

Current Perceptions of the Epidemiology of Atrial Fibrillation

William B. Kannel, MD, MPH, FACC^{a,b,*},
Emelia J. Benjamin, MD, ScM^{b,c}

KEYWORDS

- Atrial fibrillation • Epidemiology • Prognosis
- Risk factors • Cohort study

INCIDENCE, PREVALENCE, AND SECULAR TRENDS

Atrial fibrillation (AF) is a common, growing, and serious cardiac rhythm disturbance that is responsible for considerable morbidity and mortality in the population. The currently diagnosed estimate of 2.3 million people in the United States with it is expected to increase to 5.6 million by 2050. Its prevalence doubles with each decade of age, reaching almost 9% at the age of 80 to 89 years. Its population prevalence has reached epidemic proportions. This doubling with each decade of age occurs independent of the known predisposing conditions. Cardiovascular Health Study and Framingham Study data indicate that the incidence of AF per 1000 person-years in those younger than the age 64 years is 3.1 in men and 1.9 in women, increasing sharply to approximately 19.2 per 1000 person-years in those aged 65 to 74 years and to as high as 31.4 to 38 in octogenarians.^{1,2} The estimated general population prevalence of AF is 0.4% to 1%, increasing with advancing age.^{3,4} AF is uncommon before 60 years of age, but its prevalence increases markedly thereafter, afflicting approximately 10% of the population by 80 years of age.⁴ Approximately one third of all patients who have AF are aged 80 years or older, and it is estimated that by 2050, half of patients who have AF are likely to be in this age group.⁴

There is a male preponderance of risk for reasons currently unknown.⁵ The increase in incidence with age may involve age-related cardiac abnormalities, including gradual loss of nodal fibers and increased fibrous and adipose tissue in the sinoatrial node, decreased ventricular compliance from myocardial fibrosis resulting in atrial dilatation that predisposes to AF, and extensive senile amyloid infiltration of the sinoatrial node.⁶⁻⁸ There also seems to be an age-related prothrombotic diathesis. Age is a more potent AF risk factor if it is combined with other risk factors.⁹ Also, aging reflects longer exposure to predisposing conditions for AF, and even in advanced age, some individuals are clearly more vulnerable to its development than others.

Most reports on the epidemiology of AF are based on white North Americans or Europeans.¹⁰ Based on limited data, the age-adjusted risk for AF in African Americans appears to be about half that of whites.^{1,9,11} AF also is less common in African-American than in white heart failure patients.¹²

Because of the more than half-century surveillance of the Framingham Study cohort, it was possible to determine the lifetime risk for developing AF, which is 1 in 4 for men and women aged 40 years and older.¹³ These lifetime risks for AF are 1 in 6 even in the absence of predisposing

A version of this article originally appeared in *Medical Clinics of North America*, volume 92, issue 1. Funding for this study was provided by grants N01-HC 25195, RO1 HL076784, 1R01 AG028321, and 6R01-NS 17950.

^a National Heart Lung and Blood Institute's Framingham Heart Study, MA, USA

^b Boston University School of Medicine's Framingham Heart Study, 73 Mount Wayte Avenue, Suite 2, Framingham, MA 01702-5827, USA

^c School of Public Health, Boston University School of Medicine, MA, USA

* Corresponding author. The Framingham Study, 73 Mount Wayte Avenue #2, Framingham, MA 01702-5827. E-mail address: billkannel@yahoo.com (W.B. Kannel).

Cardiol Clin 27 (2009) 13-24

doi:10.1016/j.ccl.2008.09.015

0733-8651/08/\$ - see front matter © 2009 Elsevier Inc. All rights reserved.

cardiac conditions (**Table 1**). The prospective Rotterdam Study also found a similarly high lifetime AF risk (22%–24% at the age of 40 years).¹⁴ These alarming lifetime risks highlight the important public health liability posed by AF and the urgent necessity to continue investigation of predisposing conditions, preventive strategies, and more effective therapies.

The most credible explanation for the increasing prevalence of AF is that the current elderly population has more predisposing conditions, such as diabetes, obesity, heart failure, coronary and valvular heart disease, and prior cardiac surgery. This trend, brought about by advances in treatment of cardiovascular disease, has produced a population of elderly survivors containing more candidates for AF than formerly. The Rochester study, however, observed only modest increases in the prevalence of these predisposing conditions over 3 decades, which only partially explained the observed magnitude of the increased AF prevalence.¹⁵

CARDIOVASCULAR RISK FACTORS

Based on Framingham Study data, men have a 1.5-fold age- and risk factor-adjusted greater risk for AF than women. Of the standard cardiovascular risk factors, hypertension, diabetes, and obesity are the significant independent AF predictors. Because of its greater prevalence, hypertension is responsible for more AF in the population (14%) than any other risk factor

(**Table 2**).² Cigarette smoking was a significant risk factor in women adjusting only for age (odds ratio [OR] = 1.4) but was just short of significance on adjustment for other risk factors. Neither obesity nor alcohol intake seemed to be independently associated with the short-term risk for AF incidence in either gender. In other studies with sufficient power and numbers of individuals who consume alcohol in large amounts, however, it seems that alcohol abuse is a risk for AF occurrence.^{16,17}

Obesity is associated with long-term AF risk, which seems to be partially mediated by left atrial enlargement. The prevalence of obesity, diabetes, and the metabolic syndrome has reached major proportions worldwide. A retrospective analysis of AF incidence in relation to body mass index (BMI) in consecutive patients undergoing cardiac surgery found obesity to be an important determinant of new-onset AF after cardiac surgery.¹⁸ It is uncertain to what extent cardiovascular risk factors mediate the association between obesity and AF. A population-based Veterans Administration case-control study found that the association of AF with BMI seemed mediated partially by diabetes but only minimally through other cardiovascular risk factors.¹⁹ Obesity is associated with atrial enlargement and ventricular diastolic dysfunction, which are established predictors of AF.

