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Atrial Fibrillation: The New Epidemic of the Ageing World

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Abstract

The prevalence of atrial fibrillation (AF) increases with age. As the population ages, the burden of AF increases. AF is associated with an increased incidence of mortality, stroke, and coronary events compared to sinus rhythm. AF with a rapid ventricular rate may cause a tachycardia-related cardiomyopathy. Immediate direct-current (DC) cardioversion should be performed in patients with AF and acute myocardial infarction, chest pain due to myocardial ischemia, hypotension, severe heart failure, or syncope. Intravenous beta blockers, diltiazem, or verapamil may be administered to reduce immediately a very rapid ventricular rate in AF. An oral beta blocker, verapamil, or diltiazem should be used in persons with AF if a fast ventricular rate occurs at rest or during exercise despite digoxin. Amiodarone may be used in selected patients with symptomatic life-threatening AF refractory to other drugs. Digoxin should not be used to treat patients with paroxysmal AF. Nondrug therapies should be performed in patients with symptomatic AF in whom a rapid ventricular rate cannot be slowed by drugs. Paroxysmal AF associated with the tachycardia-bradycardia syndrome should be treated with a permanent pacemaker in combination with drugs. A permanent pacemaker should be implanted in patients with AF and symptoms such as dizziness or syncope associated with ventricular pauses greater than 3 seconds which are not drug-induced. Elective DC cardioversion has a higher success rate and a lower incidence of cardiac adverse effects than does medical cardioversion in converting AF to sinus rhythm. Unless transesophageal echocardiography has shown no thrombus in the left atrial appendage before cardioversion, oral warfarin should be given for 3 weeks before elective DC or drug cardioversion of AF and continued for at least 4 weeks after maintenance of sinus rhythm. Many cardiologists prefer, especially in elderly patients , ventricular rate control plus warfarin rather than maintaining sinus rhythm with antiarrhythmic drugs. Patients with chronic or paroxysmal AF at high risk for stroke should be treated with long-term warfarin to achieve an International Normalized Ratio of 2.0 to 3.0. Patients with AF at low risk for stroke or with contraindications to warfarin should be treated with aspirin 325 mg daily.

Key Words: atrial fibrillation; beta blockers; stroke; cardiovascular disease; cardioversion; digoxin; radiofrequency catheter ablation; pacemakers; antiarrhythmic drugs; warfarin; aspirin.

Introduction

Atrial fibrillation (AF) is a cardiac rhythm which has irregular undulations of the baseline electrocardiogram (ECG) of varying amplitude, contour, and spacing known as fibrillation waves, with the atrial rate between 350 and 600 beats per minute. The fibrillatory waves are seen best in leads V1, II, III, and aVF. The fibrillation waves may be large and coarse, or they may be fine with an almost

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flat ECG baseline. The ventricular rate in AF is irregular unless complete atrioventricular (AV) block or dissociation is present. The contour of the QRS complex in AF is normal unless there is prior bundle branch block, an intraventricular conduction defect, or aberrant ventricular conduction.

AF is associated with a slow regular ventricular response, there is complete AV block with an AV junctional escape rhythm or idioventricular escape rhythm. Myocardial infarction, degenerative changes in the conduction system, and drug toxicity such as digitalis toxicity are major causes of complete AV block. If AF is associated with a regular ventricular response between 60 to 130 beats per minute, there may be complete AV dissociation with an accelerated AV junctional rhythm caused by an acute inferior myocardial infarction, digitalis toxicity, open heart surgery, or myocarditis, usually rheumatic. Regularization of the ventricular response in AF may also occur in patients with complete AV dissociation due to ventricular tachycardia or a ventricular paced rhythm.

Prevalence

AF is the most common sustained cardiac arrhythmia. The prevalence of AF increases with age.[1-5] In the Framingham Study, the prevalence of chronic AF was 2% in persons aged 60 to 69 years, 5% in persons aged 70 to 79 years, and 9% in persons aged 80 to 89 years.[1] In a study of 2,101 persons, mean age 81 years, the prevalence of chronic AF was 5% in persons aged 60 to 70 years, 13% in persons aged 71 to 90 years, and 22% in persons aged 91 to 103 years.[2] Chronic AF was present in 16% of 1,160 men, mean age 80 years, and in 13% of 2,464 women, mean age 81 years.[3] In 5,201 persons aged 65 years and older in the Cardiovascular Health Study, the prevalence of AF was 6% in men and 5% in women.[4] In 1,563 persons, mean age 80 years, living in the community, the prevalence of chronic AF was 9%.[5] In the Cardiovascular Health Study, the incidence of AF was 19.2 per 1,000 person-years.[6] As the population ages, the burden of AF in the United States and worldwide will increase. In fact, AF has been described as an epidemic due to its increasing prevalence in the ageing population.[7] AF may be paroxysmal or chronic. Episodes of paroxysmal AF may last from a few seconds to several weeks. Sixty-eight percent of persons presenting with AF of less than 72 hours duration spontaneously converted to sinus rhythm.[8] Episodes of persistent AF last longer than 7 days but less than 1 year. AF in which cardioversion has failed or lasts longer than 1 year is usually termed permanent.

Predisposing Factors

Multiple, small reentrant circuits arising in the atria, exhibiting variable wave lengths, colliding, being extinguished, and arising again usually cause AF.[9] Rapidly firing foci are commonly located in or near the pulmonary veins and may also cause AF.[10] Factors responsible for onset of AF include triggers that induce the arrhythmia and the substrate that sustains it. Atrial inflammation or fibrosis acts as a substrate for the development of AF. Triggers of AF include acute atrial stretch, accessory AV pathways, premature atrial beats or atrial tachycardia, sympathetic or parasympathetic stimulation, and ectopic foci occurring in sleeves of atrial tissue within the pulmonary veins or vena caval junctions.[11] Predisposing factors for AF include age, alcohol, aortic regurgitation and stenosis, atrial septal defect, autonomic dysfunction, cardiac or thoracic surgery, cardiomyopathies, chronic lung disease, cocaine, congenital heart disease, coronary artery disease (CAD), congestive heart failure (CHF), diabetes mellitus, drugs (especially sympathomimetics), emotional stress, excess coffee, hypertension, hyperthyroidism, hypoglycemia, hypokalemia, hypovolemia, hypoxia, left atrial enlargement, left ventricular (LV) dysfunction, LV hypertrophy, male gender, mitral annular calcium (MAC), mitral stenosis and regurgitation, myocardial infarction (MI), myocarditis, neoplastic disease, obesity, pericarditis, pneumonia, pulmonary embolism, rheumatic heart disease, sick sinus syndrome, smoking, systemic infection, and the Wolff-Parkinson-White (WPW) syndrome. Obesity has been reported to increase the risk of developing AF by 49% in the general population.[12] This study was commented on by Banach et al.[13] Signal-averaged P-wave duration may independently predict postoperative AF at long-term follow-up after surgical correction of atrial septal defect type II.[14]

The Framingham Study demonstrated that the 20-year incidence of AF was 5.6% in persons with a

pulse pressure of 40 mm Hg or less and 23.3% for a pulse pressure greater than 61 mm Hg.[15] Persons with lone AF have a normal C-reactive protein suggesting that this marker of systemic inflammation is associated not with AF but with the underlying cardiovascular conditions associated with AF.[16] Left atrial volume is a strong and independent predictor of postoperative AF after cardiac surgery.[17]

In 254 elderly persons with AF compared to 1,445 elderly persons with sinus rhythm, mean age 81 years, 2-dimensional and Doppler echocardiography demonstrated that the prevalence of AF was increased 17.1 times by rheumatic mitral stenosis, 2.9 times by left atrial enlargement, 2.5 times by abnormal LV ejection fraction, 2.3 times by aortic stenosis, 2.2 times by MAC and by ≥1+ mitral regurgitation, 2.1 times by ≥ 1+ aortic regurgitation, and 2.0 times by LV hypertrophy.[18] The Framingham Study showed that low serum thyrotropin levels were independently associated with a 3.1 times increase in the development of new AF in older patients.[19]

Numerous drugs can induce AF.[20] A metaanalysis of 11 studies including 56, 308 patients showed that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers significantly reduced the risk of AF by 28%, with a 44% significant reduction in AF in patients with CHF.[21] This benefit was limited to patients with reduced LV ejection fraction or LV hypertrophy.[21]

Recently, many authors have reported the important role of statins in the prevention and treatment of AF since inflammation, is one of the hypotheses of AF, and the most popular hypothesis of postoperative AF.[22-27] For that reason, many authors suggested that preoperative use of statins, due to their anti-inflammatory characteristics, might decrease the risk of postoperative AF.

