Chronic Atrial Fibrillation

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Background
Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. It is an important risk factor for stroke, and is associated with adverse mortality, morbidity, and healthcare cost outcomes.

AF was probably first described in 1906 by Cushny and Edmunds in their article “paroxysmal irregularity of the heart and auricular fibrillation”. In their study, they noticed that the atria of anesthetized open-chest dogs were sometimes dilated, with the atrial walls in a state of fibrillatory contraction on myography. That same year, Einthoven published the first electrocardiographic tracing of AF which he termed “pulsus inequalis et irregularis” (1, 2).

Epidemiology
As the most common clinically significant cardiac arrhythmia, chronic AF afflicts over 2.3 million adults in the United States, a figure projected to increase to 5.6 million by year 2050. AF has a prevalence of about 1% in the general population. Prevalence increases with age, from 0.1% in those 50 years or younger, to 9% among those 80 years or older (3). The prevalence of AF among those aged 65 or older is also rising with time, from 3% in 1992 to 6% in 2002 (4).

In the Framingham Study, non-valvular AF was associated with a five-fold increase in the risk of ischemic stroke compared with controls. An even more substantial 17-fold increase in stroke risk exists in patients with AF and rheumatic heart disease (5, 6). The rate of ischemic stroke among elderly patients with AF that were not treated with anticoagulation is around 5% per year.

AF is associated with 470,000 hospitalizations and nearly 80,000 deaths annually in the United States alone (7). In a study of Medicare patients aged 65 or older with AF and cardiovascular disease, the 3-year mortality rate ranges from 34–71% (higher in males and in older age groups), which is 30% higher than those without AF. The presence of AF also raises hospital costs, with around 9 to 22-fold greater adjusted total spending in 1 year (8).

Pathophysiology
The mechanisms for arrhythmogenesis in AF is still not completely understood. Current literature supports 2 prevailing theories, the “multiple wavelet hypothesis” and the “automatic focus theory”. These mechanisms are not mutually exclusive, and both may occur in the same patient.

The first theory holds that AF consists of multiple wavelets of functional re-entry. Small reentrant circuits are constantly arising in the atria, colliding, combining or dividing, thereby spawning daughter wavelets that perpetuate the process. AF is sustained by a critical number of wavelets, which travel throughout the atria. Conditions that increase atrial size, decrease the conduction velocity or decrease the refractory period permit multiple wavelets and promote AF (9).

The second, more recent hypothesis points to a rapidly firing focus (or foci) in the pulmonary vein as a source of premature atrial beats that can initiate and maintain paroxysms of AF (10). The muscular sleeve of the pulmonary veins displays electrophysiologic properties (including shorter refractory periods) distinct from those of both the adjacent left atrial muscle and the muscular sleeve of the pulmonary veins in control subjects without AF (11). Repeated firing of this ectopic focus leads to a marked shortening of the atrial refractory period and the loss of the normal lengthening of atrial refractoriness at slower heart rates, a phenomenon termed termed “atrial electrical remodeling” (12, 13).

Prolonged AF leads to progressive atrial mechanical remodeling, with subsequent impairment in atrial

(Continued on page 3)
transport and distensibility. AF is associated with loss of atrial contribution to ventricular filling, resulting in up to 20% decrease in ventricular stroke volume. The irregular ventricular response also contributes to hemodynamic impairment because of wide swings and peaks in ventricular rhythm. Persistently uncontrolled rapid ventricular response results in ultrastructural changes causing ventricular dysfunction (termed “tachycardia-mediated cardiomyopathy”) that may be reversible with restoration of sinus rhythm or with rate control (14).

The loss of organized mechanical contraction during AF predisposes to thrombus formation in the left atrium and left atrial appendage. Thrombus formation begins with Virchow’s triad of stasis, endothelial dysfunction and hypercoagulable state. Although it is presumed that thrombus formation requires persistence of AF for approximately 48 hours, thrombi have been identified by transesophageal echocardiography within shorter intervals (22).