Interrelations among AF risk factors, such as obesity, diabetes, and the “metabolic syndrome,” suggest that an insulin-resistant state is operative. A prospective analysis of consecutive hospitalized

Table 1

Lifetime risk for atrial fibrillation in the absence of antecedent or concurrent diagnosis of congestive heart failure or myocardial infarction

Index Age, Years	Men	Women
Lifetime risk for AF without antecedent or concurrent congestive heart failure		
40	20.5	17.0
50	20.5	17.3
60	20.3	17.4
70	19.1	17.0
80	17.6	15.9
Lifetime risk for AF without antecedent or concurrent congestive heart failure or myocardial infarction		
40	16.3	15.6
50	16.6	15.9
60	16.8	16.1
70	16.5	15.9
80	16.0	14.8

All values are percentages.

Data from Lloyd-Jones DM, Wang TJ, Leip E, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004;110:1042–6.

Table 2
Cardiovascular risk factors for atrial fibrillation in a 38-year follow-up: Framingham Study

Risk Factors	Odds Ratios			
	Age-Adjusted		Risk Factor-Adjusted	
	Men	Women	Men	Women
Diabetes	1.7**	2.1***	1.4*	1.6**
ECG LV hypertrophy	3.0**	3.8**	1.4	1.3
Hypertension	1.8**	1.7**	1.0**	1.4*
Cigarettes	1.0	1.4*	1.1	1.4
BMI	1.03	1.02	—	—
Alcohol	1.01	0.95	—	—

Abbreviations: BMI, body mass index; ECG, electrocardiography; LV, left ventricular; —, not retained in the model.

* $P < .05$; ** $P < .01$; *** $P < .001$.

Data from Benjamin EJ, Levy D, Vaziri SM, et al. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. *JAMA* 1994;271:840–4.

patients without obvious heart disease comparing subjects with and without the metabolic syndrome found that paroxysmal AF or atrial flutter occurred in 9% of patients with the syndrome and in only 4% of patients without it ($P = .02$). Multivariable analysis indicated that the metabolic syndrome remained a significant risk factor independent of left atrial diameter or age (OR = 2.8; $P < .01$). Among the five components of the metabolic syndrome, BMI was the most strongly associated with AF or atrial flutter (OR = 3.0; $P = .02$). It was concluded that the metabolic syndrome is strongly associated with AF or atrial flutter in patients without heart disease and that obesity may be an important underlying mechanism.²⁰

The Framingham Study prospectively investigated BMI as a long-term risk for new onset of AF.²¹ During a mean follow-up of 13.7 years, age-adjusted incidence rates for AF increased across BMI categories (normal, overweight, and obese) in men (9.7, 10.7, and 14.3 per 1000 person-years) and women (5.1, 8.6, and 9.9 per 1000 person-years). On adjustment for cardiovascular risk factors and interim myocardial infarction or heart failure, a 4% increase in AF risk per unit increase in BMI was observed in men and women. The adjusted hazard ratios (HRs) for AF associated with obesity were 1.5 for men and women compared with normal BMI. After adjustment for echocardiographic left atrial diameter in addition to clinical risk factors, BMI no longer was associated with AF risk. It was concluded that obesity is an important and potentially modifiable risk factor for AF, the excess risk for which seems to be mediated chiefly by left atrial dilatation. These data suggest that weight control may reduce the population burden of AF.

For men and women, respectively, diabetes conferred a 1.4- and 1.6-fold AF risk and hypertension conferred a 1.5- and 1.4-fold risk after adjusting for other associated conditions. Diabetes was also found to be a significant independent predictor of AF in four other studies, associated with an average relative risk (RR) of 1.8; however, in two other studies, it was not.⁹ Because the strength of diabetes as a predictor seems to be greater in lower risk patients who have AF, it is speculated that it also may be associated with noncardioembolic strokes. Diabetes is a less powerful independent predictor than prior stroke or transient ischemic attack (TIA), hypertension, or age, but further analysis is needed to refine its predictive value for thromboembolism in patients who have AF. The reduction in stroke in warfarin-treated patients who had diabetes was lower than average in two studies.⁹

Because of its high prevalence, hypertension seems to be responsible for more AF in the population (14%) than any other risk factor.^{2,5} Increased pulse pressure, a reflection of aortic stiffness, increases the cardiac load and, in the Framingham Study, increased AF risk.²² Cumulative 20-year AF incidence rates were 5.6% for subjects who had a pulse pressure of 40 mm Hg or less (twenty-fifth percentile) and 23.3% for those who had a pulse pressure greater than 61 mm Hg (seventy-fifth percentile). Even adjusting for age; gender; baseline and time-dependent change in mean arterial pressure; and clinical risk factors for AF, including BMI, smoking, valvular heart disease, diabetes, electrocardiography (ECG) left ventricular (LV) hypertrophy, hypertension treatment, and prevalent myocardial infarction or heart failure, pulse pressure was associated with an increased

risk for AF (adjusted HR = 1.26 per 20-mm Hg increment; $P = .001$). Systolic pressure was also significantly related to AF (HR = 1.14 per 20-mm Hg increment; $P = .006$). When diastolic pressure was added, the model fit improved and the diastolic relation was inverse (adjusted HR = 0.87 per 10-mm Hg increment), consistent with a pulse pressure effect. Furthermore, the association between pulse pressure and AF persisted in models that adjusted for baseline left atrial dimension, LV mass, and LV fractional shortening (adjusted HR = 1.23, 95% confidence interval [CI]: 1.09–1.39; $P = .001$). It seems that pulse pressure is an important risk factor for incident AF. Further research is needed to determine whether or not interventions that reduce pulse pressure can help to retard the growing incidence of AF.

CARDIOVASCULAR CONDITIONS

Persons who develop AF usually are elderly and more likely than persons of the same age to have predisposing cardiac abnormalities.^{2,5} Adjusting for cardiovascular risk factors, valvular heart disease, myocardial infarction, and heart failure substantially increases AF occurrence. Echocardiographic predictors of AF include left atrial enlargement, LV fractional shortening, LV wall thickness, and mitral annular calcification, offering prognostic information for AF beyond traditional clinical risk factors.