An important study on this subject was the ARMYDA-3 Study (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery).[25] The authors included 200 patients undergoing elective cardiac surgery with cardiopulmonary bypass without previous statin treatment or history of AF. Patients were randomized to atorvastatin 40 mg daily or placebo starting 7 days before operation. The primary end point was incidence of postoperative AF; secondary end points were length of stay, 30-day major adverse cardiac and cerebrovascular events, and postoperative C-reactive protein variations. They showed that atorvastatin significantly reduced the incidence of AF versus placebo (35% versus 57%, p=0.003). Accordingly, length of stay was longer in the placebo versus atorvastatin arm (6.9±1.4 vs. 6.3±1.2 days, p=0.001). Peak C-reactive protein levels were significantly lower in patients without AF, irrespective of randomization assignment. Multivariable analysis showed that atorvastatin treatment conferred a 61% reduction in risk of AF, whereas high postoperative C-reactive protein levels were associated with increased risk. The authors concluded that preoperative treatment with atorvastatin at a dose of 40 mg daily significantly reduced the incidence of postoperative AF after elective cardiac surgery with cardiopulmonary bypass and shortened the hospital stay.

These results might influence practice patterns with regard to adjuvant pharmacological therapy before cardiac surgery. These results were also confirmed, among others, in the study by Mariscalco et al,[26] where the authors assessed the efficacy of preoperative statins in prevention of AF in patients after coronary artery bypass grafting (CABG). Four hundred and five consecutive patients who underwent isolated CABG procedures were included in the study. Postoperative AF occurred in 29.5% of the patients with preoperative statin therapy compared with 40.9% patients without such treatment (p=0.021).[26] These investigators observed that preoperative statins were associated with a 42% reduction in risk of AF development after CABG . This study confirmed the result of the ARMYDA-3 study and showed that preoperative statins could significantly reduce postoperative AF after CABG.

A meta-analysis of 9 studies with 28,786 patients undergoing isolated surgical revascularization showed that 7,019 patients (24.4%) developed postoperative AF.[28, 29] Important factors predicting postoperative AF were advanced age, preoperative LV ejection fraction, history of AF, hypertension, CHF, peripheral vascular disease, chronic obstructive pulmonary disease, neurological event, significant stenosis of the left main coronary artery before surgery, and postoperative use of inotropic

therapy.[28, 29]

Associated Risks

Patients with diabetes mellitus undergoing coronary angiography with AF have a higher prevalence of obstructive CAD and of 3-vessel obstructive CAD than those with sinus rhythm.[30] In the Framingham Study, the incidence of death from cardiovascular causes was 2.7 times higher in women and 2.0 times higher in men with chronic AF than in women and men with sinus rhythm.[31] The Framingham Study also showed that after adjustment for preexisting cardiovascular conditions, the odds ratio for mortality in persons with AF was 1.9 in women and 1.5 in men.[32] At 42-month follow-up of 1,359 elderly persons with heart disease, mean age 81 years, patients with chronic AF had a 2.2 times increased risk of having new coronary events than patients with sinus rhythm after controlling for other prognostic variables.[33] In the Copenhagen City Heart Study, the effect of AF on the risk of cardiovascular death was significantly increased 4.4 times in women and 2.2 times in men.[34] In the Euro Heart Survey on Atrial Fibrillation, women with AF had a 1.83 times significantly increased risk of stroke than men with AF.[35] AF after isolated coronary artery surgery significantly increased mortality at 51-month median follow-up (adjusted hazard ratio = 2.13).[36]

AF occurred in 22% of 106,780 persons aged ≥65 years with acute MI in the Cooperative Cardiovascular Project.[37] Compared with sinus rhythm, patients with AF had a higher in-hospital mortality (25% versus 16%), 30-day mortality (29% versus 19%), and 1-year mortality (48% versus 33%).[37] AF was an independent predictor of in-hospital mortality (odds ratio = 1.2), 30-day mortality (odds ratio = 1.2), and 1-year mortality (odds ratio = 1.3). Elderly patients developing AF during hospitalization had a worse prognosis than elderly patients presenting with AF.[37] In the Global Use of Strategies To Open Occluded Coronary Arteries (GUSTO-III) study, 906 of 13,858 patients (7%) developed AF during hospitalization.[38] After adjusting for baseline differences, AF increased the 30-day mortality (odds ratio = 1.6) and the 1-year mortality (odds ratio =

Table 1 Conditions Favorable and Unfavorable for Cardioversion of Atrial Fibrillation

Favorable Conditions for Cardioversion of Atrial Fibrillation
Less than 1 year duration of atrial fibrillation
No or minimal cardiomegaly
Echocardiographic left atrial dimension less than 45 mm
After treatment of a precipitating cause such as acute myocardial infarction , cardiac or thoracic surgery, hyperthyroidism, pneumonia, or pericarditis
After corrective valvular surgery
stenosis or hypertrophic obstructive cardiomyopathy
Unfavorable Conditions for Cardioversion of Atrial Fibrillation
Duration of atrial fibrillation greater than 1 year
Moderate to severe cardiomegaly
Echocardiographic left atrial dimension greater than 45 mm
Digitalis toxicity (contraindicated)
Chronic obstructive lung disease
Mitral valve disease
Heart failure
Recurrent atrial fibrillation despite antiarrhythmic drugs
Inability to tolerate antiarrhythmic drugs

1.6).[38]

In the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptors Suppression Using Integrilin Therapy (PURSUIT) trial, AF developed in 6.4% of 9,432 patients with acute coronary syndromes without ST-segment elevation.[39] After adjustment for other variables, patients with AF had a higher 30-day mortality (hazard ratio = 4.0) and 6-month mortality (hazard ratio = 3.0) than patients without AF.[39]

AF is also an independent risk factor for stroke, especially in elderly persons.[1, 2] In the Framingham Study, the relative risk of stroke in patients with nonvalvular AF compared with patients with sinus rhythm was increased 2.6 times in patients aged 60 to 69 years, increased 3.3 times in patients aged 70 to 79 years, and increased 4.5 times in patients aged 80 to 89 years.[1] Chronic AF was an independent risk factor for thromboembolic (TE) stroke with a relative risk of 3.3 in 2,101 older persons, mean age 81 years.[2] The 3-year incidence of TE stroke was 38% in older persons with chronic AF and 11% in older persons with sinus rhythm.[2] The 5-year incidence of TE stroke was 72% in older persons with AF and 24% in older persons with sinus rhythm.[2] At 37-month follow-up of 1,476 patients who had 24-hour ambulatory ECGs (AECGs), the incidence of TE stroke was 43% for 201 patients with AF (relative risk = 3.3), 17% for 493 patients with paroxysmal supraventricular tachycardia, and 18% for 782 patients with sinus rhythm.[40]

In the Copenhagen City Heart Study, the effect of AF on the risk of stroke was significantly increased 7.6 times in women and 1.7 times in men.[34] AF is also a risk factor for impaired cognitive function.[41] In 2,384 older persons, mean age 81 years, AF was present in 17% of older persons with LV hypertrophy and in 8% of persons without LV hypertrophy[31] Both AF (risk ratio = 3.2) and LV hypertrophy (risk ratio = 2.8) were independent risk factors for new TE stroke at 44-month follow-up.[42] The higher prevalence of LV hypertrophy in older patients with chronic AF contributes to the increased incidence of TE stroke in elderly patients with AF.

