Clin. Cardiol. 31, 55–62 (2008)

Review

Update on Atrial Fibrillation: Part I

IRINA SAVELIEVA, M.D. and JOHN CAMM, M.D., F.R.C.P., F.E.S.C., F.A.C.C., F.A.H.A.

St George's University of London, London, U.K.

Summary

Atrial fibrillation (AF) is an epidemic, affecting 1% to 1.5% of the population in the developed world. Projected data from the population-based studies suggest that the prevalence of AF will grow at least 3-fold by 2050. The health and economic burden imposed by AF and AF-related morbidity is enormous.

Atrial fibrillation has a multiplicity of causes ranging from genetic to degenerative, but hypertension and heart failure are the commonest and epidemiologically most prevalent conditions associated with AF as both have been shown to create an arrhythmogenic substrate. Several theories emerged regarding the mechanism of AF, which can be combined into two groups: the single focus hypothesis and the multiple sources hypothesis. Several lines of evidence point to the relevance of both hypotheses to the mechanism of AF, probably with a different degree of involvement depending on the variety of AF (paroxysmal or persistent). Sustained AF alters electrophysiological and structural properties of the atrial myocardium such that the atria become more susceptible to the initiation and maintenance of the arrhythmia, a process known as atrial remodeling. Angiotensin II has been recognized as a key element in atrial remodeling in association with AF opening the possibility of exploitation of "upstream" therapies to prevent or delay atrial remodeling.

The clinical significance of AF lies predominantly in a 5-fold increased risk of stroke. The limitations of warfarin prompted the development of new antithrombotic drugs, which include anticoagulants, such as direct oral thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban). Novel mechanical approaches for the prevention of cardioembolic stroke have recently been evaluated: percutaneous left atrial appendage occluders, minimally invasive surgical isolation of the left atrial appendage, and implantation of carotid filtering devices.

Key words: atrial fibrillation, mechanisms, remodeling, antithrombotic drugs, antiarrhythmic drugs, catheter ablation, prevention

Clin. Cardiol. 2008; 31: 55–62.

Atrial Fibrillation—A New Epidemic

Atrial fibrillation (AF) is said to be an epidemic, affecting 1–1.5% of the population in the developed world.[1] Lifetime risks for development of AF are 1 in 4 for men and women 40 years of age and older.[2,3] The prevalence of AF will grow dramatically in the coming decades as the elderly proportion of the population increases because of the postwar baby boomers (now approaching 60 years of age) and greatly improved health care. Projected data from the cross-sectional AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) study of 17,974 adults who were enrolled in a large health maintenance organization in California and were diagnosed with AF in 1996–1997, have suggested that the number of Americans with AF will increase to more than 5.6 million, (2.5-fold), during the next 50 years.[4] Recent analysis from Mayo Clinic, based on the Poisson estimates of an increase in AF in Olmsted County between 1980 and 2000, has shown that the projected number of adults with AF for the year 2050 could be 15.9 million (a 3-fold upsurge from 2000), if a continuous rise in the incidence of AF is present[5] (Fig. 1). However, even these projections may represent conservative estimates because of silent AF.

Address for reprints:
John Camm, M.D., F.R.C.P., F.E.S.C., F.A.C.C., F.A.H.A.
Division of Cardiac and Vascular Sciences
St. George's University of London
Cranmer Terrace
London SW17 0RE, U.K.
e-mail: jcamm@sgul.ac.uk

Received: February 26, 2007
Accepted: March 6, 2007

Published online in Wiley InterScience
(www.interscience.wiley.com).
DOI:10.1002/clc.20138

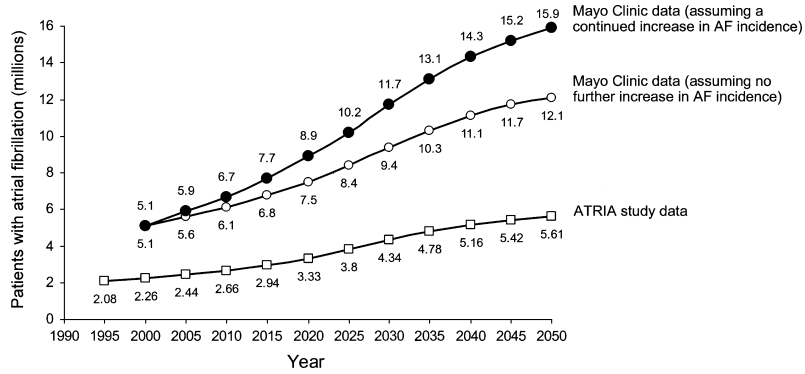

FIG. 1 Projected number of adults with atrial fibrillation in the United States by 2050. Modified from: Go AS et al.[4] and Miyasaka Y et al.[5] ATRIA = AnTicoagulation and Risk Factors In Atrial Fibrillation.