Approximately 20% of men and 30% of women with AF have valvular heart disease, approximately a quarter of both genders have heart failure, and 26% of men and 13% of women have myocardial infarctions. Prospectively, these overt cardiac conditions impose a substantial risk for AF. Adjusting for other relevant conditions, heart failure is associated with a 4.5- and 5.9-fold risk and valvular heart disease with a 1.8- and 3.4-fold risk for AF in men and women, respectively. Myocardial

infarction significantly increased the risk factor-adjusted likelihood of AF by 40% in men only (Table 3).

Mitral annular calcification is associated with adverse cardiovascular disease outcomes and stroke. Prospective data are limited on the association of mitral annular calcification with AF in particular. The Framingham Study investigated the association between mitral annular calcification and long-term (>16 years of follow-up) risk for AF in the original cohort attending routine examinations between 1979 and 1981.²³ In multivariable-adjusted analyses, mitral annular calcification was associated with a 1.6-fold increased risk for AF. This association was attenuated somewhat on further adjustment for left atrial size (HR = 1.4, 95% CI, 0.9–2.0), suggesting that the association between mitral annular calcification and AF is mediated partially through left atrial enlargement.²³

ECG LV hypertrophy seems to predispose to AF. In a double-blind, randomized, parallel-group study of subjects who had hypertension and ECG LV hypertrophy enrolled in the Losartan Intervention for Endpoint Reduction in Hypertension Study, occurrence of new-onset AF was investigated in relation to in-treatment regression or continued absence of ECG LV hypertrophy.²⁴ Quantified regression of ECG LV hypertrophy was associated with a reduced likelihood of acquiring AF, independent of blood pressure lowering and treatment.

ECHOCARDIOGRAPHIC ABNORMALITIES

Echocardiographic enlargement of the left atrial dimension and abnormal mitral or aortic valve function were each associated independently with increased prevalence and incidence of AF in the Cardiovascular Health Study.^{1,11} In the Framingham Study, echocardiographic predictors of AF include left atrial enlargement (39% increase in risk

Table 3
Risk for atrial fibrillation by specified cardiac conditions in subjects aged 55 to 94 years: Framingham Study

Cardiac Conditions	Odds Ratios			
	Age-Adjusted		Risk Factor-Adjusted	
	Men	Women	Men	Women
Myocardial infarction	2.2**	2.4**	1.4*	1.2
Heart failure	6.1***	8.1***	4.5***	5.9***
Valve disease	2.2***	3.6***	1.8**	3.4***

* $P < .05$; ** $P < .01$; *** $P < .001$.

Data from Benjamin EJ, et al. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. JAMA 1994;271:840–4.

per 5-mm increment), LV fractional shortening (34% per 5% decrement), and LV wall thickness (28% per 4-mm increment) (Table 4). These echocardiographic features offer prognostic information for AF beyond the traditional clinical risk factors.^{5,25}

CLINICAL MANIFESTATIONS

AF can cause palpitations, fatigue, lightheadedness, and exertional dyspnea by precipitating myocardial decompensation. When there is underlying coronary disease, it can bring on or aggravate angina because of an often associated rapid heart rate. AF is often undetected, however, because of lack of symptoms it often is first detected by routine ECG examination in the course of a myocardial infarction or stroke, on implanted pacemakers, or on ambulatory ECG monitoring.

AF was diagnosed incidentally in 12% of patients in the Cardiovascular Health Study¹ and in 45% of patients in the Stroke Prevention in Atrial Fibrillation Trials²⁶ having ECG for unrelated reasons. In a study of patients with paroxysmal AF, there were 12 times more asymptomatic than symptomatic episodes of AF and 38% of the patients with implanted pacemakers who experienced AF for more than 48 hours were unaware of it.²⁷ The 1.6% prevalence of AF in the absence of clinical and subclinical cardiovascular disease in the Cardiovascular Health Study indicates that "lone AF" is fairly uncommon in the elderly.¹¹

PROGNOSIS

AF is associated with an increased long-term risk for stroke, heart failure, and all-cause mortality, particularly in women.²⁸ The doubled mortality rate of patients who have AF is linked to the severity of the underlying heart disease.^{29–31} Approximately two thirds of the 3.7% mortality over 8.6 months in the *Activité Liberale la Fibrillation Auriculaire* study was attributed to cardiovascular causes.³² AF also independently predicts excess mortality and an increased incidence of embolic

stroke, however, accounting for between 75,000 and 100,000 strokes per year in the United States.³ AF is, per se, a powerful risk factor for stroke among older patients. The epidemic of AF in the twenty-first century seems to be occurring in conjunction with an increasing prevalence of heart failure, obesity, type 2 diabetes mellitus, and the prediabetic metabolic syndrome.³³

Framingham Study data indicate that AF and heart failure often coexist and that each may have an adverse impact on the other.³⁴ The decreased survival rate associated with AF occurs across a wide age range and is partially attributable to the vulnerability of patients who have AF to heart failure. Reported differences in mortality attributable to AF among studies may be influenced by the proportion of deaths from heart failure and thromboembolism. In large trials of heart failure, AF is a strong independent risk factor for mortality and major morbidity. In the Carvedilol or Metoprolol European Trial (COMET), there was no difference in all-cause mortality in subjects with AF at entry, but mortality increased in those who developed AF during follow-up.³⁵ In the Valsartan Heart Failure Trial of patients with chronic heart failure, development of AF was associated with significantly worse outcomes.³⁶ Managing AF in conjunction with heart failure is a major challenge requiring more trial data to guide and optimize its management.

The chief and most feared consequence of AF is a stroke, the risk for which is increased four- to fivefold.³⁷ AF assumes greater importance as a stroke hazard with advancing age, and by the ninth decade of life, it becomes the dominant factor. The attributable risk for stroke associated with AF increases steeply from 1.5% at the age of 50 to 59 years to 23.5% at the age of 80 to 89 years. The decreased survival rate associated with AF occurs across a wide age range.