**Risk Factors**

The Framingham Study found that advanced age, diabetes mellitus, hypertension, myocardial infarction, congestive heart failure, left ventricular hypertrophy, and valvular heart disease were independent risk factors for the development of AF. Men were 1.5 times more likely to develop AF than women (16). Other reported cardiac causes of AF include myocarditis, hypertrophic cardiomyopathy, conduction system disease (Wolff-Parkinson-White syndrome, sick sinus syndrome), congenital heart disease (atrial septal defect, patent ductus arteriosus, etc.), and pericardial disease.

Reported noncardiac etiologies of AF include thyrotoxicosis, pheochromocytoma, severe infections, pulmonary pathology (pulmonary infections, pulmonary embolism, and chronic lung disease), alcohol use (“holiday heart syndrome”), electrolyte disorders, cardiothoracic surgery, hypothermia, and electrocution. More recently, obesity and obstructive sleep apnea have been shown to independently predict incident AF (17). In patients with structurally normal heart valves, clinically silent mild to moderate mitral regurgitation may also be a risk factor for AF (18).

A genetic basis for AF has been recently proposed with the discovery of “connexin 40”, a gap junction protein expressed selectively in atrial myocytes that mediates the coordinated electrical activation of the atria. Mutation in GJA5, the gene encoding connexin 40, may impair gap junction assembly and electrical coupling, predisposing patients to idiopathic AF (19).

**Symptomatology**

AF can be symptomatic or asymptomatic, even in the same patient. Most patients are asymptomatic, and up to 90% of AF episodes may go unrecognized (20). Symptoms consistent with AF may include palpitations, chest pain, dyspnea, fatigue, lightheadedness, confusion, and syncope. Syncope is a rare but serious complication that usually indicates a sinus node dysfunction, an accessory atrioventricular pathway, valvular aortic stenosis, hypertrophic cardiomyopathy, or cerebrovascular disease. Physical findings may include irregular pulse, congestive heart failure, hypoxia, and thromboembolism (21).

**Classification**

Several terms are used to describe the pattern of AF. Newly-diagnosed AF is classified as “first-detected” AF. When a patient has had 2 or more episodes with demonstration of reversion to sinus rhythm in between, AF is considered “recurrent” (self-terminating). If the arrhythmia terminates spontaneously, recurrent AF is designated “paroxysmal”.

When sustained beyond 7 days, AF is designated “persistent” or “chronic” (not self-terminating). Persistent AF is labeled “long-standing” if sustained beyond 1 year. The term “permanent” AF is applied to cases of long-standing AF when cardioversion has failed or has not been attempted (22).

In the SPAF trial, patients with intermittent AF had stroke rates similar to patients with sustained AF and
similar stroke risk factors. High-risk patients with intermittent AF can be identified using the same clinical criteria that apply to patients with sustained AF (23).

The term “lone” AF has no standard definition, but is usually applied to young individuals (below 60 years of age), without clinical or echocardiographic evidence of hypertension, cardiac, or pulmonary disease. Patients with lone AF have favorable prognosis in terms of mortality and thromboembolism.

**Diagnosis**

The diagnosis of AF is based on history and clinical examination, and confirmed by at least a single-lead electrocardiographic documentation of the arrhythmia. The initial goal of clinical examination involves defining the AF pattern as either paroxysmal or chronic, determining possible causes, and identifying associated cardiac or noncardiac factors significant to further management.

Aside from history and physical examination, minimum diagnostic tests required for the initial evaluation of a patient with suspected or confirmed AF include electrocardiogram (EKG) and transthoracic echocardiogram. Routine blood tests include a hemogram and serum testing for renal, hepatic and thyroid function (22).

Electrocardiography is essential to diagnosis. If AV conduction is intact, a typical EKG tracing would show absent P waves and the presence of fibrillatory (f) waves. The f waves vary in amplitude, morphology and intervals, with a rate that is between 350–600 beats/minute. The R-R interval is irregularly irregular, with a ventricular rate that ranges from 90–170/min. Ventricular rates below 60/minute are seen in AV conduction defects (AV nodal disease, nodal-blocking drugs, high vagal tone), while rates above 200/minute may indicate catecholamine excess, parasympathetic withdrawal, or an accessory bypass tract [24]. The QRS complexes are narrow, unless AV conduction is abnormal. A portable EKG recorder (Holter, event recorder, telemetric monitor) may establish the diagnosis in cases of paroxysmal AF.

