependent on the patient's heart rate, the nature of the underlying heart disease, and the precipitating factors causing AF. The most common precipitating factors are respiratory disease, acute myocardial infarction, cardiothoracic surgery, and hyperthyroidism, and sometimes removal of the precipitant can lead to spontaneous cardioversion. However, even when a precipitating factor is obvious, cardioversion may be required urgently if the patient is hemodynamically compromised.

History and physical examination are of value in eliciting the cause of AF and may lead to the diagnosis of conditions such as mitral stenosis, hyperthyroidism, alcohol-induced AF, and also precipitating factors such as a respiratory tract infection. Ambulatory 24-h ECG monitoring is necessary at times to determine the period of time a person is in AF and whether the ventricular rate is well controlled, and may demonstrate underlying sinus node disease. Echocardiography permits accurate cardiac diagnosis and sometimes suggests that antiarrhythmic drugs with a negative inotropic effect should not be prescribed to those patients with impaired ventricular function. Echocardiography can identify patients at high risk of developing intra-atrial thrombi and who need long-term anticoagulation. Mitral stenosis, poor left ventricular function, prosthetic heart valves, and the presence of left atrial thrombus are strong indicators for anticoagulation in AF. Spontaneous contrast is a cloud of intra-atrial echos with slow circular movements that change in confirmation and acoustic density. It is thought to be due to red cell and platelet aggregations[70] and is a marker for an increased risk of thromboembolism.[71] Improved sensitivity of left atrial thrombus is achieved by transesophageal echocardiography.[72] The left atrial appendage is a cul-de-sac with trabeculated ridges from pectinate muscle and does not contract during AF. This predisposes to thrombus formation, and transesophageal echocardiography is better than transthoracic echo at demonstrating this area. Prospective studies are needed to assess whether transesophageal echo should be performed in all patients with AF and to determine whether only some patients require anticoagulation based on echocardiographic findings of left atrial thrombus, left atrial spontaneous contrast, or poor left atrial appendage contraction.

Electrical Cardioversion of Atrial Fibrillation

This involves delivery of an electrical impulse to the heart, synchronized to the QRS complex to avoid the vulnerable period of the cardiac cycle.[73, 74] The patient is sedated, usually with a benzodiazepine such as midazolam, and serum potassium should be at or above 4 mM, especially in patients on antiarrhythmic drugs such as the class 1 antiarrhythmics. Digoxin does not need to be withheld unless the serum drug level is above the therapeutic range. If the patient is taking anticoagulants, it is essential to check that there is adequate anticoagulation. About 90% of patients cardiovert successfully, but the

duration of sinus rhythm varies from a few seconds to permanent resumption. The energy required to cardiovert is related to the duration of the arrhythmia.[75]

Elderly patients often have a slow ventricular response to AF without digoxin therapy suggesting a damaged or diseased atrioventricular (AV) node; often sinus node disease is also present. Therefore, when cardioverted, such patients frequently have periods of sinus arrest with a slow escape rhythm that gradually gives way to sinus bradycardia and finally a normal rhythm. If cardioversion is deemed necessary in an elderly patient with known sick sinus, introduction of a temporary pacing wire prior to cardioversion or external pacing is recommended after cardioversion.

Anticoagulation is required for at least 3 weeks prior to elective cardioversion and 3 weeks following cardioversion. The incidence of thromboembolic events in nonanticoagulated patients undergoing cardioversion is 5.3%, and it is 0.8% in those who are anticoagulated.[76] It is prudent to consider anticoagulation in all patients who present with AF and who are candidates for cardioversion. However, if the AF is definitely of less than 3–4 days' duration and there is no underlying structural heart disease, such as valvular heart disease, dilated cardiomyopathy, or hypertrophic cardiomyopathy, there may be no reason to anticoagulate fully with warfarin, and short-term heparinization could be carried out prior to cardioversion.