AF is an established major independent risk factor for embolic stroke or TIA, but there is also evidence that a stroke may precipitate the onset of AF because of its hemodynamic and autonomic

Table 4
Echocardiographic predictors of atrial fibrillation in subjects aged 50 to 59 years: Framingham Study

Echocardiographic Feature	Atrial Fibrillation Risk
Left atrial diameter, mm	39% increase per 5 mm
Fractional shortening, %	34% increase per 5% decrease
LV wall thickness	28% increase per 4 mm
Two or more of previous features versus none	17% versus 3.7%

Data from Vaziri SM, Larson MG, Benjamin EJ, et al. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. *Circulation* 1994;89:724–30.

consequences. Approximately half of elderly patients with AF have hypertension as a concomitant major risk factor for stroke. Hypertension is a powerful independent predictor of stroke in AF and an important risk factor for developing AF. The strong association between AF, hypertension, and stroke could depend on reduced aortic compliance, LV hypertrophy, diastolic dysfunction, and left atrial dilatation, giving rise to stasis and thrombus formation.^{26,38,39}

AF accounts for approximately 45% of all embolic strokes. The reported risk for stroke in placebo-treated patients in randomized warfarin trials is 4.5% per year.^{38,40} Collaborative analysis of five randomized trials by the Atrial Fibrillation Investigators identified five major risk factors for stroke in patients who have AF: advanced age, prior stroke or TIA, a history of hypertension, heart failure, and diabetes.³⁹ Stroke risk increases at least fivefold in patients who have clinical risk factors. Other factors, such as female gender, systolic blood pressure (>160 mm Hg), and LV dysfunction, are also linked variably to stroke in patients who have AF. In patients aged 80 to 89 years, 36% of strokes occur in those who have AF. The annual risk for stroke in octogenarians who have AF ranges from 3% to 8% per year, depending on the burden of associated stroke risk factors.³⁷

Ischemic stroke and systemic arterial occlusion in AF are generally attributed to embolism of a thrombus from the fibrillating left atrium; however, up to 25% of strokes in patients who have AF may result from intrinsic cerebrovascular disease, other cardiac sources of embolism, or atherosclerotic pathologic findings in the proximal aorta.^{9,38} Although 12% harbor carotid artery stenosis, carotid atherosclerosis is not substantially more common in patients with AF who have a stroke, and therefore seems to be a minor contributing factor.^{41,42}

In the distant past, paroxysmal AF was considered more dangerous than persistent AF, with the former postulated to be more likely to embolize. The Framingham Study found chronic sustained AF to be at least as dangerous.⁴³ Analyses of pooled data from five randomized controlled trials suggest that paroxysmal and chronic AF have similar risks for stroke.³⁹

Before the Framingham Study report in 1982, there were many misconceptions about AF.⁴³ Its prognosis was believed to depend entirely on the underlying cardiac condition rather than on AF per se. AF unassociated with overt cardiovascular disease was considered to be a benign condition. Risk for embolism was not considered excessive unless AF was intermittent or associated with

mitral stenosis. The Framingham Study report established that AF further increased stroke risk associated with coronary heart disease and heart failure.⁴³

AF is responsible for substantial morbidity and mortality in the general population, chiefly from stroke, and leads to more hospital admissions than any other dysrhythmia.^{37,44,45} In addition to often disabling symptoms and impaired quality of life, AF can precipitate heart failure and trigger potentially fatal ventricular dysrhythmias. Reflecting this widespread epidemic of AF, data from US, Scottish, and Danish studies reported a 2- to 2.5-fold increase in hospitalization rates for AF between the 1980s and 1990s.⁴⁶⁻⁴⁸

PUBLIC HEALTH BURDEN AND COST

AF, first described in 1909, has acquired increasing clinical and public health importance because of the expanding elderly population containing vulnerable candidates.⁴⁷ Data from a National Hospital Discharge Survey indicate that hospital admissions resulting from AF increased two- to threefold from 1985 to 1999. During this period, hospitalizations listing AF increased from fewer than 800,000 to more than 2 million, predominantly in the elderly and men. Coyne and colleagues,⁴⁹ assessing direct costs of treating AF in the United States, list AF as one of the principal discharge diagnoses for 350,000 hospitalizations and 5 million office visits in 2001. The total costs in 2005 dollars were estimated at \$6.65 billion, including \$2.93 billion for hospitalizations.

Thus, AF is a costly public health problem.⁵⁰ Many factors contribute to the high cost of AF, with hospitalizations constituting the major contributor (52%), followed by drugs (23%), consultations (9%), further investigations (8%), loss of work (6%), and paramedical procedures (2%). The annual cost per patient is close to \$3600. Considering the prevalence of AF, the total economic burden is huge.⁹

THYROID DISEASE

For decades, hyperthyroidism has been an undisputed condition predisposing to AF. The prevalence of AF reported in patients at the time of diagnosis of overt hyperthyroidism varies from 2% to 30%.⁵¹⁻⁵³ Approximately 10% to 15% of persons who have overt hyperthyroid disease with AF are reported to have an arterial embolic event.⁵⁴⁻⁵⁶ Studies also suggest that subclinical abnormalities of thyroid-stimulating hormone have detrimental effects on the cardiovascular system.⁵⁷ Although AF is an acknowledged

manifestation of hyperthyroidism, older people in whom AF is common do not often have overt hyperthyroidism.

It was not firmly established that subclinical hyperthyroidism imposed a risk for AF until the Framingham Study investigated this hypothesis prospectively in relation to serum thyrotropin concentrations over 10 years in participants older than the age of 60 years. A low-serum thyrotropin level (<0.1 mU/L) was found to be associated with a three-fold higher risk for developing AF over a decade, even after adjusting for other known risk factors.⁵⁸

The increased AF risk for hyperthyroidism was confirmed in the Cardiovascular Health Study of subjects aged 65 years or older.⁵⁹ Eighty-two percent of participants had normal thyroid function, 15% had subclinical hypothyroidism, 1.6% had overt hypothyroidism, and 1.5% had subclinical hyperthyroidism. Individuals with subclinical hyperthyroidism had a twofold adjusted greater incidence of AF compared with those with normal thyroid function. No differences were seen in the subclinical hyperthyroidism and euthyroidism groups for incident coronary heart disease, stroke, cardiovascular death, or all-cause mortality. Likewise, there were no differences in the subclinical hypothyroidism or overt hypothyroidism group versus the euthyroidism group for cardiovascular outcomes or mortality. These data show an association between subclinical hyperthyroidism and development of AF but do not support the hypothesis that unrecognized subclinical hyperthyroidism or subclinical hypothyroidism is associated with other cardiovascular disorders that might predispose to AF.