Both AF (risk ratio = 3.3) and 40% to 100% extracranial carotid arterial disease (ECAD) (risk ratio = 2.5) were independent risk factors for new TE stroke at 45-month follow-up of 1,846 older persons, mean age 81 years.[43] Elderly persons with both chronic AF and 40% to 100% ECAD had a 6.9 times higher probability of developing new TE stroke than elderly persons with sinus rhythm

Table 1 | **CRisk Factors for Stroke in Elderly Patients With Atrial Fibrillation**

Age [1,42,154-158]
Echocardiographic left ventricular dysfunction [159-162]
History of heart failure [158,162,164]
Hypertension [157, 160,162, 164]
Prior thromboembolic events [2,42,157-159,161-165]
Women older than 75 years of age [162]
Rheumatic mitral stenosis [159,160]
Mitral annular calcium [157,166]
Diabetes mellitus [158]
History of myocardial infarction [157, 158, 160,167]
Echocardiographic left atrial enlargement [160,161]
Echocardiographic left ventricular hypertrophy [42, 43, 159,160]
Extracranial carotid arterial disease [43]
Hypercholesterolemia [159]
Low serum high-density lipoprotein cholesterol [159]

and no significant ECAD.[43]

Cerebral infarctions were documented in 22% of 54 autopsied patients aged ≥70 years with paroxysmal AF.[44] Symptomatic cerebral infarction was 2.4 times more common in elderly patients with paroxysmal AF than in elderly patients with sinus rhythm.[44] AF also causes silent cerebral infarction.[45]

AF predisposes to CHF in elderly patients. As much as 30% to 40% of LV end-diastolic volume may be attributable to left atrial contraction in older persons. Absence of a coordinated left atrial contraction reduces late diastolic filling of the LV because of loss of the atrial kick. In addition, a rapid ventricular rate in AF shortens the LV diastolic filling period, further reducing LV filling and stroke volume.

A retrospective analysis of the Studies of Left Ventricular Dysfunction Prevention and Treatment Trials demonstrated that AF was an independent risk factor for all-cause mortality (relative risk = 1.3), progressive pump failure (relative risk = 1.4), and death or hospitalization for CHF (relative risk = 1.3).[46] AF was present in 37% of 355 patients, mean age 80 years, with prior MI, CHF, and abnormal LV ejection fraction and in 33% of 296 patients, mean age 82 years, with prior MI, CHF, and normal LV ejection fraction.[47] In this study, AF was an independent risk factor for mortality with a risk ratio of 1.5.[47] A $CHADS_2$ score in persons with AF gives 1 point for CHF, 1 point for hypertension, 1 point for age older than 75 years, 1 point for diabetes mellitus, and 2 points for previous stroke or transient ischemic attack and estimates the risk of stroke.[48] At 31-month follow-up of 521 persons with AF, a $CHADS_2$ score of 5 or 6 had a 52 times significantly increased risk for stroke than a CHADS2 score of 0.[49]

A very fast ventricular rate associated with chronic or paroxysmal AF may cause a tachycardia-related cardiomyopathy which may be an unrecognized curable cause of CHF.[50, 51] Reducing the rapid ventricular rate by radiofrequency ablation of the AV node with permanent pacing caused an improvement in LV ejection fraction in patients with medically refractory AF.[52] In a substudy of the Ablate and Pace Trial, 63 of 161 patients (39%) with AF referred for AV junction ablation and right ventricular pacing had an abnormal LV ejection fraction.[53] Forty-eight of the 63 patients had follow-up echocardiograms. Sixteen of the 48 patients [33%) had a marked improvement in LV ejection fraction to a value >45% after ventricular rate control by AV junction ablation.[53]

Clinical Symptoms

Patients with AF may be symptomatic or asymptomatic with their arrhythmia diagnosed by physical examination or by an ECG. Examination of a patient after a stroke may lead to the diagnosis of AF. Symptoms caused by AF may include pal-

Table 3 **American College of Cardiology/American Heart Association/European Society for Cardiology Class I Indications for Treating Patients With Atrial Fibrillation With Antithrombotic Therapy**

1. Administer aspirin 81 to 325 mg daily for patients with no risk factors
2. Administer aspirin 81 to 325 mg daily or warfarin to maintain an INR between 2.0-3.0 for patients with 1 moderate-risk factor
3. Administer warfarin to maintain an INR between 2.0-3.0 for patients with any high-risk factor or more than 1 moderate-risk factor.
Moderate-risk factors include age ≥75 years, hypertension, heart failure, LV ejection fraction ≤35%, or diabetes mellitus
High-risk factors include prior stroke, transient ischemic attack or embolism, mitral stenosis, prosthetic heart value*
*If mechanical valve, the INR should be maintained between 2.5-3.5 Adapted from Fuster V et al [183]

pitations, skips in heartbeat, exercise intolerance, fatigue on exertion, cough, chest pain, dizziness, and syncope. A very fast ventricular rate and loss of atrial contraction decrease cardiac output and may lead to angina pectoris, CHF, hypotension, acute pulmonary edema, and syncope, especially in patients with aortic stenosis, mitral stenosis, or hypertrophic cardiomyopathy.

Diagnostic Tests

When AF is suspected, a 12-lead ECG with a 1-minute rhythm strip should be obtained to confirm the diagnosis. If paroxysmal AF is suspected, a 24-hour AECG should be obtained. All patients with AF should have an M-mode, 2-dimensional, and Doppler echocardiogram to determine the presence and severity of the cardiac abnormalities causing AF and to identify risk factors for stroke. Appropriate tests for noncardiac causes of AF should be obtained when clinically indicated. Thyroid function tests should be obtained as AF or CHF may be the only clinical manifestations of apathetic hyperthyroidism in elderly patients. Transthoracic echocardiographic predictors of left atrial appendage thrombus are mitral stenosis, AF, tricuspid tregurgitation, valvular prosthesis, LV dysfunction, and right ventricular dysfunction.[54]

Management of Underlying Causes

Management of AF should include treatment of the underlying disease (such as hyperthyroidism, pneumonia, or pulmonary embolism) when possible. Surgical candidates for mitral valve replacement should have mitral valve surgery if it is clinically indicated. If mitral valve surgery is not performed in patients with significant mitral valve disease, elective cardioversion should not be attempted in patients with AF since early frequent relapses are common if AF converts to sinus rhythm. Precipitating factors such as CHF, infection, hypoglycemia, hypokalemia, hypovolemia, and hypoxia should be treated immediately. Alcohol, coffee, and drugs (especially sympathomimetics) that precipitate AF should be avoided. Paroxysmal AF associated with the tachycardia-bradycardia (sick sinus syndrome) should be treated with permanent pacing in combination with drugs to decrease a very fast ventricular rate associated with AF.[55]

Management Of Very Fast Ventricular Rate

Direct-current (DC) cardioversion should be performed immediately in patients who have paroxysmal AF with a very rapid ventricular rate associated with an acute MI, chest pain caused by myocardial ischemia, hypotension, severe CHF, syncope, or preexcitation syndromes. Intravenous beta blockers,[56-59] diltiazem,[60] or verapamil[61] may be administered to slow immediately a very rapid ventricular rate associated with AF except in patients with preexcitation syndromes.

Propranolol should be administered intravenously in a dose of 1.0 mg over a 5-minute period and then given intravenously at a rate of 0.5 mg/minute to a maximum dose of 0.1 mg/kg. Esmolol administered intravenously in a dose of 0.5 mg/kg over 1 minute followed by 0.05 to 0.1 mg/kg per minute may also be used to slow a very rapid ventricular rate in AF. After the very rapid ventricular rate is slowed, oral propranolol should be started with an initial dose of 10 mg given every 6 hours. This dose may be increased progressively to a maximum dose of 80 mg every 6 hours if necessary. Other beta blockers can be used with appropriate doses administered.