Transthoracic echocardiogram is routinely done to assess left atrial (LA) and ventricular (LV) dimensions and function. It is invaluable in excluding valvular or pericardial disease, as well as hypertrophic obstructive cardiomyopathy. Transesophageal echocardiography is often performed to rule out LA thrombus prior to cardioversion.

Other diagnostic tests may be required in some cases, if clinically indicated. Chest radiograph is obtained to evaluate the lung parenchyma and vasculature. Exercise testing might reproduce exercise-induced AF, and is used to assess adequacy of rate control or to exclude ischemia prior to anti-arrhythmic therapy. Electrophysiological study may be required to identify a predisposing arrhythmia or seek sites for curative ablation.

**Management Goals for Chronic AF**

The 3 goals of chronic AF management includes rate control, prevention of thromboembolism, and correction of rhythm disturbance. The initial management decision involves primarily a rate-control or rhythm-control strategy. Regardless of which strategy is pursued, attention should also be directed to antithrombotic therapy to prevent thromboembolism. (22).

**Rate Control Strategy**

Rapid ventricular rates (RVR) during AF may acutely lead to hemodynamic instability from inadequate ventricular filling time and rate-related ischemia. Chronically, it could cause tachycardia-mediated cardiomyopathy, a form of left ventricle dysfunction resulting from poor AF control. It is therefore paramount to maintain adequate rate control in patients with chronic AF to prevent such complications.

(Continued on page 5)
There are no standard criteria for adequate heart rate control in AF, but it is usually defined as achieving ventricular rates between 60–80 beats per minute at rest, and between 90–115 beats per minute during moderate exercise. Ventricular rates may rise excessively during exercise, even though it may be well controlled at rest. Evaluation of heart rate response to submaximal or maximal exercise via treadmill stress test, or extended heart rate monitoring via 24-hour Holter recording may be useful (22).

Pharmacologic Rate-Control.

Beta-blockers and non-dihydropyridine calcium channel blockers are first-line maintenance agents for chronic AF. In the AFFIRM study, beta-blockers were more effective, achieving 70% target heart rates, compared to 54% for calcium-channel blockers (23). Orally administered metoprolol (25–100 mg twice daily), propranolol (80–240 mg daily in divided doses), verapamil (120–360 mg daily) and diltiazem (120–360 mg daily) are effective, both at rest and during exercise. Esmolol, atenolol, nadolol and sotalol are also efficacious.

On the other hand, digoxin (0.125–0.375 mg daily) is effective only at rest due to the loss of its vagal effects during exercise. It is indicated in heart failure, LV dysfunction, and in sedentary or elderly individuals. Combination therapy may be done to optimize rate control. The choice of medication should be individualized and the dose should be modulated to avoid bradycardia. If the first-line agents are ineffective, amiodarone (200 mg daily orally as maintenance) may be useful in slowing down the ventricular rate, especially in patients with heart failure.

Non-Pharmacologic Rate-Control.

If drug therapy is unsuccessful or not tolerated, radiofrequency catheter ablation of the AV node or His bundle, or modification of the AV nodal conduction, can be performed. In radiofrequency catheter ablation, the interruption of conduction usually produces complete AV block, requiring implantation of a permanent pacing device to adequately control the ventricular rate. The procedure has an 86% success rate, an 8.5% early complication rate, and a long-term total mortality rate of 17% (25).

Alternatively, radiofrequency energy can be used to modify, rather than completely abolish, AV nodal conduction. The AV node has two atrial pathways, and ablation of one of these pathways can reduce the number of impulses that successfully reach the infranodal conduction system and the ventricles. The procedure has a success rate of 70–74%, and a recurrence rate of 11% (26, 27). The modification procedure holds a major cost advantage over ablation, with 10-year cumulative charges amounting to 40% less than that of the ablation procedure (28).