Even though short-term success rates with cardioversion of chronic AF are good, in the long term many patients revert back to AF. One study showed that by 3 months only 30% patients and at 1 year only 25% were still in sinus rhythm.[77] A study by Van Gelder et al. in 1991 showed that the duration of the arrhythmia and the patient's age determined conversion rates, whereas functional class and the presence or absence of rheumatic mitral valve disease predicted the length of the arrhythmia-free episode.[78] The 1-year success rate of initial cardioversion in the presence of antiarrhythmic drugs, for example, class 1a, 1c, and class 3 drugs varies but is approximately 50%.[79] Class 1a and class 3 drugs may be effective if the arrhythmia depends on shortening of refractoriness, and class 1c drugs may act by suppressing arrhythmogenic premature beats or by rate-dependent prolongation of refractoriness.[80] One recent trial carried out by Crijns et al. demonstrated that an older age, a large number of previous episodes of arrhythmia, a long previous duration of arrhythmia, and the presence of mitral valve disease were predictive of medical refractoriness during serial treatment.[81] However, a trial to determine the value of electrical cardioversion and oral antiarrhythmics versus long-term anticoagulation and rate control has not been carried out. Many physicians feel that there is no justification for using class 1 antiarrhythmic drugs in the elderly after successful electrical cardioversion, as side effects are common and recently the long-term use of such drugs has been shown to be associated with an increased mortality.[82] Several groups have suggested that left atrial dimensions ≥ 45 mm are associated with a low likelihood of pharmacologic and electrical cardioversion and will also predict successful maintenance of sinus rhythm.[83–85] With the use of amiodarone and class 1c agents, success rates with cardioversion and long-term main-

tenance of sinus rhythm are good up to a left atrial dimension of 60 mm.[86]

If external electrocardioversion fails, shocks delivered between a catheter within the right atrium and a body surface anode have a higher efficacy, especially if patients are pretreated with amiodarone.[87] In the elderly if the onset of AF is recent and a precipitating cause has been sought and eliminated, electrical cardioversion may be adequate to maintain the patient in sinus rhythm for some time.

Paroxysmal Atrial Fibrillation

In the presence of a definite autonomic pattern to the paroxysms of AF, beta blockade (in those with a clear history of exercise-induced AF) or anticholinergic drugs such as disopyramide or quinidine (when there are paroxysms during periods of high vagal tone) should be used. Flecainide, propafenone, and sotalol have been shown to reduce the incidence of AF,[88, 89] but these drugs have side effects and may aggravate arrhythmias. Prophylactic digoxin does not lower the ventricular rate at the onset of AF.[90] In the elderly, low-dose amiodarone or sotalol may be used as they are also effective against hypertension (sotalol) and angina (sotalol and amiodarone) which are common in this age group.

In the sick sinus syndrome, pacing and antiarrhythmic drugs may be necessary and, as ventricular pacing promotes AF, pacing should be atrial or dual-chamber.

Pharmacologic Cardioversion

The antiarrhythmic drugs are classified according to the Vaughan Williams classification[91] (Table III). The most effective agents for termination and prevention of AF are those of classes 1a, 1c, and 3. Up to 70% of patients may cardiovert with these drugs alone and they may also be used to maintain sinus rhythm after successful cardioversion.

Class 1a: These drugs work primarily by blocking the fast sodium channels, reducing the upstroke velocity of phase 0 of the action potential, and reducing the velocity of the impulse conduction through the myocardium. This is manifested as a widening of the QRS complex on the ECG. They also prolong myocardial refractoriness, reducing myocardial excitability. Repolarization time is extended and this is manifested as an increased QT interval. Some class 1 drugs such as quinidine and disopyramide depress the action of the vagus nerve on the atrial tissue. Quinidine and disopyramide also exert more effect on atrial tissue than does procainamide and are therefore more important in the treatment of AF.[92]

Quinidine is used to cardiovert AF and to maintain sinus rhythm. It is associated with a high incidence of side effects, mostly gastrointestinal and anticholinergic in origin.[93] Cinchonism is a dose-related toxic side effect. A meta-analysis of quinidine use in AF showed that sinus rhythm was maintained in 67, 58, and 50% of patients 3, 6, and 12 months post successful cardioversion, respectively, compared with 45, 35, and 25%, respectively, in the control group.[94] However, the total

mortality in the quinidine group was 2.9% compared with 0.8% in the control group. Quinidine prolongs the QT interval and predisposes to torsade de pointes, and while treatment is effective in maintaining sinus rhythm it is also associated with increased mortality.

Disopyramide is effective in cardioversion of AF and maintenance of sinus rhythm; however it is negatively inotropic and should only be used in patients with good left ventricular function. Other important side effects are related to its anticholinergic properties. Prolongation of the QT interval and torsade de pointes occur but are less common than with quinidine.[95, 96] Disopyramide may be specifically indicated for the treatment of paroxysmal AF which is vagal in origin.