The clinical significance of AF lies in increased risk of stroke and congestive heart failure.[6,7] Strokes in AF are typically more severe and are associated with greater disability. AF leads to more hospital admissions than any other arrhythmia and according to recent surveys, the number of AF-related hospitalizations almost tripled in 2000 compared with two decades ago.[8] Although AF is classically caused by hypertension, heart failure, myocardial infarction, mitral stenosis, thyrotoxicosis, and alcohol, previously unrecognized risk factors, such as obesity, metabolic syndrome, diastolic dysfunction, sleep apnea, psychological stress, and tall stature, have emerged.[9] Genetic predisposition to AF or specific genetically predetermined forms of the arrhythmia have also been described.[10]

The high lifetime risk for AF and increased longevity underscore the important public health burden imposed by AF across the world. The arrhythmia presently costs approximately 1% of the health care budget in the United Kingdom and France.[11] On the basis of retrospective analyses of 3 federally funded databases in the United States in 2001 data, total annual costs for treatment of AF were estimated at $6.65 billion, including $2.93 billion (44%) for hospitalizations for AF, $1.95 billion (29%) for the incremental inpatient cost of AF as a comorbid diagnosis, $1.53 billion (23%) for outpatient treatment of AF, and $235 million (4%) for prescription drugs.[12]

Silent Atrial Fibrillation

Recently, the challenge of asymptomatic or silent AF has been recognized.[13] The prevalence of sustained silent AF is believed to be 25–30%, but modern implantable rhythm control devices, such as pacemakers and cardioverter-defibrillators, have revealed that up to 50–60% may have unsuspected episodes of the arrhythmia, with almost half of these lasting more than 48 h.[14] Pharmacological therapy and catheter ablation have been shown to convert symptomatic into asymptomatic AF.[13,15] Patients with unrecognized AF do not receive appropriate preventative therapy and are at greater risk of stroke or, in the case of persistent rapid ventricular rates, tachycardia-induced cardiomyopathy.

Mechanisms and Remodeling

Several theories emerged regarding the mechanism of AF, which can be combined into two groups: the single focus hypothesis (automatic focus, mother wave, fixed rotor, moving rotor) and the multiple sources hypothesis (multiple foci, multiple wavelets, unstable reentry circuits, the combination of a single focus and multiple wavelets) (Fig. 2). Those who advocate the single focus hypothesis believe that AF is due to a single rapid macro-reentry circuit, with wavefronts emanating from the primary driver circuit (rotor) breaking against regions of varying refractoriness, giving rise to irregular global activity characterizing the arrhythmia.[16] A single focus fires at a regular but very rapid rate which cannot be followed by the rest of the atrial tissue in a 1:1 fashion, thus producing fibrillatory conduction.

According to the multiple sources hypothesis, electrical activation in AF proceeds as multiple reentrant wavelets separated by lines of functional conduction block, generating irregular reentrant activity, which occurs in a dyssynchronous fashion in various atrial regions (multiple circuit reentry). These wavelets continuously initiate themselves (leading circle reentry) or each other (random reentry). The lines of the conduction block can occur around the anatomical structures within the atria with different inherent electrophysiological properties, acquired anatomical obstacles such as scars, patchy fibrosis, stretch-induced longitudinal dissociation or areas of myocardium at different stages of recovery and excitability. Spatial orientation of atrial myocytes, structural changes (e.g., increased cellular volume and sarcomere misalignment), and gap junction properties play an essential role. A critical mass of atrial tissue is required to sustain the minimal number of simultaneous circuits necessary for self-perpetuation of AF. Consequently, an increase in left atrial size by 5 mm was found to amplify the risk of AF by 40% in the population-based studies.[17] Others held that AF was caused by multiple ectopic foci producing fibrillation by virtue of dyssynchronous activity and colliding wavefronts.