NOVEL RISK FACTORS

Many novel modifiable and nonmodifiable risk factors for AF have been identified. These include reduced vascular compliance, atherosclerosis, insulin resistance, environmental factors, inflammatory markers, the obesity-induced metabolic syndrome, thrombogenic tendencies, sleep apnea, decreased arterial compliance, left atrial volume, diastolic dysfunction, and natriuretic peptides. There is emerging evidence that genetic variation also contributes to the risk for AF.

An inflammatory contribution for AF is supported by its frequent occurrence after cardiac surgery (25%–40%) and its association with pericarditis and myocarditis. The time course of AF after cardiac surgery parallels activation of the complement system and release of proinflammatory cytokines.^{60,61} C-reactive protein, a marker of inflammation, predicts adverse cardiac events linked to AF.^{60,61} In the Cardiovascular Health

Study, C-reactive protein was associated independently with AF at baseline and predicted an increased risk for developing future AF.⁶² It seems likely that indices of inflammation are markers for the underlying inflammatory atherosclerotic vascular disease.^{62–64}

There is other evidence suggesting a role of inflammation. A cross-sectional, community-based, Swedish observational study in a primary health care facility investigated AF prevalence in patients who had hypertension and type 2 diabetes, seeking possible mechanisms for its occurrence in these conditions. AF was found to be significantly associated with combined hypertension and type 2 diabetes even after adjusting for other cardiovascular risk factors. The BMI AF risk was attenuated on adjustment for ischemic ECG findings and lost significance with adjustment for insulin resistance (OR = 1.3, 95% CI: 0.5–3.1), suggesting that AF may be associated with the diabetes-hypertension combination because of insulin resistance.⁶⁵ The insulin-resistant “metabolic syndrome” is considered to be proinflammatory, and AF is linked to inflammation. The finding that new-onset AF is related significantly to BMI in multivariate analysis, adjusting for age and gender, also has some credibility because obesity is an independent predictor of diastolic dysfunction, which is also a major determinant of AF.⁶⁶

Obesity-promoted natriuretic peptides secreted from cardiomyocytes have a fundamental role in cardiovascular remodeling, volume homeostasis, and response to ischemia. Framingham Study investigation of the relation of B-type natriuretic peptide and N-terminal proatrial natriuretic peptide indicates that these natriuretic peptides are linked with an increased risk for AF and its predisposing cardiovascular conditions, such as heart failure and stroke (**Table 5**).⁶⁷

There is a well-documented relation between obesity and sleep apnea. A high recurrence rate of AF after cardioversion and AF recurrences in general is more common in untreated than treated obstructive sleep apnea. Patients undergoing cardioversion are reported to have a 49% prevalence of sleep apnea compared with a 39% frequency among other cardiac patients without AF. This is not attributable to other predisposing conditions.^{68,69} Postulated mechanisms include hypoxia, hypercarbia, autonomic imbalance, atrial stretching, and LV wall stress. Increased right-sided cardiac pressure stimulates the atrial natriuretic peptide release that is encountered in AF. Prospective studies of the relation of sleep-disordered breathing to AF are needed, however, taking into account its relation to obesity, metabolic syndrome, coronary artery disease, heart failure, and stroke.^{70,71}

Table 5
Plasma B-type natriuretic peptides and risk for cardiovascular disease and atrial fibrillation: Framingham Study

Outcome	Adjusted Hazard Ratio per 1-SD Increment in log B-type Natriuretic Peptide Values (%)	Adjusted Hazard Ratio for B-type Natriuretic Peptide Values Greater than Eightieth Percentile
Heart failure ^{b,c}	1.8***	3.1**
AF ^c	1.7***	1.9*
Stroke or TIA ^{a,b}	1.5**	2.0*
First cardiovascular event ^b	1.3*	1.8*
Death ^a	1.3**	1.6*

Adjusted for age, gender, hypertension, total/high-density lipoprotein cholesterol, smoking, diabetes, BMI, and serum creatinine. Eightieth percentile: women 23.3 pg/mL, men 20 pg/mL. Peptide levels not significantly related to coronary heart disease.

* $P < .05$; ** $P < .01$; *** $P < .001$.

^a Analysis was also adjusted for prevalent cardiovascular disease.

^b Analysis was also adjusted for prevalent AF.

^c Analysis was also adjusted for valvular disease and prevalent myocardial infarction.

Data from Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004;350:655–63.

Diastolic dysfunction commonly accompanies aging, hypertension, obesity, diabetes, heart failure, and coronary artery disease in the elderly. There is a graded relation of diastolic dysfunction to AF occurrence. On echocardiographic examination, elderly patients developed new-onset AF at a 1% rate with mild diastolic dysfunction compared with 12% with moderate diastolic dysfunction and 20% with severe diastolic dysfunction. Diastolic dysfunction provides incremental predictive information for the development of AF over that obtained from clinical risk factors. As left atrial volumes increase, diastolic function deteriorates, providing predictive information for the development of AF and stroke. Furthermore, left atrial volume is a predictor of other cardiovascular events, including myocardial infarction, stroke, and coronary revascularization, all of which predispose to AF.^{72,73}

GENETIC INFLUENCES

Alleged genetically determined risk factors, such as blood pressure, obesity, and greater stature, predispose to AF. It is uncertain how these constitutional factors promote AF, but metabolic disorders and genetic factors may be implicated. A familial occurrence of AF has been recognized but is considered uncommon. The Framingham Study confirmed that observed parental AF increases its risk for offspring two- to threefold after excluding persons with predisposing conditions. This observation supports a genetic susceptibility for this dysrhythmia.⁷⁴ In such AF families, familial linkage studies are beginning to explore the

genetics of AF, particularly in younger persons.^{75–77} Identification of a gene defect linked to chromosome 10q in a Spanish family, nearly half the members of which had AF, supports the hypothesis of familial AF.^{76,78} Most patients with AF in these families are younger than the age of 65 years, however, suggesting that the postulated genes causing AF may not be involved directly in the elderly.