Procainamide is not as effective in atrial arrhythmias as the other class 1a agents, and long-term use leads to side effects such as a lupus-like syndrome and, rarely, agranulocytosis.

Class 1b: These agents have no substantial effects on atrial tissue and are therefore not useful in the treatment of AF.

Class 1c: These agents slow the upstroke of phase 0 of the action potential and prolong intraventricular conduction. However, unlike class 1a drugs, they have no effect on repolarization time and therefore do not extend the QT interval.

Flecainide is beneficial in converting AF to sinus rhythm. When given intravenously, approximately 80% of patients cardiovert if the duration of AF is < 24 h.[97] Quinidine appears to be more effective than flecainide (but neither are very effective) in cardioverting patients with chronic AF, while these drugs are equally effective in patients with recent-onset AF.[98] Flecainide is a potent, negatively inotropic agent and must not be prescribed to patients with poor ventricular function. Flecainide and encainide can provoke serious ventricular arrhythmias in patients taking the drugs prophylactically.[99, 100]

Table III Antiarrhythmic drugs

Class	Action	ECG	Drugs
1: Membrane stabilizers	Sodium ion inhibition		
1a	Reduction in upstroke velocity; prolongs repolarization	QRS widen QT lengthen	Quinidine
			Procainamide
			Disopyramide
1b	No change in upstroke velocity or repolarization	None	Lignocaine Mexitiline
1c	Reduction in upstroke velocity; no change in repolarization	QRS widen	Encainide Flecainide Propafenone
2: Beta blockers	Block catecholamine action	Bradycardia PR increase QT decrease	Propranolol Acebutolol Atenolol
3: Anti-arrhythmics	Block potassium efflux; prolong repolarization	QT increase	Amiodrone Sotalol
4: Ca-channel blockers	Blocks calcium channels	PR increase	Verapamil Diltiazem

Abbreviations: ECG = electrocardiogram, CA = calcium.

Propafenone seems to be effective in maintaining sinus rhythm after electrical cardioversion. When given intravenously, cardioversion occurs in >70% of patients if AF has been present for < 48 h, but in only 26% if AF has persisted for longer.[101] Aggravation of arrhythmia occurs, but the incidence seems to be lower than that reported with encainide and flecainide.[102]

Class 3: These agents block outward potassium currents leading to a prolonged repolarization phase of the action potential and increased myocardial refractoriness and QT interval prolongation.

Amiodarone prolongs repolarisation but also has a mild sodium-channel blocking effect, a noncompetitive beta-blocking effect, and a calcium-channel blocking effect. It requires a substantial loading dose because adipose tissue forms an extensive volume of distribution for the drug and must be saturated before measurable concentrations appear in the serum or the myocardium.[103] Amiodarone has many side effects, including gastrointestinal upset, headaches, weakness, myalgias, nightmares, hypo/hyperthyroidism, abnormal liver function, pulmonary fibrosis, and eye and skin abnormalities. Recurrence of AF, after successful electrocardioversion, was suppressed in 78% of patients taking amiodarone in one trial, after trying on average three other drugs prior to amiodarone.[104] Age was not predictive of the response to amiodarone. Even though amiodarone prolongs the QT interval, the incidence of torsade de pointes on amiodarone is rare.

Bepridil is another class 3 agent and, although in one study it cardioverted more patients than did amiodarone (64 vs. 40%), it was associated with ventricular arrhythmias and torsade de pointes.[105]

Sotalol is a racemic mixture of d and l stereoisomers; the d isomer has class 3 properties and the l isomer has beta-blocking activity and class 3 properties. Sotalol is as effective as quinidine at maintaining sinus rhythm after successful cardioversion, but those taking sotalol have fewer side effects and if AF recurs the ventricular rate is slow and symptoms are less frequent.[106] However, the antiarrhythmic potential of sotalol has yet to be elucidated.

Beta blockers have not been shown to cardiovert AF to sinus rhythm. However, propranolol reduces the incidence of AF post coronary artery bypass grafting from 18 to 8%.[107] Beta blockers may also play a specific role in potentiation of the effects of the class 1 agents.