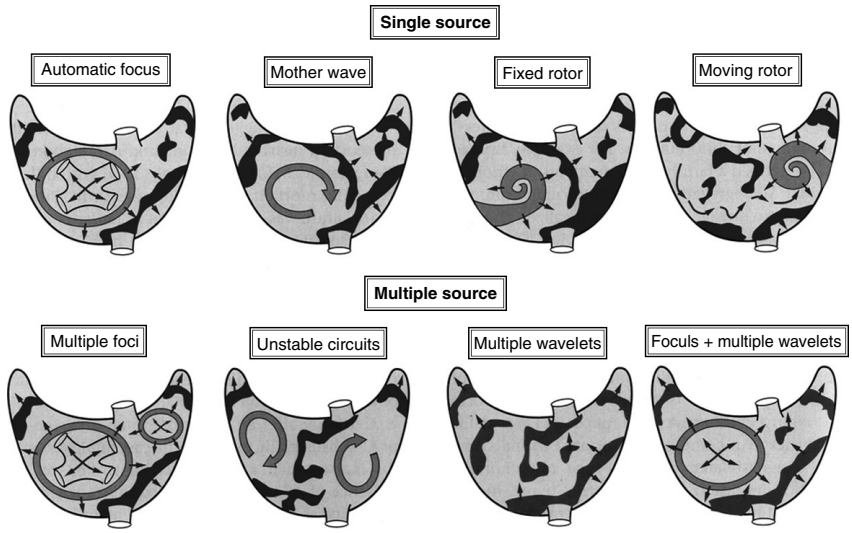

FIG. 2 Mechanisms of atrial fibrillation. Reproduced with permission from: Crijns HJGM, Allessie MA, Lip GYH: "Atrial Fibrillation: Epidemiology, Pathogenesis, and Diagnosis." In: Camm AJ, Lüsher TF, Serruys PW (EDs): The ESC Textbook of Cardiovascular Medicine. Blackwell Publishing Ltd, Oxford (2006).

With the development of methods to study cardiac electrophysiology, these theories have been further refined. Several lines of evidence point to the relevance of both hypotheses to the mechanism of clinical AF, probably with a different degree of involvement depending on the variety of AF (paroxysmal or persistent). There is emerging experimental evidence suggesting that certain cases of AF are maintained by small localized reentrant sources (rotors) with dominant high frequency that result in a hierarchical distribution of excitation frequencies throughout the atria.[18] Further to this theory, waves emanating from relatively stable rotors in the left atrium undergo complex, spatially distributed conduction block patterns as they propagate toward the right atrium, manifesting as "fibrillatory conduction." Others found multiple wavelets rather than single rotors at the sites with high frequency using models of sustained AF.

It has become obvious over the last few years that atrial electrical properties are altered by sustained AF, such that the atria become more susceptible to the initiation and maintenance of the arrhythmia.[19] Sustained AF in turn induces further electrophysiological and structural alterations of the atrial myocardium, a process known as atrial remodeling. Early in the development of AF, tachycardia-induced calcium overload of atrial myocytes prompts alterations in gene expression leading to down-regulation of the L-type calcium current. This results in a shortening of the atrial effective refractory period in order to compensate for calcium overload at the expense of a decrease in wavelength, thus promoting multiple wave reentry (electrical remodeling). If AF persists, ultrastructural changes such as increased cellular volume, sarcomere misalignment, proteolysis and loss of contractile elements and accumulation of glycogen may occur, leading to atrial myopathy.[20] Metabolism of atrial myocytes also changes shifting to a more fetal phenotype, so-called dedifferentiation. Further changes involve remodeling of gap-junctions with reduction in the expression of connexins Cx40 and Cx43. The concept of electrical and structural remodeling is therefore important as it explains why paroxysmal AF tends to become chronic, why longer-lasting AF is harder to treat and why AF recurrence is particularly likely in the first few days after electrical cardioversion.

Angiotensin II-Mediated Remodeling

Recently, angiotensin II has been recognized as a key element in atrial remodeling in association with AF. Atrial stretch increases local synthesis of angiotensin II. The density of angiotensin II receptors in the atria is generally greater than in the ventricles, making the atria more vulnerable to the effects of angiotensin. Subsequently, stimulation of angiotensin II type 1 (AT-1) receptors initiates a cascade of phosphorylation processes that activate a family of mitogen-activated protein kinases (MAP kinases).[21] The MAP kinases promote myocyte hypertrophy, fibroblast proliferation, accumulation of collagen, and apoptosis, further contributing to structural remodeling. In addition, angiotensin II modifies atrial electrophysiology by indirect effects on ion channels and may also impair cell-to-cell coupling associated with gap junction remodeling. There is strong experimental evidence that angiotensin receptor blockers (ARBs) and angiotensin converting enzyme (ACE) inhibitors can prevent electrical remodeling and reduce interstitial fibrosis in heart failure or rapid atrial pacing models of AF independently of the reduction in intra-atrial pressures.[22,23] These observations open the possibility of exploitation of these agents to prevent or delay atrial remodeling in patients with AF even in the absence of routine indications for such therapy.