Rhythm Control Strategy

It has been hypothesized that irregular heart rate in itself causes cardiac impairment in AF, independent of ventricular rate (29). Restoration of sinus rhythm produces a rapid increase in LVEF in most patients, from 47 to 55% upon cardioversion, primarily due to improved diastolic filling. Maximum improvement in LVEF (around 60%) occurs one month after cardioversion, which coincides with the time to full recovery of left atrial contractile function (30, 31). Cardioversion may be performed electively in patients with persistent AF, but it is emergently required if the arrhythmia causes hypotension, acute heart failure, or angina.

A definite risk for thromboembolism after conversion to sinus rhythm exists, especially in patients where AF has been present over 48 hours, unless prophylactic anticoagulation is started. In chronic AF, cardioversion results in further deterioration in atrial mechanical function, called atrial mechanical “stunning”, in the immediate period following return to sinus rhythm. Atrial stunning is considered pivotal in the heightened thromboembolic risk in the first few days following cardioversion. It may last up to 4 weeks before atrial

(Continued on page 6)
transport function returns to normal. It is therefore recommended that anticoagulation be continued for at least 1 month after successful cardioversion of AF (15, 22, 32).

**Pharmacologic Rhythm Control.**

Antiarrhythmic agents proven to be effective in the cardioversion of AF include amiodarone, dofetilide, flecainide, and propafenone. Less effective agents include quinidine, procainamide, beta blockers, calcium channel blockers, digoxin, disopyramide, and sotalol.

For the maintenance of sinus rhythm after cardioversion, amiodarone (100–400 mg daily), dofetilide (500–1000 mcg daily), disopyramide (400–750 mg daily), flecainide (200–300 mg daily), propafenone (450–900 mg daily), sotalol (160–320 mg daily), and beta blockers have been found efficacious. Pharmacologic agents are successful in maintaining sinus rhythm in over 80% of patients after 1 year, but efficacy declines by about 10% after each subsequent year (23). Amiodarone is more effective than either class I drugs, sotalol, or placebo in the long-term maintenance of sinus rhythm in patients with paroxysmal or persistent AF (33, 34, 35). It is, however, associated with high incidence of toxic effects. Digoxin, procainamide, quinidine, and calcium channel blockers are no longer recommended because of unproven efficacy or adverse events (22).

The “pill in the pocket” approach for recurrent AF has been shown to be safe and feasible, leading to marked reduction in emergency room visits and hospitalization. The strategy involves self-administering single oral dose of either flecainide (200–300 mg) or propafenone (450–600 mg) upon onset of symptomatic palpitations (36). With an 84–94% efficacy, this is an attractive strategy that improves quality of life and reduces healthcare costs in select patients.

**Non-Pharmacologic Rate-Control.**

Synchronized transthoracic direct current (DC) cardioversion can be performed in patients who failed drug therapy. It is the procedure of choice if emergent conversion of AF is required because of hemodynamic compromise. In elective DC cardioversion, a success rate of 83% is attained using the standard step-up energy protocol (200 joules initial shock, followed by 300 joules then 360 joules, if needed). A higher success rate of 92% may be attained in employing an experimental protocol using high energy (360 joules) in the initial and subsequent shocks (37). Without concomitant antiarrhythmic drugs, the recurrence rate is high after the procedure, with less than 40% of patients maintaining sinus rhythm after 1 month (38). Complete shock failure occurs in nearly 20% of cases. Restoration and maintenance of sinus rhythm are less likely when AF has been present for longer than 1 year. Risks include arrhythmias and 1–7% incidence of thromboembolic events, especially if prophylactic anticoagulation is not given.

Electrophysiologic mapping of the pulmonary veins led to the discovery of ectopic beats that initiate paroxysms of AF. Abolishment of these ectopic foci was possible using focal radiofrequency catheter ablation of the pulmonary vein. Initial experience with the procedure yielded a long-term success rate of over 60% (10). The presence of multiple ectopic sites distributed throughout the atria reduces efficacy of targeted pulmonary vein ablation in patients with chronic AF. This led to the development of approaches that involve more extensive ablation in an attempt to completely disconnect electrically all four pulmonary veins from the left atrium. Several techniques have been described, including circumferential pulmonary vein ablation and pulmonary vein isolation, which involve the creation of confluent ablation lesions that encircle the pulmonary veins. Success rates of 74–85% were noted, with patients maintaining sinus rhythm during long-term follow-up without antiarrhythmic medications. Maintenance of sinus rhythm was associated with a significant decrease in both the severity of symptoms and left atrial diameter (39, 40).