Calcium-channel blockers: There is little evidence that verapamil can cardiovert AF, but it is as effective as quinidine in the maintenance of sinus rhythm after cardioversion.[108] The rate of recurrence of AF after cardioversion is high if no antiarrhythmics are given. There are side effects associated with all antiarrhythmic agents, and the CAST study[82] raised a number of concerns about the use of class 1c, and perhaps all class 1 agents.

In the elderly patient, the side effects of these antiarrhythmic drugs are very important to consider as the elderly are more likely to have concomitant disease and may also be on other medication which may interact with the antiarrhythmic drugs. In an elderly patient with asymptomatic AF who has

been successfully cardioverted, it is hard to justify the use of antiarrhythmic drugs that have side effects when the benefits of these drugs have not been specifically evaluated in the older age groups.

Control of Ventricular Rate in Atrial Fibrillation

The ventricular rate response to AF is dependent on the refractory period of the AV node and the concealed conduction within the AV node. The AV nodal filter function is in turn dependent upon the relative degree of autonomic tone, the presence of endogenous catecholamines, and a variety of pharmaceuticals. Ventricular rates at rest < 90/min suggest AV nodal damage or disease, whereas more rapid rates may indicate increased catecholamines/adrenergic sensitivity due to conditions such as thyrotoxicosis, pyrexia, heart failure, or dehydration. Mean ventricular rates in untreated patients are between 100 and 160 beats/min. There is loss of the "atrial kick," decreased diastolic filling of the ventricles, and an increased oxygen demand with fast AF, and this may precipitate myocardial ischemia. In the elderly with a noncompliant left ventricle due to long-standing hypertension or myocardial ischemia, there may be a significant elevation of left atrial pressure and consequent pulmonary edema. A poorly controlled ventricular rate in AF can lead to ventricular dysfunction, and one study showed that patients with an ejection fraction < 35%, who underwent catheter ablation for poorly controlled AF, had a rise in mean ejection fraction from 25 to 45%.[109]

It is not possible to generalize about an optimal heart rate in AF, but generally the resting heart rate should be < 90 beats/min to maintain good cardiac output. While in young people with AF control of the ventricular rate during exercise is an important issue, in the elderly this becomes less relevant. However, acute control of heart rate in the elderly with new onset AF may be urgent, as the tachycardia may precipitate pulmonary edema.

Digoxin: The main effect of digoxin in AF is to slow the ventricular rate. It is vagotonic and mediates its effect by slowing AV nodal conduction and increasing AV nodal refractoriness.[110-112] It has no effect on the sympathetic nervous system and, if catecholamine levels are high, digoxin will be ineffective. Digoxin also has a positive inotropic effect on the heart[113] and its use is appropriate for rate control in patients with impaired left ventricular function, congestive cardiac failure, and AF. Failure to control the rate with adequate doses of digoxin (1 mg over 24 h) may indicate intrinsic or drug-induced hyperadrenergic states. Digoxin can be combined with either a beta blocker or a calcium-channel blocker to control the ventricular rate. Most elderly patients requiring digoxin for initial rate control can be maintained on the drug as monotherapy. Prophylactic digoxin does not lower the ventricular rate at the onset of paroxysmal atrial fibrillation.[90]

Beta blockers are effective in slowing the ventricular response to exercise in those with AF. In thyrotoxicosis-induced AF, beta blockade is the treatment of choice. However, unsuspected heart failure may be exacerbated by their negative in-

otropic effect. Xamoterol has selective beta-1 receptor partial agonist properties at low levels of sympathetic activity, but it acts as a competitive antagonist at high levels of sympathetic activity such as during exercise. However, one large multicenter trial of xamoterol in heart failure was associated with increased mortality despite symptomatic improvement.[114]

Calcium-channel blockers are also used to control heart rate especially in those patients who cannot tolerate beta blockers, for example, patients with asthma and chronic obstructive airways disease. In the elderly, digoxin is often sufficient to control heart rate in AF, but adjunctive therapy may be necessary. Other antiarrhythmics such as amiodarone can be used, but the disadvantages of this drug are its long half life and potential toxic side effects.