Stroke Prevention

Risk Stratification

A number of models have been devised to predict the risk of stroke and the likelihood of benefit from therapy with either warfarin or aspirin.[24–28] Major risk factors were identified based on the pooled analysis of 1,593 untreated patients from five primary prevention trials of warfarin (known as Atrial Fibrillation Investigators' risk stratification model)[25] and the results from 2,012 participants from the aspirin arms of the Stroke Prevention in Atrial Fibrillation (SPAF) I–III studies.[26] All subsequent risk stratification schemes used a combination of these factors (Table 1).

The $CHADS_2$ scheme is an amalgamation of the individual risk factors: Congestive heart failure, Hypertension, Age >75 years, Diabetes mellitus, each of which is assigned one point, and prior Stroke or transient ischemic attack (TIA) which is given 2 points (hence, the subscript "2").[27] The $CHADS_2$ score system was designed to simplify the determination of stroke risk in general practice and is currently under validation. Using this system, the stroke rate per 100 patient-years without antithrombotic therapy is expected to increase by a factor of 1.5 for each 1-point increase from 1.9 for a score of 0 to 18.2 for the highest score of 6. The 2006 revised ACC/AHA/ESC guidelines for the management of patients with AF employed risk factors recognized by the AF and SPAF Investigators, but downgraded several risk factors rendering them "less validated or weaker" on the grounds of lack of evidence.[28]

Transesophageal echocardiography (TEE)-based risk factors have also been identified, such as an enlarged left atrial appendage with reduced inflow and outflow velocities and spontaneous echo contrast or thrombi and complex aortic plaque, but these risk markers are not routinely assessed in all AF populations.[29] Assessment of indexes of hypercoagulability and endothelial dysfunction or damage (e.g., von Willebrand factor, P-selectin, fibrin D-dimer, thrombomodulin, etc.) for prediction of stroke in AF remains a research tool.

A plethora of large randomized clinical trials have convincingly demonstrated the benefits of oral anticoagulation. Warfarin has consistently reduced the risk of ischemic stroke or systemic embolism by about two thirds compared with no treatment and by 30–40% compared with aspirin in high-risk patients with AF.[30] However, the effect of warfarin is sensitive to changes in diet, liver function, and drug interactions involving the P450 cytochromes and the drug has a very narrow therapeutic window. Consequently, a subtherapeutic INR of 1.5–1.9 reduced the preventive efficacy of warfarin by a factor of 3.6 in AF patients under 75 years and by a factor of 2 in patients over 75 years compared with the recommended INR values.[31] Risk of intracranial hemorrhage with controlled anticoagulation is small (0.3–0.5% per 100 patient-years), but it increases exponentially to 2.7% per 100 patient-years at INR values between 4 and 4.5 and to 9.4% per 100 patient-years when an INR exceeded 4.5.

Novel Pharmacological Therapies

Anticoagulant drugs with novel mechanisms of action are currently at different stages of clinical investigation (Table 2).[32] These agents have theoretical advantages compared to conventional therapy: rapid achievement of therapeutic effect, more dependable pharmaco kinetics and lack of interactions, and no need for anticoagulation monitoring. Some of these agents have proven noninferior to warfarin in stroke prevention and marginally superior to warfarin with regard to bleeding rates. However, the development of ximelagatran (AstraZeneca, London, U.K.), an oral direct thrombin inhibitor, has been terminated because of excess liver enzyme elevation in about 6% of patients and drug-related liver failure and death after the long-term exposure.

Dabigatran (Boehringer-Ingelheim) has the potential to become a replacement for warfarin in various clinical settings, but further work is needed to establish the safety and efficacy of this agent for the long-term use in AF. Pooled analysis of the dose-ranging, 12-week Prevention of Embolic and ThROmbotic events (PETRO) study (n = 502) and its open-label extension PETRO-EX study (n = 353) in patients with persistent AF and risk factors for stroke has shown that the efficacy and the adverse event rates of dabigatran 150 mg twice daily are comparable with those of dose-adjusted warfarin. The drug has recently entered a phase III randomized clinical trial of the prevention of stroke and systemic embolism (a primary endpoint) in AF. The Randomized Evaluation of Long-term anticoagulant therapY (RELY) trial, which started in December 2005, will randomize approximately 15,000 patients with AF to 2 blinded doses of dabigatran (150 mg twice daily or 300 mg once daily) or open-label warfarin. However, liver involvement may be an inherent safety issue with oral direct thrombin inhibitors, although the reported incidence of a significant (>3-fold) increase in liver enzymes was lower with dabigatran (approximately 2%) than with ximelagatran.