The National Heart Lung and Blood Institute is sponsoring projects to examine the genetic contribution to AF and other cardiovascular phenotypes in the community. Two studies in particular plan to genotype thousands of candidate genes (Candidate Gene Association Resource project) and a 550,000 genome-wide scan of genetic polymorphisms (SNP Health Association Resource [SHARe]), with thousands of participants across many of the institute's cohort studies. Data from these studies should be available for analysis by investigators who have approved projects and ethical oversight. The aggregate results of these studies is to be posted on the Web.⁷⁹ Over the next decade, the advent of large-scale genotyping efforts should lead to advances in understanding the contribution of common complex genetic variation to AF in the community.

MULTIVARIABLE RISK ASSESSMENT

Multivariable risk assessment for stroke in patients who have AF is desirable for selecting those who most and least need aggressive anticoagulant therapy. The number needed to treat to prevent one event is inversely related to the level of risk;

thus, estimating the risk for stroke for individual patients with AF is crucial for the decision to prescribe anticoagulation therapy. The threshold risk warranting anticoagulation remains controversial, however. Patients who have a stroke risk of 2% or less per year do not benefit to a large extent from oral anticoagulation, and it would require treating 100 or more patients for 1 year to prevent a single stroke.⁹ For high-risk patients with AF, who have stroke rates of 6% per year or greater, the comparable needed-to-treat number is 25 or less, strongly favoring anticoagulation. For patients at intermediate stroke risk (annual rate from 3% to 5%), opinion about routine anticoagulation remains divided.

AF is a major component of the Framingham Study stroke risk prediction algorithm.⁸⁰ Framingham Study investigators sought to stratify risk further and elucidate which individuals who had AF were at particularly increased risk for stroke or stroke and death.⁸⁰ Their multivariable analysis examined risk factors for stroke among 705 patients who had recently detected AF, excluding those who had sustained an ischemic stroke, TIA, or death within 30 days of diagnosis. The significant predictors of ischemic stroke in subjects with AF were age (RR = 1.3 per decade), female gender (RR = 1.9), prior stroke or TIA (RR = 1.9), and diabetes (RR = 1.8). Systolic blood pressure became a significant predictor of stroke if warfarin was included in a time-dependent Cox proportional hazards model. With a scoring system based on age, gender, systolic hypertension, diabetes, and prior stroke or TIA, the proportion of patients classified as low risk varied from 14.3% to 30.6% depending on whether or not selected stroke rate thresholds were less than 1.5% per year or less than 2% per year.

SUMMARY

We are faced with a burgeoning epidemic of AF, which urgently demands improved prevention and treatment of this condition and its cardiovascular substrate. AF and the left atrial enlargement associated with it are likely direct causes of embolic stroke, requiring early detection and treatment. Targeted multivariable profile screening to detect persons who are likely candidates for AF is needed.

Disappointing results of therapy to suppress or eliminate the rhythm disturbance have justifiably focused greater attention on preventive treatment. Many AF risk factors also predispose to cardiovascular diseases that beget its development. Treatment of modifiable risk factors specific for AF in high-risk candidates enables early intervention,

when preventative or corrective measures are most effective. In the future, identification of genetic and biologic markers for AF and its complications may provide pathophysiologic insights and improve risk stratification for more personalized and targeted therapy.

Use of multivariable risk profiles to prevent a stroke, coronary disease, or cardiovascular disease in general should carry a bonus of prevention of AF. Therapies for predisposing factors using angiotensin-converting enzyme inhibitors and angiotensin receptor blockers recommended for hypertensive cardiovascular disease seem to reduce the rate of recurrence of AF after cardioversion and to protect against development of AF in patients with LV dysfunction.^{81–83} They also may inhibit the proinflammatory and sympathetic effects of angiotensin and interfere with the triggers and substrate of AF.⁹

Warfarin anticoagulant therapy is highly effective for prevention of stroke in patients who have AF.^{26,38} Meta-analysis, according to the principle of intention to treat, shows that adjusted-dose oral anticoagulation is highly efficacious for primary and secondary and disabling stroke prevention, with a risk reduction of 62% versus placebo.³⁹ Using “on-treatment analysis,” the preventive efficacy of oral anticoagulation exceeds 80%. Despite this, a survey of treatment for patients having cerebrovascular disease indicates that only 50% are being treated to recommended standards of care. The deficits found in adherence to recommended processes for basic care for cardiovascular disease in general and for AF in particular pose serious threats to the health of the population. Strategies to reduce these deficits in care are urgently needed.

REFERENCES

1. Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation* 1997;96:2455–61.
2. Benjamin EJ, Levy D, Vaziri SM, et al. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. *J Am Med Assoc* 1994;271:840–4.
3. Feinberg WM, Blackshear JL, Laupacis A, et al. Prevalence, age distribution and gender of patients with atrial fibrillation: analysis and implications. *Arch Intern Med* 1995;155:469–73.
4. Go AS, Hylek EM, Phillips KA, 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. *J Am Med Assoc* 2001;285:2370–5.