The initial dose of diltiazem administered intravenously to slow a very rapid ventricular rate in AF is 0.25 mg/kg given over 2 minutes. If this dose does not reduce the very fast ventricular rate or cause adverse effects, a second dose of 0.35 mg/kg administered intravenously over 2 minutes should be given 15 minutes after the first dose. After slowing the very rapid ventricular rate, oral diltiazem should be started with an initial dose of 60 mg given every 6 hours. If necessary, this dose may be increased to a maximum dose of 90 mg every 6 hours.

The initial dose of verapamil administered intravenously is 0.075 mg/kg (to a maximum dose of 5 mg). If this dose does not slow the very rapid ventricular rate or cause adverse effects, a second dose of 0.075 mg/kg (to a maximum dose of 5 mg) should be given intravenously 10 minutes after the first dose. If the second dose of intravenous verapamil does not decrease the very rapid

ventricular rate or cause adverse effects, a dose of 0.15 mg/kg (to a maximum dose of 10 mg) should be given intravenously 30 minutes after the second dose. After slowing the very rapid ventricular rate, oral verapamil should be started with an initial dose of 80 mg every 6 to 8 hours. This dose may be increased to 120 mg every 6 hours over the next 2 to 3 days.

Management Of Rapid Ventricular Rate

Digitalis glycosides are ineffective in converting AF to sinus rhythm.[62] Digoxin is also ineffective in slowing a rapid ventricular rate in AF if there is associated fever, hyperthyroidism, acute blood loss, hypoxia or any condition involving increased sympathetic tone.[63] However, digoxin should be used to decrease a rapid ventricular rate in AF unassociated with increased sympathetic tone, hypertrophic cardiomyopathy, or the WPW syndrome, especially if there is LV systolic dysfunction.

The usual initial dose of digoxin given to undigitalized patients with AF is 0.5 mg orally. Depending on the clinical response, a second oral dose of 0.25 mg may be given in 6 to 8 hours, and a third oral dose of 0.25 mg may be administered in another 6 to 8 hours to slow a rapid ventricular rate. The usual maintenance oral dose of digoxin given to patients with AF is 0.25 mg to 0.5 mg daily, with the dose reduced to 0.125 mg to 0.25 mg daily for older patients who are more susceptible to digitalis toxicity.[64]

Oral beta blockers,[65] diltiazem,[66] or verapamil[67] should be added to the therapeutic regimen if a rapid ventricular rate in AF occurs at rest or during exercise despite digoxin. These drugs act synergistically with digoxin to depress conduction through the AV junction. In a study of atenolol 50 mg daily, digoxin 0.25 mg daily, diltiazem-CD 240 mg daily, digoxin 0.25 mg plus atenolol 50 mg daily, and digoxin 0.25 mg plus diltiazem-CD 240 mg daily, digoxin and diltiazem as single drugs were least effective and digoxin plus atenolol was most effective in controlling the ventricular rate in AF during daily activities.[68]

Amiodarone is the most effective drug for slowing a rapid ventricular rate in AF.[69, 70] The noncompetitive beta receptor inhibition and calcium channel blockade are powerful AV nodal conduction depressants. However, the adverse side effect profile of amiodarone limits its use in the treatment of AF. Oral doses of 200 mg to 400 mg of amiodarone daily may be used in selected patients with symptomatic life-threatening AF refractory to other drugs.

Dronedarone is a new antiarrhythmic drug with an electropharmacologic profile related to amiodarone but with modifications intended to eliminate thyroid adverse effects.[71] In 2 double-blind, randomized trials in patients in sinus rhythm with a history of AF in the preceding 3 months and no CHF, 828 patients were treated with dronedarone 400 mg twice daily and 409 patients with placebo.[72] At 1-year follow-up, 67% of patients randomized to dronedarone and 78% of patients randomized to placebo had recurrence of AF.[72] The serum creatinine significantly increased in patients treated with dronedarone (2.4%) compared to patients treated with placebo (0.2%).[72]

In the Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA), 627 persons were randomized to dronedarone or placebo.[71] This study was prematurely stopped because of an excess risk of death in the persons treated with dromedarone.[71] Therapeutic concentrations of digoxin do not lower the frequency of episodes of paroxysmal AF or the duration of episodes of paroxysmal AF diagnosed by 24-hour AECGS.[73,74] Digoxin has been found to increase the duration of episodes of paroxysmal AF, a result consistent with its action in reducing the atrial refractory period.[73]

Therapeutic concentrations of digoxin also do not prevent a rapid ventricular rate from occurring in patients with paroxysmal AF.[73-75] After a brief episode of AF, digoxin increases the shortening that occurs in atrial refactoriness and predisposes to the reinduction of AF.[76] Therefore, digoxin should be avoided in patients with sinus rhythm with a history of paroxysmal AF.

Nondrug Therapies

Radiofrequency catheter modification of AV

conduction could be performed in patients with symptomatic AF in whom a rapid ventricular rate cannot be slowed by drugs.[77, 78] If this procedure does not slow the rapid ventricular rate associated with AF, complete AV block produced by radiofrequency catheter ablation followed by permanent pacemaker implantation should be performed.[79] In a randomized controlled study of 66 persons with CHF and chronic AF, AV junction ablation with implantation of a VVIR pacemaker was superior to drug treatment in controlling symptoms.[80] Long-term survival is similar for patients with AF whether they receive radiofrequency ablation of the AV node and implantation of a permanent pacemaker or drug therapy.[81] In 44 patients, mean age 78±5 years, radiofrequency catheter ablation followed by pacemaker implantation was successful in ablating the AV junction in 43 of 44 patients (98%) with AF and a rapid ventricular rate not controlled by drug therapy.[82]

Surgical techniques have been developed for use in patients with AF in whom the ventricular rate cannot be slowed by drug treatment.[83, 84] The maze procedure is a surgical dissection of the right and left atrium creating a maze through which the electrical activation is compartamentalized, preventing the formation and perpetuation of the multiple wavelets needed for maintenance of AF. This procedure is typically performed in association with mitral valve surgery or CABG. At 2 to 3 years follow-up, 74% of 39 patients and 90% of 100 patients undergoing the maze procedure remained in sinus rhythm.[85, 86] Thirty-five of 43 patients [85%) with drug-refractory, lone paroxysmal AF were arrhythmia free after maze surgery.[87] At 29-month follow-up, 18 of 28 patients (64%), mean age 71 years, who had an intraoperative radiofrequency maze procedure for treating AF at the time of valve surgery or CABS were in sinus rhythm.[88]

Another intraoperative approach for treating AF in patients undergoing mitral valve surgery is cryoablation limited to the posterior left atrium. Sinus rhythm was restored in 20 of 29 patients [69%) with chronic AF undergoing this procedure.[89]

Ablation of pulmonary vein foci that cause AF is a developing area in the treatment of AF. However, recurrent AF develops in 40% to 60% of patients despite initial efficacy with this procedure.[90] Another problem with this approach is a 3% incidence of pulmonary vein stenosis occurring after this procedure.[90]

Recent randomized studies documented that circumferential pulmonary vein radiofrequency ablation was significantly more effective than antiarrhythmic drug therapy in preventing recurrence of AF (93% versus 35%) in 198 patients at 1 year[91] and (87% versus 37%) in 67 patients at 1 year.[92] At 15-month follow-up, 27 of 55 persons with AF (49%) with isolation of each individual pulmonary vein and 37 of 55 persons with AF (67%) with isolation of large areas around both ipsilateral pulmonary veins had no AF or atrial flutter (AFL) after a single radiofrequency ablation.[93] There are no long-term follow-up data showing a reduction in stroke risk in patients apparently cured of AF with radiofrequency catheter ablation. Modification of the substrate responsible for AF can be accomplished in the right and/or left atrium with linear lesions. This catheter maze-ablation approach is effective in a small percentage of patients.[94]

The Atrioverter, an implantable defibrillator connected to right atrial and right coronary sinus defibrillation leads, causes restoration of sinus rhythm by low-energy shock and has an 80% efficacy in terminating AF.[95] Further efforts are needed to improve patient tolerability and to prevent earlier recurrence of AF after successful transvenous atrial defibrillation. The implanted atrial defibrillator is currently available only in combination with a ventricular defibrillator. The Atrioverter may also convert atrial tachycardia to sinus rhythm using an atrial pacing overdrive algorhythm before such tachycardias induce AF.