Indirect factor Xa inhibitors, such as fondaparinux and its longer acting congener idraparinux (both sanofi-aventis), are synthetic analogs of the pentasaccharide sequence of heparin that irreversibly inhibit factor Xa via antithrombin III-mediated mechanisms and can be administered subcutaneously or intravenously (fondaparinux). Idraparinux has the advantage that it can be administered only once a week; its anticoagulant effect has a rapid onset within 2 h and is predictable therefore obviating the need for coagulation monitoring. However, there are concerns about potential risks of irreversible factor Xa inhibition in the long-term and the current lack of any specific antidote. Biotinylated idraparinux (SSR 126 517), which can be neutralized by a protein avidin,

TABLE 1 Risk stratification systems for prediction of risk of stroke in atrial fibrillation

Year	Model	Risk factors	Event rate or recommendation
1994	AFI pooled analysis*	Hypertension, prior stroke or TIA, diabetes	Age < 65 years, no RF: 1.0% per year Age < 65 years+ ⩾ 1 RF: 4.9% per year Age 65–75 years+ ⩾ 1 RF: 5.7% per year Age < 75 years+ > 1 RF: 8.1% per year
1999	SPAF I-III†	SBP > 160 mm Hg; females > 75 years; males age > 75 years with hypertension; prior stroke or TIA	High risk: 7.1% per year
		Age ⩽ 75 years and hypertension or diabetes	Moderate risk: 2.6% per year
		No risk factors	Low risk: 0.9% per year
2001	ACCP guidelines	Age > 75 years; hypertension; left ventricular dysfunction or CHF; prior stroke, TIA or systemic embolism; rheumatic mitral valve disease or prosthetic heart valve	High risk: Warfarin
		Age 65–75 years, diabetes, coronary artery disease	Moderate risk: Warfarin or Aspirin
		Age ⩽ 65 years, no risk factors	Low risk: Aspirin
2001	$CHADS_2$	CHF (1 point), Hypertension (1), Age ⩾ 75 years (1), Diabetes (1), prior Stroke or TIA (2 points)	Score 0-1: 1.9-2.8% per 100 patient-years
			Score 2-4: 4.0-5.9% per 100 patient-years
			Score 5-6: 12.5-18.2% per 100 patient-years
2006	ACC/AHA/ESC guidelines	High-risk factors: previous stroke, TIA or systemic embolism; mitral stenosis; prosthetic heart valve	Any 1 high-risk or >1 moderate-risk factors: Warfarin
		Moderate-risk factors: age ⩾ 75 years; hypertension; CHF; ejection fraction ⩽ 35%; diabetes	Any 1 moderate-risk factors: Warfarin or Aspirin
		Less validated or weaker factors: female gender: age 65-74 years: coronary artery disease: thyrotoxicosis	No risk factors: Aspirin 81-325 mg

Source: ACC/AHA/ESC = American College of Cardiology/American Heart Association/European Society of Cardiology guidelines for the management of patients with atrial fibrillation;[28] ACCP = American College of Chest Physicians risk stratification process and therapeutic guidelines;[24] AFI = Atrial Fibrillation Investigators pooled analysis of 5 trials;[25] CHADS2 Score System, SPAF I-III = Stroke Prevention in Atrial Fibrillation I-III trials.[26]

* A separate analysis based on three randomized trials (BAATAF [Boston Area Anticoagulation Trial for Atrial Fibrillation], SPAF I [Stroke Prevention in Atrial Fibrillation I], and SPINAF [Veterans Affairs Stroke Prevention IN Atrial Fibrillation]) has shown that moderate-to severe left ventricular dysfunction was a strong independent predictor of stroke (relative risk 2.5) in the 1,010 patients in whom echocardiographic values for left ventricular function were available (Atrial Fibrillation Investigators data, Arch Intern Med 1998;158:1316-1320).

† The SPAF I and II Investigators identified left ventricular dysfunction defined as recent CHF or fractional shortening ≤ 25% as an independent risk factor for stroke, based on data from 854 SPAF I and II participants. However, the subsequent analysis of 2,012 participants in the SPAF I-III studies found that stroke was not significantly associated with a recent history of CHF or fractional shortening ≤ 25% (relative risk 1.2-1.7, p>0.05).

Abbreviations: CHF = congestive heart failure, SPB = systolic blood pressure, TIA = transient ischemic attack.