5. Kannel WB, Wolf PA, Benjamin EJ, et al. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998;82:2N-9N.
6. Falk RH. Etiology and complications of atrial fibrillation: insights from pathology studies. *Am J Cardiol* 1998;82:10N-7N.
7. Manyari DE, Patterson C, Johnson D, et al. Atrial and ventricular arrhythmias in asymptomatic elderly subjects. Correlation with left atrial size and left ventricular mass. *Am Heart J* 1990;119:1069-76.
8. Lie JT, Hammond PI. Pathology of the senescent heart: anatomic observations on 237 autopsy studies of patients 90 to 105 years old. *Mayo Clin Proc* 1988;63:552-64.
9. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: 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): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006;114:e257-354.
10. Ryder KM, Benjamin EJ. Epidemiology and significance of atrial fibrillation. *Am J Cardiol* 1999;84:131R-8R.
11. Furberg CD, Psaty BM, Manolio TA, et al. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol* 1994;74:236-41.
12. Ruo B, Capra AM, Jensvold NG, et al. Racial variation in the prevalence of atrial fibrillation among patients with heart failure: the epidemiology, practice, outcomes, and costs of heart failure (EPOCH) study. *J Am Coll Cardiol* 2004;43:429-35.
13. Lloyd-Jones DM, Wang TJ, Leip E, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004;110:1042-6.
14. Heeringa J, van der Kuip DA, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006;27:949-53.
15. Tsang TS, Petty GW, Barnes ME, et al. The prevalence of atrial fibrillation in incident stroke cases and matched population controls in Rochester, Minnesota: changes over three decades. *J Am Coll Cardiol* 2003;42:93-100.
16. Mukamal KJ, Tolstrup JS, Friberg J, et al. Alcohol consumption and risk of atrial fibrillation in men and women: the Copenhagen City Heart study. *Circulation* 2005;112:1736-42.
17. Djousse L, Levy D, Benjamin EJ, et al. Long-term alcohol consumption and the risk of atrial fibrillation in the Framingham Study. *Am J Cardiol* 2004;93:710-3.
18. Zacharias A, Schwann TA, Riordan CJ, et al. Obesity and risk of new-onset atrial fibrillation after cardiac surgery. *Circulation* 2005;112:3247-55.
19. Dublin S, French B, Glazer NL, et al. Risk of new-onset atrial fibrillation in relation to body mass index. *Arch Intern Med* 2006;166:2322-8.
20. Umetani K, Kodama Y, Nakamura T, et al. High prevalence of paroxysmal atrial fibrillation and/or atrial flutter in metabolic syndrome. *Circ J* 2007;71:252-5.
21. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new onset atrial fibrillation. *JAMA* 2004;292:2471-7.
22. Mitchell GF, Vasan RS, Keyes MJ, et al. Pulse pressure and risk of new onset atrial fibrillation. *J Am Med Assoc* 2007;297:709-15.
23. Fox CS, Parise H, Vasan R, et al. Mitral annular calcification is a predictor for incident atrial fibrillation. *Atherosclerosis* 2004;173:291-4.
24. Okin PM, Wachtell K, Devereux RB, et al. Regression of electrocardiographic left ventricular hypertrophy and decreased incidence of new-onset atrial fibrillation in patients with hypertension. *J Am Med Assoc* 2006;296:1242-8.
25. Vaziri SM, Larson MG, Benjamin EJ, et al. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. *Circulation* 1994;89:724-30.
26. The SPAF III. Writing Committee for the Stroke Prevention in Atrial Fibrillation Investigators. The SPAF III Writing Committee for the Stroke Prevention in Atrial Fibrillation Investigators. Patients with nonvalvular atrial fibrillation at low risk of stroke during treatment with aspirin: Stroke Prevention in Atrial Fibrillation III Study. *J Am Med Assoc* 1998;279:1273-7.
27. Israel CW, Gronefeld G, Ehrlich JR, et al. 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.
28. Stewart S, Hart CL, Hole DJ, et al. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002;113:359-64.
29. Kannel WB, Abbott RD, Savage DD, et al. Coronary heart disease and atrial fibrillation: the Framingham Study. *Am Heart J* 1983;106:389-96.
30. Krahn AD, Manfreda J, Tate RB, et al. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up study. *Am J Med* 1995;98:476-84.
31. Flegel KM, Shipley MJ, Rose G. Risk of stroke in non-rheumatic atrial fibrillation. [published erratum appears in *Lancet* 1987;1:878]. *Lancet* 1987;1:526-9.
32. Levy S, Maarek M, Coumel P, et al. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study. The College of French Cardiologists. *Circulation* 1999;99:3028-35.