Pulmonary vein stenosis is a major complication of ablation procedures. It may present as dyspnea on

(Continued on page 7)
exertion or at rest, cough, chest pain, and hemoptysis, usually occurring 2–5 months after the procedure. Once as frequent as 20%, the incidence of ablation-related pulmonary vein stenosis has dropped to 1% with increasing experience and improvement in techniques \(^{(41)}\).

Atrial pacemaker implantation has been proposed to prevent or terminate recurrent AF, and maintain sinus rhythm. Results of studies, mostly directed on recurrent AF, have shown mixed results so far. A 2005 Scientific Advisory Panel from the American Heart Association concluded that available data do not support the use of permanent pacing in the management of AF in the absence of a bradycardia indication \(^{(42)}\).

**Surgical Approaches To Rhythm Control.**

Surgical techniques were developed to control refractory AF and to maintain sinus rhythm, usually as adjunctive therapy in patients who are undergoing cardiac surgery for some other reason (e.g. valve operations or coronary bypass grafting).

The Maze procedure, introduced in 1987, involves placing multiple incisions within the left and right atrial myocardium, primarily involving the structures around which reentry can develop to interrupt potential reentry pathways. The procedure is relatively complicated and time-consuming, but has an excellent long-term efficacy, with an 89% rate of freedom from AF at 10 years \(^{(43)}\). It is also associated with a significant reduction in stroke rates, down to less than 1% in over 10 years of follow-up \(^{(44)}\). Potential complications include extensive damage to the atrial myocardium with resultant atrial dysfunction that may limit the hemodynamic benefit, as well as sinus node dysfunction.

The radial incision approach involves placement of atrial incisions that radiate from the sinus node toward the atrioventricular margin, parallel to the coronary arteries. It was developed as alternative to the maze procedure to preserve a more physiological activation sequence and the atrial transport function. This approach is technically easier, has the same efficacy (90%) as the maze procedure in restoring sinus rhythm, and is associated with greater improvement in atrial transport function \(^{(45)}\).

**Rate Control vs Rhythm Control**

Cardioversion of AF and maintenance of sinus improves hemodynamics, and it was previously believed that rhythm control resulted in improved symptom control, quality of life, and thromboembolic risk outcomes compared to rate control alone. Large randomized trials comparing the 2 approaches, however, all showed similar results, each demonstrating equivalent outcomes in both arms.

The PIAF (2000) and HOT CAFE (2004) trials showed that rhythm control strategy led to increased mean exercise tolerance, but was associated with increased hospital admissions compared to rate control. There was no difference in the major endpoints otherwise, including all-cause mortality, thromboembolic event rate, or major bleeding \(^{(46, 47)}\).

The RACE (2002) and STAF (2003) trials both concluded that in patients at high risk for AF recurrence, there was no difference in mortality, morbidity, and quality of life endpoints between rhythm and rate control strategies. Rate control may be the appropriate therapy as there is no benefit in attempting rhythm control in these patients \(^{(48, 49)}\).

The AFFIRM trial (2002), which enrolled the largest sample size among the major studies, concluded that rhythm-control strategy offers no survival advantage over the rate-control strategy. Rate control strategy has potential advantages, including less adverse drug events and less hospitalization rates \(^{(50)}\).

According the AHA/ACC/ESC Guidelines, rate control may be reasonable initial therapy in older patients with persistent AF who have hypertension or heart disease.

(Continued on page 8)
Rhythm control may be a better initial approach for younger individuals, depending on symptoms. Medications that exert both antiarrhythmic and rate-controlling effects are often required. Catheter ablation should be considered to maintain sinus rhythm in selected patients who failed to respond to antiarrhythmic drug therapy (22).

Anticoagulation

In high-risk patients with AF, majority of strokes occur after warfarin is stopped or when the international normalized ratio is subtherapeutic, regardless of whether a rhythm-control or a rate-control strategy is employed. Anticoagulation should therefore be continued to prevent thromboembolism in chronic AF, irrespective of the treatment strategy pursued (50).