Pacemakers in Atrial Fibrillation

Atrial fibrillation is commonly associated with conduction system disease of the heart, and the treatment of AF interferes with the conduction system. Elderly patients with AF with or without treatment may have significant pauses on their 24-h ECG. One study showed daytime pauses of up to 2.8 s and nighttime pauses up to 4 s or longer and concluded that such findings do not require a pacemaker in asymptomatic patients.[115] Patients with cerebral symptoms and AF frequently have long pauses (>2 s) on 24-h tapes, but they generally do not need a pacemaker unless symptoms correlate with pauses. Resolution of symptoms is common and pacing has not been shown to affect survival.[116] Indications for pacemakers include tachy-bradycardia syndrome when pauses after AF occur, and when drugs are given to control the AF the pauses can become longer. Permanent pacemakers abolish pause-related symptoms. After catheter ablation of the AV node a permanent pacemaker is required; it is also required in the person who has a slow ventricular rate at rest but who needs drugs for exertionally induced tachycardia. These include beta blockers and calcium-channel blockers which suppress AV nodal conduction and can cause symptomatic bradycardia at rest. Some elderly patients require beta blockers or calcium-channel blockers for severe angina or hypertension and these can slow the heart rate sufficiently to cause symptoms. A permanent pacemaker may be needed to control the symptoms. Temporary pacemakers are required when electrocardioversion is being carried out in patients known to have sick sinus syndrome or advanced AV nodal disease indicated by a slow ventricular response. Cardioversion may lead to long asystolic pauses or bradycardia causing clinical deterioration in patients with sick sinus syndrome, and this can be prevented by a temporary pacemaker.

Dual-chamber or atrial pacemakers are preferred in patients with paroxysmal AF who need to be paced for other reasons because the incidence of chronic AF, thromboembolism, and heart failure is increased in ventricularly paced patients. The reason for this is probably multifactorial and includes loss of atrial contraction, increased atrial pressure due to loss of AV synchrony, and retrograde stimulation of the atria.

Rate-responsive pacing is preferred to fixed-rate pacing in patients with AF with a slow resting heart rate and a blunted ventricular response to exercise.

Other Forms of Treatment

In some patients, control of the ventricular rate is difficult with standard medical therapy and in these catheter ablation of the AV node should be considered. Catheter ablation of an accessory pathway is particularly useful in the prevention of AF in persons with Wolff-Parkinson-White (WPW) syndrome. The prevalence of AF in patients with WPW syndrome and with symptoms of arrhythmia has been shown to be 10 to 35%.[117-121] Atrial fibrillation is more common as patients age. Treatment with digoxin or verapamil to slow the ventricular rate during fast AF can paradoxically speed the ventricular rate in WPW syndrome and therefore these drugs are contraindicated in this condition.

A recent study on 14 consecutive patients with drug-resistant AF (mean age 65 ± 3 years) showed improved control of the ventricular rate and an increased improvement in cardiac performance after AV node ablation, using radiofrequency current and pacemaker implantation.[122]

The corridor and maze procedure are two surgical operations which attempt to cure AF. The corridor procedure isolates a segment of tissue (connecting the sinus to the AV node) from the rest of the fibrillating atria, and the maze procedure abolishes AF by placing sufficient incisions in the atria to prevent reentry excitation sufficient to perpetuate AF. With the corridor procedure, the irregular heart beat of AF is eliminated but it does not restore AV synchrony and the left atrium can continue to fibrillate, thereby not reducing the risk of thromboembolism. The maze procedure theoretically can restore sinus rhythm, maintain normal hemodynamics, and reduce the risk of thromboembolism; however, a permanent pacemaker is often needed after the procedure.[123]

Anticoagulation Therapy in Atrial Fibrillation

There is a 4–5% annual incidence of stroke in patients with nonrheumatic AF and a 17% incidence of stroke in patients with rheumatic AF. The risk of stroke in patients with AF increases with age (Fig. 3). Of all ischemic strokes, 15–20% are attributed to AF, that is, cardiac embolism is assumed to be the cause.[124, 125] The incidence of embolic complications during paroxysmal AF is 2%, but after transition to chronic AF the incidence rises to 5%.[126]