Pacing

Paroxysmal AF associated with the tachycardia-abradycardia (sick sinus) syndrome should be treated with a permanent pacemaker combined with drugs to slow a rapid ventricular rate associated with AF.[55] Ventricular pacing is an independent risk factor for the development of chronic AF in patients with paroxysmal AF associated with the tachycardia-bradycardia syndrome.[96] Patients with paroxysmal AF associated with the tachycar-

dia-bradycardia syndrome and no signs of AV conduction abnormalities should be treated with atrial pacing or dual-chamber pacing rather than with ventricular pacing because atrial pacing is associated with less AF, fewer TE complications, and a lower risk of AV block than is ventricular pacing.[97]

Many elderly persons are able to tolerate AF without the need for therapy because the ventricular rate is slow due to concomitant AV nodal disease.

These persons should not be treated with drugs that depress AV conduction. A permanent pacemaker should be implanted in patients with AF who develop cerebral symptoms such as dizziness or syncope associated with ventricular pauses longer than 3 seconds which are not drug-induced, as documented by a 24-hour AECG.[98] If patients with AF have drug-induced symptomatic bradycardia, and the causative drug cannot be discontinued, a permanent pacemaker must be implanted. Atrial pacing is effective in treating vagotonic AF[99] and may be considered if treatment with a vagolytic antiarrhythmic drug such as disopyramide is ineffective. Atrial pacing is also effective in treating patients with the sick sinus syndrome.[97] However, when bradycardia is not an indication for pacing, atrial-based pacing may not prevent episodes of AF.[100] Dual-site atrial pacing is more efficacious than single-site pacing for preventing AF.[101] However, the patients in this study had a bradycardia indication for pacing and continued to need antiarrhythmic drugs.[101]

Dual-site atrial pacing with continued sinus overdrive for AF in patients with bradycardia prolonged time to AF recurrence and decreased AF burden in patients with paroxysmal AF.[102] However, there was no difference in AF checklist symptom scores or overall quality-of-life scores.[102] The absence of an effect on symptom control suggests that pacing should be used as adjunctive therapy with other treatment modalities for AF.[102]

Biatrial pacing after CABS has also been shown to decrease the incidence of AF.[103] All ECGs in patients with paced rhythm should be examined closely for underlying AF to prevent under-recognition of AF and under-treatment with anticoagulants.[104] Permanent pacing to prevent AF is not indicated.[105]

Percutaneous Left Atrial Appendage Transcatheter Occlusion

In 2 prospective multicenter trials, percutaneous left atrial appendage occlusion using the PLAATO system was attempted in 111 patients, mean age 71 years, with a contraindication to anticoagulant therapy and at least 1 additional risk factor for stroke.[106] Implantation was successful in 108 of 111 patients (97%). At 9.8-month follow-up, 2 patients (2%) developed stroke.[106] Long-term studies are necessary to confirm the long-term safety of the device and a reduction in TE stroke.

The WATCHMAN Left Atrial Appendage System is another left atrial appendage occlusion device.[107] At 45-day follow-up, 54 of 58 persons (93%) treated with this device had successful sealing of the left atrial appendage.[107] Two patients (4%) developed transient ischemic attack at 24-month follow-up. Anticoagulation is required for 45 days to 6 months until endothelialization of this device is complete.

Wolff –parkinson –white Syndrome

DC cardioversion should be performed if a rapid ventricular rate in patients with paroxysmal AF associated with the WPW syndrome is life-threatening or fails to respond to drug therapy. Drug treatment for paroxysmal AF associated with the WPW syndrome includes propranolol plus procainamide, disopyramide, or quinidine.[108] Digoxin, diltiazem, and verapamil are contraindicated in patients with AF with the WPW syndrome because these drugs shorten the refractory period of the accessory AV pathway, resulting in more rapid conduction down the accessory pathway. This results in a marked increase in ventricular rate. Radiofrequency catheter ablation or surgical ablation of the accessory conduction pathway should be considered in patients with AF and rapid AV conduction over the accessory pathway.[109] In 500 patients with an accessory pathway, radiofrequency catheter ablation of the accessory pathway was successful in treating 93% of patients.[110]

Elective Cardioversion

Elective DC cardioversion has a higher success rate than does medical cardioversion in converting AF to sinus rhythm.[111] Table 1 shows favorable and unfavorable conditions for elective cardioversion of chronic AF.

The American College of Cardiology (ACC)/American Heart Association (AHA)/European Society for Cardiology (ESC) guidelines state that Class I indications for cardioversion of AF to sinus rhythm include 1) immediate DC cardioversion in patients with paroxysmal AF and a rapid ventricular rate who have ECG evidence of acute MI or symptomatic hypotension, angina, or CHF that does not respond promptly to pharmacological measures and 2) DC or drug cardioversion in patients with chronic AF without hemodynamic instability when symptoms of AF are unacceptable.[112]

Elective cardioversion of AF either by DC or by antiarrhythmic drugs should not be performed in asymptomatic older patients with chronic AF. Rectilinear, biphasic shocks have been found to have greater efficacy and need less energy than the traditional damped sine wave monophasic shocks.[113] Therefore, biphasic shocks to cardiovert AF should become the clinical standard.

Antiarrhythmic drugs that have been used to convert AF to sinus rhythm include amiodarone, disopyramide, dofetilide, encainide, flecainide, ibutilide, procainamide, propafenone, quinidine, and sotalol. None of these drugs is as successful as DC cardioversion, which has a success rate of 80% to 90% in converting AF to sinus rhythm. All of these drugs are proarrhythmic and may aggravate or cause cardiac arrhythmias.

Encainide and flecainide caused atrial proarrhythmic effects in 6 of 60 patients (10%).[114] The atrial proarrhythmic effects included conversion of AF to atrial flutter with a 1-to-1 AV conduction response and a very fast ventricular rate.[114] Flecainide has caused ventricular tachycardia (VT) and ventricular fibrillation (VF) in patients with chronic AF.[115] Antiarrhythmic drugs including amiodarone, disopyramide, flecainide, procainamide, propafenone, quinidine, and sotalol caused cardiac adverse effects in 73 of 417 patients (18%) hospitalized for AF.[116] Class IC drugs such as encainide, flecainide, and propafenone should not be used in patients with prior MI or abnormal LV ejection fraction because these drugs may cause life-threatening ventricular tachyarrhythmias in these patients.[117]

Dofetilide and ibutilide are Class III antiarrhythmic drugs that have been used for the conversion of AF to sinus rhythm. Eleven of 75 patients (15%) with AF treated with intravenous dofetilide converted to sinus rhythm.[118] Torsade de pointes occurred in 3% of patients treated with intravenous dofetilide.[118] After 1-month, 22 of 190 patients (12%) with AF and CHF had sinus rhythm restored with dofetilide compared to 3 of 201 patients (1%) treated with placebo.[119] Torsade de pointes developed in 25 of 762 patients (3%) treated with dofetilide and in none of 756 patients (0%) treated with placebo.[119] Dofetilide has also been reported to be useful for the prevention of AF after CABG.[120] This study was commented on by Mariscalco et al.[121]

Twenty-three of 79 patients (29%) with AF treated with intravenous ibutilide converted to sinus rhythm.[122] Polymorphic VT developed in 4% of patients who received intravenous ibutilide in this study.[122] Baseline bradycardia with AF may predispose to ibutilide-induced polymorphic VT.