Rates of ischemic stroke in AF declined from 47% in 1992 to 20% in 2002, attributed to increased use of anticoagulant therapy (4). As such, the AHA/ACC/ESC Guidelines recommend that all patients with chronic AF should be treated except for those with lone AF or contraindications to antithrombotic therapy (50).

With regards to antithrombotic therapy in chronic AF, the American College of Chest Physicians (ACCP) classifies patients into high-, moderate- and low-risk categories. High-risk patients include those with prior stroke, transient ischemic attack or systemic embolism, hypertension, diabetes, valvular disease or prosthetic valve, heart failure, or age 75 years or older. Those with moderate risk include patients aged 65–75 years with no other risk factors. Patients under age 65 years and with no other risk factors are considered low risk. The ACCP Consensus Guidelines recommend chronic warfarin therapy (INR of 2.0–3.0, target of 2.5) in high-risk patients with AF. Moderate-risk patients can choose either aspirin therapy (325 mg daily) or warfarin (INR of 2.0–3.0, target of 2.5). Aspirin therapy (325 mg daily) is recommended for low-risk patients (51).

Vitamin K Antagonists.

Several major trials (52, 53, 54, 55, 56) all confirmed that both warfarin and aspirin superior to placebo in preventing thromboembolic complications in AF, and both regimens virtually have the same bleeding complication rates. Warfarin is three times more effective than aspirin therapy, with a 62% stroke risk-reduction thereby it is recommended in high-risk patients.

The target intensity of anticoagulation involves weighing the risk of stroke and the risk of significant bleeding. The ideal INR for nonvalvular AF seems to be between 2.0 and 3.0. Patients maintained with INR of 2.0 or above had 18 times lower stroke rates compared to those with INR below 1.5, and 5 times lower compared to those with INR between 1.5 and 2.0. Risk of major bleeding intracranial hemorrhage, however, increases over 9-fold with INR 4.0 or above. In patients with AF-related stroke, INR above 2.0 was also associated with better mortality and neurologic outcomes compared to low-intensity regimen (57).

Although effective, only 46.5% of high-risk patients with AF are on anticoagulant therapy (58, 59). Warfarin therapy requires frequent INR monitoring and dose adjustments. It also interacts with food and other medicines, resulting in impaired compliance and inadequate anticoagulation.

Antiplatelet Agents.

Aspirin offers only modest protection against stroke for patients with AF, with a stroke reduction of 19% (60). The difference in efficacy between aspirin and anticoagulation is not much evident in the low-risk as it is in the high-risk patients. Aspirin is thus recommended in low-risk groups. Aspirin prevents nondisabling strokes more than disabling strokes. It may also be more efficacious for AF patients with hypertension or diabetes (61).
Studies with other cyclooxygenase inhibitors (indobufen and trifusal) for AF thromboprophylaxis showed no advantages over vitamin K antagonists. Combination clopidogrel and aspirin has also been found to be inferior to warfarin in high-risk AF patients (22).

Combination of aspirin and anticoagulation therapy, which is usually driven by presence of coronary artery disease, increases bleeding risk by 50% (62). There is no evidence that combining anticoagulation with aspirin reduces the risk of stroke compared with anticoagulant therapy alone. If clinically indicated, the ACC/AHA/ESC recommends maximizing anticoagulation to INR of 3.5–4.0 instead of routinely adding aspirin (22).

**Direct Thrombin Inhibitors And Factor Xa Inhibitors**

Oral direct thrombin inhibitors (dabigatran) and direct inhibitors of factor Xa (rivaroxaban, apixaban) have been available for clinical use for stroke prevention in AF. These drugs have a rapid, predictable and stable dose-related anticoagulant effect with a very few drug-drug interactions, thereby these agents can be used in fixed doses without the need for laboratory monitoring.