Prevention

The Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) compared low-dose warfarin with placebo in nonrheumatic AF and found that the risk reduction of stroke was 86% in warfarin users (0.4 vs. 3%). This study also found a significantly lower mortality among warfarin users.[127] The Copenhagen AFASAK trial recruited an older age group (av-
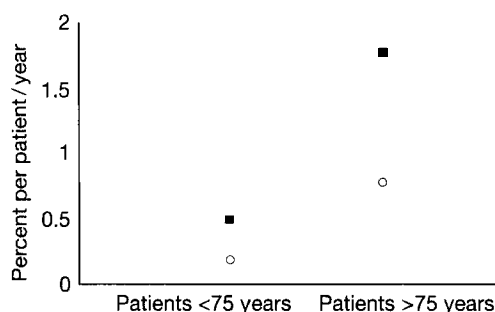
FIG. 4   Rates of intracranial hemorrhage according to antithrombotic therapy and age. ■ = Warfarin, ○ = aspirin 325 mg. Data from Ref. 131.

erage 74 years) but also showed a reduction in stroke in patients taking warfarin. There was no benefit in patients taking 75 mg of aspirin,[128] and no statistically significant reduction in mortality in those taking warfarin. The Stroke Prevention in Atrial Fibrillation trial (SPAF) also showed a 67% reduction in stroke in patients taking warfarin and some benefit in those under the age of 75 years taking 325 mg/day of aspirin.[129] One study showed that age > 75 years and elevated systolic blood pressure to be significant risk factors for the development of stroke in AF.[130] The rate of intracranial bleeding, the most feared complication of anticoagulation trials, was < 0.5% per year with little or no additional bleeding at other sites.

The results of the recent SPAF 2 trial have recently been reported.[131] In this study, warfarin was compared with aspirin for the prevention of ischemic stroke and systemic thromboembolism. Entry criteria were not as rigid as those in other anticoagulation trials and therefore elderly people with hypertension were included. The rates of major hemorrhage among patients aged > 75 years on aspirin and warfarin were 1.6 and 4.2% per year, respectively (compared with 0.9 and 1.7% in the < 75 years group), and the rates of intracranial hemorrhage in those on warfarin were 1.8% in the > 75 years group and 0.5% in the younger group (Fig. 4). In this trial higher degrees of anticoagulation were used compared with the other anticoagulation trials. Warfarin was particularly beneficial versus aspirin if the patient had a clinical risk factor for thromboembolism (history of hypertension, recent heart failure or previous thromboembolism).

When cardioverting a patient with chronic AF either electrically or pharmacologically, it is necessary to anticoagulate. Cardioversion carries a 3–6% risk of thromboembolism when anticoagulation is not used. How long prior to cardioversion a patient needs to be anticoagulated is not clear, but most physicians anticoagulate for about 3 weeks. Manning et al.[132] showed that it takes approximately 3 weeks after cardioversion for atrial function to resume, and as poor atrial function can predispose to thrombi it is probably necessary to anticoagulate for at least 3 weeks after cardioversion.

All elderly patients with AF should be assessed for risk of thromboembolism (clinically and echocardiographically), and if they are at high risk, warfarin should be considered.

The decision to anticoagulate should be based on an assessment of the risk/benefit ratio. The risk of bleeding is increased with uncontrolled hypertension, preexisting coagulation disorders, and in the presence of other conditions predisposing to hemorrhage. Age itself is not a contraindication to prophylactic oral anticoagulation.[133] However, care must be taken that accurate follow-up can be made and that there are no contraindications to anticoagulation. The necessary range of the International Normalized Ratio is still unclear but lower intensities of anticoagulation will reduce the incidence of hemorrhage in the elderly.

While patients with nonrheumatic AF and a history of peripheral embolus are usually anticoagulated long-term, the case is not that clear for patients with AF presenting with a pulmonary embolus.

Conclusions

Atrial fibrillation increases with age and is therefore relatively common in the elderly. It is associated with increased mortality and morbidity and may account for 15% of all strokes. Treatment of atrial fibrillation is difficult in the elderly as they are more difficult to cardiovert and to maintain in sinus rhythm. The drugs that are used to cardiovert atrial fibrillation are not without side effects as are the anticoagulants which are used to prevent thromboembolism.

Controlling the ventricular rate in atrial fibrillation can improve the ejection fraction, but sometimes this is difficult with standard medical therapy and catheter ablation of the atrioventricular node and other forms of surgical techniques should be considered.

There are many diseases which cause atrial fibrillation, and prevention of this arrhythmia depends partly on reducing the prevalence of these diseases. Aging predisposes to atrial fibrillation and perhaps, if this process could be elucidated and reversed in the heart, many elderly would not experience the morbidity associated with this common arrhythmia.

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