Vernakalant is a relatively atrium-selective , early-activating K+, and frequency-dependent Na+ channel blocker with a half-life of 2 to 3 hours .[123] In patients with an AF duration of 3 hours to 7 days, 75 of 145 patients (52%) randomized to vernakalant and 3 of 75 patients randomized to placebo (4%) converted to sinus rhythm.[123] In patients with an AF duration of 8 to 45 days, 8 of 76 patients (11%) randomized to vernakalant and 0 of 40 patients (0%) randomized to placebo converted to sinus rhythm.[123] In the 221 patients treated with vernakalant, hypotension developed in 2 patients, cardiogenic shock in 1 patient, and complete AV block in 1 patient.[123]

DC cardioversion of AF has a higher success rate in converting AF to sinus rhythm and a lower incidence of cardiac adverse effects than treatment with any antiarrhythmic drug. How-

ever, pretreatment with ibutilide has been found to facilitate transthoracic cardioversion of AF.[124]

Unless transesophageal echocardiography has demonstrated no thrombus in the left atrial appendage before cardioversion,[125] oral warfarin should be administered for 3 weeks before elective DC or drug conversion of patients with AF to sinus rhythm.[126] Anticoagulant therapy should also be administered at the time of cardioversion and continued until sinus rhythm has been maintained for 4 weeks.[126] After DC or drug cardioversion of AF to sinus rhythm, the left atrium becomes stunned and contracts poorly for 3 to 4 weeks, predisposing to TE stroke unless the patient is maintained on oral warfarin.[127, 128] The maintenance dose of oral warfarin should be titrated by serial prothrombin times so that the International Normalized Ratio (INR) is 2.0 to 3.0.[126]

In a multicenter, randomized, prospective study, 1,222 patients with AF of >2 days duration were randomized to either treatment guided by the findings on transesophageal echocardiography or to management with conventional therapy.[129]

The primary endpoint was cerebrovascular accident, transient ischemic attack, and peripheral embolism
within 8 weeks. The incidence of embolic events at 8 weeks was 0.8% in the transesophageal echocardiography treatment group and 0.5% in the conventional treatment group.[129] At 8 weeks, there were also no significant differences between the 2 groups in the rates of death, maintenance of sinus rhythm, or functional status.[129] However, there was a trend toward a higher rate of death from any cause in the transesophageal echocardiography treatment group (2.4%) than in the conventional treatment group (1.0%) (p=0.06).[129] This study showed the importance of maintaining therapeutic anticoagulation in the period after cardioversion even if there is no transesophageal echocardiographic evidence of thrombus.[128,130] The best management strategy for patients with evidence of an atrial thrombus on initial transesophageal echocardiography remains controversial.[131] In the absence of data from a randomized trial, patients probably should have follow-up transesophageal echocardiography after 1 month of warfarin therapy to demonstrate resolution of the atrial thrombus.[131,132]

Antiarrhythmic Drugs To Maintain Sinus Rhythm

The efficacy and safety of antiarrhythmic drugs after cardioversion of AF to maintain sinus rhythm has been questioned. A meta-analysis of 6 double-blind, placebo-controlled studies of quinidine involving 808 patients who had direct-current cardioversion of chronic AF to sinus rhythm showed that 50% of patients treated with quinidine and 25% of patients treated with placebo remained in sinus rhythm at 1 year follow-up.[133] However, the mortality was significantly higher in patients treated with quinidine (2.9%) than in patients treated with placebo (0.8%).[133] In a study of 406 elderly patients, mean age 82 years, with heart disease and complex ventricular arrhythmias, the incidence of adverse effects causing drug cessation was 48% for quinidine and 55% for procainamide.[134] The incidence of total mortality at 2-year follow-up was insignificantly higher in elderly patients treated with quinidine or procainamide compared with elderly patients not receiving an antiarrhythmic drug.[134]

In another study, 85 patients were randomized to quinidine and 98 patients to sotalol after DC cardioversion of AF to sinus rhythm.[122] At 6-month follow-up, 48% of quinidine-treated patients and 52% of sotalol-treated patients remained in sinus rhythm.[135] At 1-year follow-up of 100 patients with AF cardioverted to sinus rhythm, 37% of 50 patients randomized to sotalol and 30% of 50 patients randomized to propafenone remained in sinus rhythm.[136]

In a study of 403 patients with at least 1 episode of AF in the prior 6 months, 201 patients were treated with amiodarone and 202 patients were treated with sotalol or propafenone.[137] At 16-month follow-up, AF recurred in 35% of patients treated with amiodarone and in 63% of patients treated with sotalol or propafenone.[137] Adverse effects causing cessation of drug occurred in 18% of patients treated with amiodarone and in 11% of patients treated with sotalol or propafenone.[137]

After cardioversion of 394 patients with AF to sinus rhythm, 197 patients were randomized to

metoprolol CR/XL and 197 patients to placebo.[138] At 6-month follow-up, the percent of patients in sinus rhythm was significantly higher on metoprolol CR/XL (51%) than on placebo (40%).[138] The heart rate in patients who relapsed into AF was also significantly lower in pts treated with metoprolol CR/XL than in patients treated with placebo.[138]

In a study of 384 patients with a history of AF or atrial flutter, azimilide lengthened the median time to first symptomatic arrhythmia recurrence from 17 days in the placebo group to 60 days in the azimilide group.[139] However, additional data on both efficacy and safety of azimilide are needed before knowing its role in clinical practice.

Of the 1,330 patients in the Stroke Prevention in Atrial Fibrillation (SPAF) Study, 127 persons were taking quinidine, 57 procainamide, 34 flecainide, 20 encainide, 15 disopyramide, and 7 amiodarone.[140] Patients who were taking an antiarrhythmic drug had a 2.7 times higher adjusted relative risk of cardiac mortality and a 2.3 times higher adjusted relative risk of arrhythmic death compared with patients not taking an antiarrhythmic drug.[140] Patients with a history of CHF who were taking an antiarrhythmic drug had a 4.7 times increased risk of cardiac death and a 3.7 times increased risk of arrhythmic death than patients with a history of CHF not taking an antiarrhythmic drug.[140]

A meta-analysis of 59 randomized, controlled trials comprising 23,229 patients that investigated the use of aprindine, disopyramide, encainide, flecainide, imipramine, lidocaine, mexiletine, moricizine, phenytoin, procainamide, quinidine, and tocainide after MI also demonstrated that mortality was significantly higher in patients receiving Class I antiarhythmic drugs (odds ratio = 1.14) than in patients not receiving an antiarrhythmic drug [141]. None of the 59 studies showed a decrease in mortality by antiarrhythmic drugs.[141]

Amiodarone is the antiarrhythmic drug with the highest success rate in maintenance of sinus rhythm after cardioversion of AF.[137] However, in the Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation Study, the incidence of pulmonary toxicity was 10% at 2 years in patients receiving amiodarone in a mean dose of 158 mg daily.[142] The incidence of adverse effects from amiodarone also approaches 90% after 5 years of therapy.[143]

Ventricular Rate Control

Because maintenance of sinus rhythm with antiarrhythmic drugs may require serial cardioversions, exposes patients to the risks of proarrhythmia, sudden cardiac death, and other adverse effects, and requires the use of anticoagulants in patients in sinus rhythm who have a high risk of recurrence of AF, many cardiologists prefer the management strategy of ventricular rate control plus use of anticoagulants in patients with AF, especially in older patients with AF. Beta blockers such as propranolol 10 mg to 30 mg given 3 to 4 times daily can be administered to control ventricular arrhythmias[144] and after conversion of AF to sinus rhythm. Should AF recur, beta blockers have the added advantage of slowing the ventricular rate. Beta blockers are also the most effective drugs in preventing and treating AF after CABS.[145] Logistic regression analysis showed that postoperative treatment with carvedilol prevented postoperative paroxysmal AF after CABG ($p = 0.0159$).[146] This study was commented on by Banach et al.[147]