TABLE 2 New antithrombotic agents and devices under investigation for stroke prevention in atrial fibrillation

Drug/device	Mechanism of action	Evidence base in atrial fibrillation	Potential
Clopidogrel	Antiplatelet agent	Several small studies; ACTIVE program	Combination therapy with clopidogrel and aspirin is inferior to dose-adjusted warfarin
Enoxaparin, Dalteparin	Low molecular weight heparins	TEE-guided cardioversion studies; ACUTE II	Probably effective for short-term use in selected patients
Idraparinux	Factor Xa inhibitor (subcutaneous)	Phase III AMADEUS study stopped prematurely	Increased rates of major bleeding, raising concerns about potential risks of irreversible factor Xa inhibition and the current lack of any specific antidote
Apixaban,*	Factor Xa inhibitors (oral)	Phase III studies are underway	Non-inferiority to dose-adjusted warfarin
Ximelagatran, Dabigatran	Oral direct thrombin inhibitors	SPORTIF program; withdrawn PETRO and PETRO-extension studies; phase III RELY study ongoing	Non-inferiority to dose-adjusted warfarin, but potential liver toxicity
PLAATO WATCHMAN®	Percutaneous left atrial appendage occlusion	Limited experience worldwide within the clinical studies Phase III study vs warfarin ongoing	Probably useful in high-risk patients with absolute contraindications to warfarin
LAAO	Surgical left atrial appendage occlusion	Very limited experience; ongoing LAAOS trial in patients undergoing coronary bypass grafting	Limited to patients undergoing open heart surgery; left atrial appendage closure using a minimally-invasive or transthoracic approach has been described

Abbreviations: ACTIVE = Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events study, ACUTE II = Assessment of Cardioversion Using Transesophageal Echocardiography, AF = atrial fibrillation; AMADEUS = The Atrial fibrillation trial of Monitored, Adjusted Dose vitamin K antagonist, comparing Efficacy and safety with Unadjusted SanOrg 34 006/idraparinux study; LAAOS = Left Atrial Appendage Occlusion Study, PETRO = Prevention of Embolic and ThROmbotic events, PLAATO = percutaneous left atrial appendage transcatheter occluder, RELY = Randomized Evaluation of Long-term anticoagulant therapY study, TEE = transesophageal echocardiography; * =Rivaroxaban.

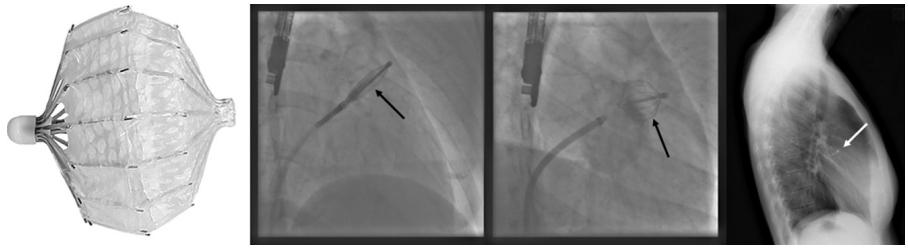

FIG. 3 (A) A percutaneous left atrial appendage transcatheter occluder (PLAATO, ev3 Inc., Plymouth, Minn., USA) in the left atrium before its release from the delivery catheter. The implant is constructed of a nitinol frame covered with an occlusive expanded polytetrafluoroethylene membrane. Small anchors along the frame and passing through the occlusive membrane assist with device anchoring. (B) A cineangiographic frame of the PLAATO device before its release into the left atrial appendage. (C) A cineangiographic frame of the PLAATO device after its deployment in the left atrial appendage. (D) The device in-situ as seen on a plain radiograph.

is currently under investigation. Unlike pentasaccharides for parental use, fondaparinux and idraparinux, new oral factor Xa inhibitors, such as rivaroxaban (BAY 59–7939, Bayer), apixaban (BMS-562 247, Bristol-Myers Squibb, New York, N.Y.), YM150 (Astellas Pharma Inc., Tokyo, Japan), inhibit factor Xa directly, without antithrombin III mediation, and therefore have the advantage of targeting both free factor Xa and inactivated factor Xa bound to platelets within the prothrombinase complex. Large-scale, phase III studies of rivaroxaban and a pixaban in AF are under way.

With the advent of more potent antiplatelet agents with better adverse event profiles such as clopidogrel, combined antiplatelet therapy might be more effective than aspirin alone or might be an alternative treatment to oral anticoagulation. However, the Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE) failed to show equivalence of combined antiplatelet therapy (aspirin and clopidogrel) over dose-adjusted warfarin in 6,706 high-risk AF patients.[33] The study was stopped prematurely due to clear evidence of superiority of conventional anticoagulation therapy. The efficacy of combination therapy with clopidogrel and aspirin may be more effective than either drug alone in patients who have contraindications or are unwilling to take warfarin.