**Dabigatran** is a competitive, direct thrombin inhibitor (of both free and clot-bound thrombin), preventing conversion of fibrinogen into fibrin during the coagulation cascade and thereby development of a thrombus. Dabigatran prolongs the coagulation markers such as aPTT, ECT, and TT. The aPTT test provides an approximation of dabigatran’s anticoagulant effect. The recommended dose of dabigatran is 150 mg taken orally, twice daily for patients with creatinine clearance (CrCl) >30 mL/min, and 75 mg twice daily for patients with severe renal impairment (CrCl 15-30 mL/min).

The clinical efficacy of dabigatran was tested in the RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) (63), a multi-center, multinational, randomized parallel group trial comparing two blinded doses of dabigatran (110 mg twice daily and 150 mg twice daily) with open-label warfarin (dosed to target INR of 2 to 3) in patients with non-valvular, persistent, paroxysmal, or permanent atrial fibrillation and an additional risk factor [previous stroke, transient ischemic attack (TIA), or systemic embolism, left ventricular ejection fraction <40%, symptomatic heart failure, age ≥75 years or age ≥65 years with co-existent diabetes mellitus, coronary artery disease (CAD), or hypertension]. A total of 18,113 patients enrolled were followed up for a median duration 2 years. The study showed that both doses of dabigatran at 110 mg and 150 mg twice daily were non-inferior to adjusted-dose warfarin (P<0.001). Dabigatran 150 mg twice daily was superior to adjusted-dose warfarin in the prevention of stroke or systemic embolism (relative risk, 0.66; 95% confidence interval [CI], 0.53 to 0.82; P<0.001) but the 110-mg dose was not (relative risk, 0.91; 95% CI, 0.74 to 1.11; P=0.34). In addition, the rate of intracranial hemorrhage was much lower with both doses of dabigatran than with warfarin.

**Rivaroxaban** is an orally bioavailable factor Xa inhibitor that selectively blocks the active site of factor Xa and does not require a cofactor (such as Anti-thrombin III) for activity. Activation of factor X to factor Xa (FXa) via the intrinsic and extrinsic pathways plays a central role in the cascade of blood coagulation.

Dose-dependent inhibition of factor Xa activity occurs with the drug leading to a dose-dependent prolongation of the prothrombin time (PT), activated partial thromboplastin time (aPTT) and HepTestR anti X-a activity. The recommended dose of Rivaroxaban is 20 mg taken orally once daily with the evening meal for patients with creatinine clearance (CrCl) >50 mL/min, and 15 mg once daily with the evening meal for patients with CrCl 15 to 50 mL/min.

The evidence for the efficacy and safety of Rivaroxaban was derived from ROCKET AF,(64) a multi-national, double-blind study comparing Rivaroxaban to warfarin (titrated to INR 2.0 to 3.0) to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). Patients were included if they had a prior stroke (ischemic or unknown type), transient ischemic attack (TIA) or non-CNS systemic embolism, or
2 or more of the other risk factors (age ≥75 years, hypertension, heart failure or left ventricular ejection fraction ≤35%, or diabetes mellitus). A total of 14264 patients were randomized and followed on study treatment for a median of 590 days. Rivaroxaban was demonstrated non-inferior to warfarin for the primary composite endpoint of time to first occurrence of stroke (any type) or non-CNS systemic embolism [HR (95% CI): 0.88 (0.74, 1.03)], but superiority to warfarin was not demonstrated. There is insufficient experience to determine how Rivaroxaban and warfarin compare when warfarin therapy is well-controlled.

Rivaroxaban has a black-box in the US warning regarding potential thrombosis that may occur if it is discontinued and not replaced by another anticoagulant.

**Apixaban** is another oral, reversible, and selective active site inhibitor of FXa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound FXa, and prothrombinase activity. Apixaban prolongs coagulation tests such as prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT). Rotachrom® Heparin chromogenic assay can measure the effect of apixaban on FXa activity-a concentration-dependent increase in anti-FXa activity is observed with the drug. The recommended dose is 5 mg orally twice daily and 2.5 mg orally twice daily in patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.