The Pharmacological Intervention in Atrial Fibrillation trial was a randomized trial of 252 patients with AF of between 7 days and 360 days duration which compared ventricular rate control (125 patients) with rhythm control (127 patients) [148]. Diltiazem was used as first-line therapy in patients randomized to ventricular rate control. Amiodarone was used as first-line therapy in patients randomized to rhythm control. Amiodarone administration resulted in conversion of 23% of patients to sinus rhythm.[148] Symptomatic improvement was reported in a similar percentage of patients in both groups. Assessment of quality of life showed no significant difference between the 2 treatment groups. The incidence of hospital admission was significantly higher in patients treated with rhythm control (69%) than in patients treated with ventricular rate control (24%).[148] Adverse drug effects caused a change in drug therapy in significantly more patients treated with rhythm control (25%) than in patients treated with ventricular rate control (14%).[148]

The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study randomized 4, 060 patients, mean age 70 years (39% women), with paroxysmal or chronic AF of less than 6 months duration at high risk for stroke to either maintenance of AF with ventricular rate control or to an attempt to maintain sinus rhythm with antiarrhythmic drugs after cardioversion.[149] Patients in both arms of this study were treated with warfarin. All-cause mortality at 5 years was insignificantly increased 15% in the maintenance of sinus rhythm group compared to the ventricular rate control group (24% versus 21 %, p = 0.08).[149] TE stroke was insignificantly decreased in the ventricular rate control group (5.5% versus 7.1%), and all-cause hospitalization was significantly decreased in the ventricular rate control group (73% versus 80%, p < 0.001).[149] In both groups, the majority of strokes developed after warfarin was stopped or when the INR was subtherapeutic. There was no significant difference in quality of life or functional status between the 2 treatment groups.[149] Rhythm control did not improve mortality, hospitalization, or New York Heart Association class in patients with LV ejection fractions of 40% to 49%, 30% to 39%, or less than 30%.[150]

The Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group randomized 522 patients with persistent AF after a previous electrical cardioversion to receive treatment aimed at ventricular rate control or rhythm control.[151] Both groups were treated with oral anticoagulants. At 2.3-year follow-up, the composite end point of death from cardiovascular causes, heart failure, TE complications, bleeding, implantation of a pacemaker, and severe adverse effects of drugs was 17.2% in the ventricular rate control group versus 22.6% in the rhythm control group .[151] In this study, women randomized to rhythm control had a 3.1 times significant increase in cardiovascular morbidity or mortality than women randomized to ventricular rate control (p=0.002) .[152]

The 2-year mortality was similar in 1,009 patients with AF and CHF treated with rate control or rhythm control.[153] At 37-month follow-up of 1,376 patients, mean age 67 years with AF and CHF, cardiovascular mortality was 27% in patients treated with rhythm control versus 25% in patients treated with ventricular rate control.[154] The secondary outcomes of all-cause mortality, stroke, worsening CHF, and composite of cardiovascular death, stroke, or worsening CHF were also similar in both groups.[154]

During 19-month follow-up of 110 patients with a history of AF treated with antiarrhythmic drug therapy, recurrent AF was diagnosed by ECG recordings in 46% of the patients and by an implantable monitoring device in 88% of the patients .[155] AF lasting longer than 48 hours was diagnosed by the monitoring device in 50 of the 110 patients (46%).[155] Nineteen of these 50 patients (38%) were completely asymptomatic.[155]

Risk Factors For Thromboembolic Stroke

Table 2 lists risk factors for TE stroke in patients with AF.[1, 2, 42, 43, 156-167] In the SPAF Study involving patients, mean age 67 years, recent CHF (within 3 months), a history of hypertension, previous thromboembolism, echocardiographic left atrial enlargement, and echocardiographic LV systolic dysfunction were associated independently with the development of new TE events.[161,164] The incidence of new TE events was 18.6% per year if 3 or more risk factors were present, 6.0% per year if 1 or 2 risk factors were present, and 1.0% per year if none of these risk factors was present.[161]

In the SPAF Study III involving patients, mean age 72 years, patients were considered at high risk for developing TE stroke if they had either CHF or abnormal LV systolic function, prior thromboembolism, a systolic blood pressure of >160 mm Hg, or the patient was a woman older than age 75 years.[162] In a study of 312 elderly patients with chronic AF, mean age 84 years, independent risk factors for the development of new TE stroke were prior stroke (risk ratio = 1.6), rheumatic mitral stenosis (risk ratio = 2.0), LVH (risk ratio = 2.8), abnormal LVEF (risk ratio = 1.8), serum total cholesterol (risk ratio = 1.01 per 1 mg/dL increase), serum high-density lipoprotein cholesterol (risk ratio = 1.04 per 1 mg/dL decrease), and age (risk ratio = 1.03 per 1 year increase).[159]

Antithrombotic Therapy

Prospective, randomized trials[157, 158, 162, 165, 168-174] and

prospective, nonrandomized observational data from elderly patients, mean age 83 years,[163] and mean age 84 years,[175] have shown that warfarin is effective in lowering the incidence of TE stroke in patients with nonvalvular AF. Analysis of pooled data from 5 randomized, placebo-controlled studies showed that warfarin significantly lowered the incidence of new TE stroke by 68% and was significantly more effective than aspirin in reducing the incidence of new TE stroke.[172] In the Veterans Affairs Cooperative study, the incidence of new TE events was 4.3% per year in patients on placebo versus 0.9% per year in patients on warfarin in patients with no prior stroke, 9.3% per year in patients on placebo versus 6.1% per year in patients on warfarin in patients with prior stroke, and 4.8% per year in patients on placebo versus 0.9% per year in patients on warfarin in patients older than age 70 years.[172] In the European Atrial Fibrillation Trial involving patients with recent transient cerebral ischemic attack or minor ischemic stroke, at 2.3-year follow-up, the incidence of new TE events was 12% per year in patients taking placebo, 10% per year in patients taking aspirin, and 4.0 per year in patients taking warfarin.[165]

Nonrandomized observational data from elderly patients with chronic AF, mean age 83 years, found that 141 patients treated with oral warfarin to achieve an INR between 2.0 and 3.0 (mean INR was 2.4) had a 67% significant decrease in new TE stroke compared with 209 patients treated with oral aspirin.[163] Compared with aspirin, warfarin caused a 40% significant reduction in new TE stroke in patients with prior stroke, a 31% significant reduction in new TE stroke in patients with no prior stroke, a 45% significant reduction in new TE stroke in patients with abnormal LVEF, and a 36% significant reduction in new TE stroke in patients with normal LVEF.[163]

At 1.1-year follow-up in the SPAF Study III, patients with AF considered to be at high risk for developing new TE stroke who were randomized totment with oral warfarin to achieve an INR between 2.0 and 3.0 had a 72% significant decrease in ischemic stroke or systemic embolism compared with patients randomized to treatment with oral aspirin 325 mg daily plus oral warfarin to achieve an INR between 1.2 and 1.5.[162] Adjusted-dose warfarin caused an absolute reduction in ischemic stroke or systemic embolism of 6.0% per year .[162] In the Second Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation (AFASK) Study, low-dose warfarin plus aspirin was also less effective in decreasing stroke or systemic TE events in patients with AF (7.2% after 1 year) than was adjusted-dose warfarin to achieve an INR between 2.0 and 3.0 (2.8% after 1 year).[174]