Device Therapies for Stroke Prevention

A battery of novel mechanical approaches for the prevention of cardio-embolic stroke has recently been evaluated, including two devices for percutaneous occlusion of the left atrial appendage: percutaneous left atrial appendage transcatheter occluder, PLAATO, ev3 Inc., Plymouth, Minnesota) (Fig. 3) and WATCHMAN left atrial appendage system (Atritech, Inc., Minneapolis, Minn., USA). In 108 patients with a mean $CHADS_2$ score of 2.5, who received a PLAATO device, the annual rate of stroke was 2.2% compared with an expected annual risk of 6.3% for this population, an estimated 65% reduction in risk.[34] The preliminary experience with the WATCHMAN device in 66 patients showed satisfactory overall feasibility and safety. A multicenter prospective randomized study the WATCHMAN left atrial appendage system for embolic PROTECTion in patients with Atrial Fibrillation (PROTECT AF) duly will assess the effects of the device on the incidence of stroke, transient ischemic attacks, systemic embolism, and cardiovascular death compared with dose-adjusted warfarin in approximately 500 AF patients with one or more $CHADS_2$ risk scores.[36] The study started in December 2005 and will continue for 5 years.

Left atrial appendage isolation using the purse string technique, neck ligation, or surgical staplers via thoracoscopy, limited sternotomy, or as adjunct to open heart surgery, may also be considered for prevention or reduction of thromboembolism. The pilot study in 77 patients has demonstrated that the procedure is safe and can be performed at the time of coronary bypass grafting, without significantly prolonging the time of surgery.[37] However, the operation does not offer an absolute protection against stroke and complete occlusion of the left atrial appendage is technically challenging. A randomized, safety and feasibility study of the adjunct surgical closure of the appendage in 2,500 patients, Left Atrial Appendage Occlusion Study (LAAOS), is under way.

Emboli from the aortic arch and carotid arteries can account for 30–40% of embolic strokes. A permanent intra-arterial device (Diverter, MindGuard Ltd., Israel) is intended to filter the blood, which may contain clots and particles and prevent the embolic material from reaching intracranial circulation. A self-expandable tubular mesh device is deployed during a standard percutaneous endovascular procedure at the bifurcations of both common carotid arteries and diverts emboli$>$0.5 mm from the internal to the external carotid artery. Although there have been reports of successful implantation of the Diverter in humans, no data are available on its efficacy and safety compared with conventional therapy.

Conclusions

AF is likely to affect 2.5–3% of the population by 2050. Most of those who suffer from the arrhythmia will be over 70 years of age. The most significant risk associated

with AF is arterial thromboembolism and stroke. Conventional anticoagulant therapy is highly effective but is not consistently applied to all those at risk because of the inconvenience of regular INR monitoring and fears relating to bleeding complications. Although a broad array of new antithrombotic drugs are being investigated only a few have proven effective and safe and have reached the final stage of development. Agents with principally novel mechanisms of action are in the pipeline of many pharmaceutical companies. Device therapies for stroke prevention have been evaluated in small clinical trials, but they have not yet gained widespread clinical application.