Evidence for the efficacy and safety of Apixaban was derived from ARISTOTLE (65), a multinational, double-blind study in patients with nonvalvular atrial fibrillation (AF) comparing the effects of Apixaban and warfarin on the risk of stroke and systemic embolism. In ARISTOTLE, patients with nonvalvular atrial fibrillation and either prior stroke, transient ischemic attack (TIA) or systemic embolism or age ≥75 years, hypertension, diabetes mellitus,heart failure ≥New York Heart Association Class 2 or left ventricular ejection fraction ≤40% were randomized to Apixaban or to warfarin (targeted to an INR range of 2.0-3.0).

A total of 18,201 patients were randomized and followed on study treatment for a median of 89 weeks. Apixaban was superior to warfarin for the primary endpoint of reducing the risk of stroke and systemic embolism (1.27% per year in the apixaban group, as compared with 1.60% per year in the warfarin group (hazard ratio with apixaban, 0.79; 95% confidence interval [CI], 0.66 to 0.95; P<0.001 for noninferiority; P=0.01 for superiority). Superiority to warfarin was primarily attributable to a reduction in hemorrhagic stroke and ischemic strokes with hemorrhagic conversion compared to warfarin. Purely ischemic strokes occurred with similar rates on both drugs. Apixaban also showed significantly fewer major bleeds than warfarin. Apixaban treatment resulted in a significantly lower rate of all-cause death (p = 0.046) than did treatment with warfarin, primarily because of a reduction in cardiovascular death, particularly stroke deaths. Non-vascular death rates were similar in the treatment arms.

In AVERROES (66), patients with nonvalvular atrial fibrillation thought not to be candidates for warfarin therapy were randomized to treatment with Apixaban 5 mg orally twice daily (or 2.5 mg twice daily in selected patients) or aspirin 81 to 324 mg once daily. The primary objective of the study was to determine if Apixaban was superior to aspirin for preventing the composite outcome of stroke or systemic embolism. AVERROES was stopped early on the basis of a prespecified interim analysis showing a significant reduction in stroke and systemic embolism for Apixaban compared to aspirin that was associated with a modest increase in major bleeding.

**Hepaxin.**

Oral anticoagulant therapy can be interrupted (e.g. in preparation for a surgical procedure) for 1 week in most patients with AF. In those at high risk, or for longer periods of interruption, anticoagulation can be bridged using unfractionated or low molecular weight heparin (22).

(Continued on page 11)
The “syringe in the pocket” approach has recently been studied in AF patients after conversion to sinus rhythm. Patients were trained to identify AF by palpation of the radial pulse and to self-inject LMWH in case of arrhythmia recurrence. Majority of the patients were able to accurately diagnose AF recurrence and self-inject an initial dose of LMWH with a sensitivity 96.1% and specificity 60.4%. Pending further studies, this may be a potentially feasible strategy in patients who do not desire chronic anticoagulation (67).

Non-Pharmacologic Alternatives To Anticoagulation.

In chronic AF, over 90% of thrombi are located within the left atrial appendage (LAA). Patients who have relative or absolute contraindications to anticoagulation are potential candidates for LAA ligation, amputation, or occlusion. Surgical ligation or amputation of the LAA, performed routinely during mitral valve surgery or Maze procedure, reduces the likelihood of postoperative thromboembolic events. Long-term follow-up of patients showed that the incidence of an embolic event in those with LAA ligation was significantly lower than in those without (3% versus 17%). Incomplete ligation occurred in 22%, and these patients continued to be at risk for thromboembolism (68).

Percutaneous LAA occlusion is a less invasive alternative to surgical ligation. It involves implanting a device that seals the LAA via a catheter that crosses the intraatrial septum through a patent foramen ovale or transseptal puncture. Initial experience resulted in 97% procedural success, and a 2.2% annual stroke risk (69,70). Since long-term studies are still pending, indications for this type of investigational intervention have not yet been convincingly established.

Primary Prevention

There is suggestion that statins may decrease recurrence of AF after successful cardioversion, possible due to its anti-inflammatory properties (71). Angiotensin-converting enzyme inhibitors may play a preventive role on the development of atrial fibrillation (72). The LIFE and CHARM trials also showed that angiotensin receptor blocker-based therapy is associated with a decrease in incidence of new-onset AF (73,74). At this time, however, available data regarding interventions in the primary prevention of chronic AF is still insufficient as to permit definitive recommendations.

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