Analysis of pooled data from 5 randomized controlled studies demonstrated that the annual incidence of major hemorrhage was 1.0% for the control group, 1.0% for the aspirin group, and 1.3% for the warfarin group.[158] The incidence of major hemorrhage in patients, mean age 72 years, taking adjusted-dose warfarin to achieve an INR of 2.0 to 3.0 in the SPAF III Study was 2.1%.[162] In the Second Copenhagen AFASK Study, the incidence of major hemorrhage in patients, mean age 73 years, was 0.8% per year for patients treated with adjusted-dose warfarin to achieve an INR between 2.0 and 3.0 and 1.0% per year for patients treated with aspirin 300 mg daily.[174] The incidence of major hemorrhage in elderly patients with chronic AF, mean age 83 years, was 4.3% (1.4% per year) in patients treated with warfarin to maintain an INR between 2.0 and 3.0 and 2.9% (1.0% per year) in patients treated with aspirin 325 mg daily.[163]

In the SPAF III Study, 892 patients, mean age 67 years, at low risk for developing TE stroke were treated with oral aspirin 325 mg daily.[176] The incidence of ischemic stroke or systemic embolism was 2.2% per year.[176] The incidence of ischemic stroke or systemic embolism was 3.6% per year in patients with a history of hypertension and 1.1% per year in patients with no history of hypertension.[176]

In the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study, 973 patients aged 75 years and older with AF and a low prevalence of risk factors for stroke were randomized to warfarin with a target INR of 2.0-3.0 or aspirin 75 mg daily.[177] Warfarin was significantly better than aspirin in reducing disabling strokes or clinically significant arterial embolism (1.8% per year on warfarin versus 3.8% per year on aspirin).[177] Major bleeding was 1.9% per year for warfarin versus 2.0% per year for warfarin.

In a study of 13, 559 patients with nonvalvular AF hospitalized with an outpatient stroke, compared to an INR of 2.0 or greater, an INR of <2.0 at hospital admission significantly increased the odds of a severe stroke by 1.9 times and the risk of death within 30 days by 3.4 times.[178] The 30-day mortality was similar among patients who were taking aspirin or warfarin with an INR of <2.0.[163] Elderly patients taking warfarin should have an INR maintained between 2.0 and 3.0, not one <2.0 or >3.5.[179]

Predictors of paroxysmal AF in patients undergoing aortic valve replacement for aortic stenosis were heart failure, age 70 years and older, low and high body mass index, maximal transvalvular gradient, low LV ejection fraction, end-systolic and end-diastolic intraventricular septum thickness, and insignificant mitral regurgitation in the preoperative period; and LV ejection fraction and end-systolic intraventricular septum thickness in the early postoperative period.[180] Predictors of paroxysmal AF in patients undergoing aortic valve replacement for aortic regurgitation were hypertension, diabetes, and history of heart failure in the preoperative period; LV ejection fraction and left atrial dimension in the early postoperative period; and age, LV ejection fraction, LV end-systolic diameter, end-systolic intraventricular septum thickness, left atrial dimension, and insignificant mitral regurgitation in the postoperative period.[180] Prophylactic treatment should be administered to patients undergoing aortic valve replacement at high risk for developing postoperative AF.[180]

Of 3,000 patients undergoing isolated surgical revascularization, 174 (5.8%) had preoperative AF .[181] At 3-year follow-up, survival rates were 90.6% in patients without preoperative AF versus 70.7% in those with preoperative AF (p<0.01).[181]

Many physicians are reluctant to prescribe warfarin for AF in patients with chronic kidney disease because of concern of bleeding complications. Because of the high prevalence of AF and its association with an increased incidence of TE events in patients with late stage chronic kidney disease, it is very important to perform double-blind, placebo- controlled studies in these patients to determine the efficacy of oral anticoagulant therapy in preventing TE events and the incidence and type of bleeding complications.[182] Until these data are available, the authors favor treating patients with AF on hemodialysis with warfarin on an individual basis taking into account both the TE risk as well as the hemorrhagic risk.[182]

On the basis of the available data, patients with chronic or paroxysmal AF at high risk for developing TE stroke or with a history of hypertension and who have no contraindications to anticoagulation therapy should be treated with long-term oral warfarin to achieve an INR between 2.0 and 3.0.[124,183] Hypertension must be controlled. Whenever the patient has a prothrombin time taken, the blood pressure should also be checked. The physician prescribing warfarin should be aware of the numerous drugs which potentiate the effect of warfarin causing an increased prothrombin time and risk of bleeding.[184] Patients with AF at low risk for de veloping TE stroke or with contraindications to treatment with long-term oral warfarin should be treated with aspirin 325 mg orally daily .[185]

Patients younger than age 60 years in Olmstead County, Minnesota with lone AF (no heart disease) had a low risk of TE stroke at 15-year follow-up.[186] However, at 30-year follow-up in the Framingham Heart Study, the age-adjusted percentage of patients with lone AF who developed a cerebrovascular event was 28% versus 7% in the control group.[187] At 30-year follow-up of 76 patients with lone AF in Olmstead County, Minnesota, risk for stroke or transient ischemic attack was similar to the expected population risk during the first 25 years of follow-up but significantly increased thereafter (p = 0.004).[188]

Age or hypertension increased the TE risk.[188] Table 3 shows the ACC/AHA/ESC Class I indications for antithrombotic therapy in the management of patients with AF.[183]

Despite the data showing the efficacy of oral warfarin used in a dose to achieve an INR between 2.0 and 3.0 in reducing the incidence of new TE events in patients with paroxysmal or chronic AF, only about one-third of patients with AF who should be taking warfarin receive it.[189] In an academic hospital-based geriatrics practice, only 61 of 124 patients (49%), mean age 80 years, with

chronic AF at high risk for developing TE stroke and no contraindications to warfarin were being treated with warfarin therapy.[5] The Euro Heart Survey on Atrial Fibrillation found that compared to guideline-adherent antithrombotic therapy, undertreatment of AF with oral anticoagulants was associated with a 1.97 times significant increase in thromboembolic events and a 1.54 times significant increase in cardiovascular death, thromboembolism, or major bleeding.[190]

Elderly patients have a higher prevalence and incidence of AF than younger patients.[1-6] Elderly patients with AF are at higher risk for developing TE stroke than are younger patients with AF.[1,40, 42,154-158] However, physicians are more reluctant to treat elderly patients with AF with warfarin therapy. Hopefully, intensive physician education will help solve this important clinical problem.

In the Anticoagulation and Risk Factor in Atrial Fibrillation Study, women off warfarin had significantly higher annual rates of thromboembolism (3.5%) than men (1.8%).[191] Warfarin was associated with significantly lower adjusted TE rates for both women (60% reduction) and men (40% reduction) with similar annual rates of major bleeding (1.0% and 1.1%, respectively).[191]

The Atrial Fibrillation Clopidogrel Trial with Irbersartan for the Prevention of Vascular Events (ACTIVE W) demonstrated in patients with AF that the annual risk of first occurrence of stroke, non-central nervous system systemic embolus, MI, or vascular death was 3.93% in 3,371 patients randomized to warfarin to maintain an INR between 2.0 and 3.0 and 5.60% in 3,335 patients randomized to clopidogrel 75 mg daily plus aspirin 75-100 mg daily, with a 44% significant reduction in the primary outcome attributed to warfarin.[177] The incidence of major bleeding was 10% insignificantly higher in patients treated with clopidogrel plus aspirin than in persons treated with warfarin .[192]

The oral direct thrombin inhibitor ximelagatran was as effective as warfarin in decreasing TE stroke and systemic embolism in 7,329 patients treated with these 2 drugs in 2 combined studies (1.6% per year for both drugs).[193,194] The incidence of major bleeding in the 2 pooled studies was 1.9% per year on ximelagatran and 2.5% per year for warfarin. However, Ximelagatran increased serum transaminase levels in 6% of patients and was not approved by the USA Food and Drug Administration because of concerns of hepatotoxicity.

Dabigatran is another direct thrombin inhibitor which is being investigated versus warfarin in a large phase III trial in patients with AF.[195] Rivaroxaban and apixaban are oral factor Xa inhibitors which are being compared with warfarin in large phase III trials in patients with AF.[195]

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