References

1. Savelieva I, Camm AJ: Clinical trends in atrial fibrillation at the turn of the millennium. *J Intern Med* 2001;250:369–372
2. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, et al.: Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004;110:1042–1046
3. Heeringa J, van der Kuip DA, Hofman A, Hofman A, Breteler MM, et al.: Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006;27:949–953
4. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, et al.: Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001;285:2370–2375
5. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, et al.: Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006;114:119–125
6. Wolf PA, Abbot RD, Kannel WB: Atrial fibrillation as independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983–938
7. Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, et al.: Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol* 2000;35:1628–1637
8. Wattigney WA, Mensah GA, Croft JB: Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: implications for primary prevention. *Circulation* 2003;108:711–716
9. Tsang TS, Miyasaka Y, Barnes ME, Gersh BJ: Epidemiological profile of atrial fibrillation: a contemporary perspective. *Prog Cardiovasc Dis* 2005;48:1–8
10. Ellinor PT, Yoerger DM, Ruskin JN, MacRae CA: Familial aggregation in lone atrial fibrillation. *Hum Genet* 2005;118:179–184
11. Stewart S, Murphy N, Walker A, McGuire A, McMurray JJ: Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. *Heart* 2004;90:286–292
12. Coyne KS, Paramore C, Grandy S, Mercader M, Reynolds M, et al.: Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. *Value Health* 2006;9:348–356
13. Savelieva I, Camm AJ: Clinical relevance of silent atrial fibrillation: prevalence, prognosis, quality of life, and management. *J Interv Card Electrophysiol* 2000;4:369–382
14. Israel CW, Gronefeld G, Ehrlich JR, Li YG, Hohnloser SH: Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: implications for optimal patient care. *J Am Coll Cardiol* 2004;43:47–52
15. Hindricks G, Piorkowski C, Tanner H, Kobza R, Gerds-Li JH, et al.: Perception of atrial fibrillation before and after radiofrequency catheter ablation: relevance of asymptomatic arrhythmia recurrence. *Circulation* 2005;112:307–313
16. Camm AJ, Savelieva I, Bharati S, Lindsay BD, Nattel S: Atrial tachycardia, flutter and fibrillation. In *Electrophysiological Disorders of the Heart* (Eds. Saksena S, Camm AJ), pp 283–363. Philadelphia, PA: Elsevier Inc.: 2005
17. Vaziri SM, Larson MG, Benjamin EJ, Levy D: Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. *Circulation* 1994;89:724–730
18. Sanders P, Berenfeld O, Hocini M, Jais P, Vaidyanathan R, et al.: Spectral analysis identifies sites of high-frequency activity maintaining atrial fibrillation in humans. *Circulation* 2005;112:789–797
19. Allessie MA, Boyden PA, Camm AJ, Kleber AG, Lab MJ, et al.: Pathophysiology and prevention of atrial fibrillation. *Circulation* 2001;103:769–777
20. Allessie M, Ausma J, Schotten U: Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res* 2002;54:230–246
21. Goette A, Lendeckel U, Klein HU: Signal transduction systems and atrial fibrillation. *Cardiovasc Res* 2002;54:247–258
22. Kumagai K, Nakashima H, Urata H, Gondo N, Arakawa K, et al.: Effects of angiotensin II type 1 receptor antagonist on electrical and structural remodeling in atrial fibrillation. *J Am Coll Cardiol* 2003;41:2197–2204
23. Li D, Shinagawa K, Pang L, Leung TK, Cardin S, et al.: Effects of angiotensin-converting enzyme inhibition on the development of atrial fibrillation substrate in dogs with ventricular tachycardia-induced congestive heart failure. *Circulation* 2001;104:2608–2614
24. Albers GW, Dalen JE, Laupacis A, Manning WJ, Petersen P, et al.: Antithrombotic therapy in atrial fibrillation. *Chest* 2001;119: 194S–206S
25. Atrial Fibrillation Investigators: Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;154:1449–1457
26. Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW: Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. *Stroke* 1999;30:1223–1229
27. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, et al.: Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864–2870
28. Fuster V, Ryden LE, Fuster V, Ryden LE, Cannom DS, et al.: ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). *J Am Coll Cardiol* 2006;48:854–906
29. Fagan SM, Chan KL: Transesophageal echocardiography risk factors for stroke in nonvalvular atrial fibrillation. *Echocardiography* 2000;17:365–372
30. Lip GY, Edwards SJ: Stroke prevention with aspirin, warfarin and ximelagatran in patients with non-valvular atrial fibrillation: a systematic review and meta-analysis. *Thromb Res* 2006;118: 321–333
31. Hylek EM, Skates SJ, Sheehan MA, Singer DE: An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1996;335:540–546
32. Bates SM, Weitz JI: The status of new anticoagulants. *Br J Haematol* 2006;134:3–19
33. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, et al, ACTIVE Writing Group on behalf of the ACTIVE Investigators: Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;367:1903–1912
34. Ostermayer SH, Reisman M, Kramer PH, Matthews RV, Gray WA, et al.: Percutaneous left atrial appendage transcatheter occlusion (PLAATO system) to prevent stroke in high-risk patients with nonrheumatic atrial fibrillation: results from the international multi-center feasibility trials. *J Am Coll Cardiol* 2005;46:9–14
35. Sick PB, Schuler G, Grobe E, Yakubov S, et al.: Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. *J AM Coll Cardiol* 2007;49:1490–1495
36. Fountain RB, Holmes DR, Chandrasekaran K, Packer D, Asirvatham S, et al.: The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients with Atrial Fibrillation) trial. *Am Heart J* 2006;151:956–961
37. Healey JS, Crystal E, Lamy A, Teoh K, Semelhago L, et al.: Left Atrial Appendage Occlusion Study (LAAOS): results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke. *Am Heart J* 2005;150:288–293