33. Braunwald E. Shattuck lecture—cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med* 1997; 337:1360–9.
34. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;107:2920–5.
35. Swedberg K, Olsson LG, Charlesworth A, et al. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers. *Eur Heart J* 2005;26:1303–8.
36. Maggioni AP, Latini R, Carson PE, et al. Valsartan reduces the incidence of atrial fibrillation in patients with heart failure: results from the Valsartan Heart Failure Trial (Val-HeFT). *Am Heart J* 2005;149:1–10.
37. Wolf PA, Abbot RD, Kannel WB. Atrial fibrillation as independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983–8.
38. Gersh BJ, Tsang TSM, Barnes ME, et al. The changing epidemiology of non-valvular atrial fibrillation: the role of novel risk factors. *Eur Heart J Suppl* 2005;7:C5–C11.
39. 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;154:1449–57.
40. Krahn AD, Manfreda J, Tate RB, et al. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba follow-up study. *J Am Med Assoc* 1994;98:476–84.
41. Kanter MC, Tegeler CH, Pearce LA, et al. Carotid stenosis in patients with atrial fibrillation. Prevalence, risk factors, and relationship to stroke in the Stroke Prevention in Atrial Fibrillation study. *Arch Intern Med* 1994;154:1372–7.
42. Hart RG, Halperin JL. Atrial fibrillation and stroke: concepts and controversies. *Stroke* 2001;32:803–8.
43. Kannel WB, Abbott RD, Savage DD, et al. Epidemiologic features of chronic atrial fibrillation: the Framingham Study. *N Engl J Med* 1982;306:1018–22.
44. Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on risk of death: the Framingham Study. *Circulation* 1999;98:946–52.
45. Bailey D, Lehmann MH, Schumacher DN, et al. Hospitalization for arrhythmias in the United States. Importance of atrial fibrillation. *J Am Coll Cardiol* 1992;19:41A [abstract].
46. Wolf PA, Benjamin EJ, Belanger AJ, et al. Secular trends in the prevalence of atrial fibrillation: the Framingham study. *Am Heart J* 1996;131:790–5.
47. Stewart S, MacIntyre K, MacLeod MM, et al. Trends in hospital activity, morbidity and case fatality related to atrial fibrillation in Scotland, 1986–1996. *Eur Heart J* 2001;22:693–701.
48. Frost L, Engholm G, Møller H, et al. Decrease in mortality in patients with a hospital diagnosis of atrial fibrillation in Denmark during the period 1980–1993. *Eur Heart J* 1999;20:1592–9.
49. Coyne KS, Paramore C, Grandy S, et al. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. *Value Health* 2006;9: 348–56.
50. Stewart S, Murphy N, Walker A, et al. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. *Heart* 2004;90:286–92.
51. White PD, Aub JC. The electrocardiogram in thyroid disease. *Arch Intern Med* 1918;22:766–9.
52. Sandler G, Wilson GM. The nature and prognosis of heart disease in thyrotoxicosis: a review of 150 patients with 131I. *QJM* 1959;52:347–69.
53. Peterson P, Hansen JM. Stroke in thyrotoxicosis with atrial fibrillation. *Stroke* 1988;19:15–8.
54. Nordyke RA, Gilbert FI, Harada AS, et al. Disease: influence of age on clinical findings. *Arch Intern Med* 1988;148:626–31.
55. Presti CF, Hart RG. Thyrotoxicosis, atrial fibrillation and embolism revisited. *Am Heart J* 1989;117: 976–7.
56. Singer DE. Randomized trials of warfarin for atrial fibrillation. *N Engl J Med* 1992;327: 1451–3.
57. Tenerz A, Forberg R, Jansson R. Is a more active attitude warranted in patients with subclinical thyrotoxicosis? *J Intern Med* 1990;228:229–33.
58. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med* 1994;331: 1249–52.
59. Cappola AR, Fried LP, Arnold AM, et al. Thyroid status, cardiovascular risk and mortality in older adults. *J Am Med Assoc* 2006;295:1033–41.
60. Falk RH. Atrial fibrillation. *N Engl J Med* 2001;344: 1067–78.
61. Bruins P, Velthuis H, Yazdanbakhsh AP, et al. Activation of the complement system during and after cardiopulmonary bypass surgery: postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. *Circulation* 1997;96:3542–8.
62. Aviles RJ, Martin DO, Apperson-Hansen C, et al. Inflammation as a risk factor for atrial fibrillation. *Circulation* 2003;108:3006–10.
63. Boss CJ, Lip GY. The role of inflammation in atrial fibrillation. *Int J Clin Pract* 2005;59(8):870–2.
64. Chung MK, Martin DO, Sprecher D, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation* 2001;104:2886–91.
65. Powell BD, Redfield MM, Bybee KA, et al. Association of obesity with left ventricular remodeling and diastolic dysfunction in patients without coronary artery disease. *Am J Cardiol* 2006;98:116–20.

- Available at: http://www.ajconline.org/medline/record/ivp_00029149_98_116.
66. Hanna IR, Heeke B, Bush H. The relationship between stature and the prevalence of atrial fibrillation in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2006;47:1683–8.
 67. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004;350:655–63.
 68. Kanagala R, Murali NS, Friedman PA, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. *Circulation* 2003;107:2589–94.
 69. Gami AS, Pressman G, Caples SM, et al. Association of atrial fibrillation and obstructive sleep apnea. *Circulation* 2004;110:364–7.
 70. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. *J Am Med Assoc* 2003;290:1906–14.
 71. Krieger J, Laks L, Wilcox I, et al. Atrial natriuretic peptide release during sleep in patients with obstructive sleep apnea before and after treatment with nasal continuous positive airway pressure. *Clin Sci* 1989;77:407–11.
 72. Tsang TS, Gersh BJ, Appleton CP. Left ventricular diastolic dysfunction as a predictor of the first diagnosed nonvalvular atrial fibrillation in 840 elderly men and women. *J Am Coll Cardiol* 2002;40:1636–44.
 73. Benjamin EJ, D'Agostino RB, Belanger AJ, et al. Left atrial size and the risk of stroke and death. The Framingham Heart Study. *Circulation* 1995;92:835–41.
 74. Fox CS, Parise H, D'Agostino RB, et al. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. *J Am Med Assoc* 2004;291:2851–5.
 75. Darbar D, Herron KJ, Ballew JD, et al. Familial atrial fibrillation is a genetically heterogeneous disorder. *J Am Coll Cardiol* 2003;41:2185–92.
 76. Brugada R, Tapscott T, Czernuszewicz GZ, et al. Identification of a genetic locus for familial atrial fibrillation. *N Engl J Med* 1997;366:905–11.
 77. Crenshaw BS, Ward SR, Granger CB, et al. Atrial fibrillation in the setting of acute myocardial infarction: the GUSTO-I experience. *J Am Coll Cardiol* 1997;30:406–13.
 78. Chen YH, Xu SJ, Bendahhou S. KCNQ1 gain-of-function mutation in familial atrial fibrillation. *Science* 2003;299:251–4.
 79. Available at: http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000007.v3.p2. Accessed November 17, 2008..
 80. Wang TJ, Massaro JM, Levy D, et al. A risk score for predicting stroke or death in individuals with new onset atrial fibrillation in the community: the Framingham Heart Study. *J Am Med Assoc* 2003;290:1049–56.
 81. Vermees E, Tardif JC, Bourassa MG. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction: insight from the Studies of Left Ventricular Dysfunction (SOLVD) trials. *Circulation* 2003;107:2926–31.
 82. Klein HU, Goette A. Blockade of atrial angiotensin II type 1 receptors: a novel antiarrhythmic strategy to prevent atrial fibrillation? *J Am Coll Cardiol* 2003;41:2205–6.
 83. Rowan SB, Bailey DN, Bublitz CE, et al. Trends in anticoagulation for atrial fibrillation in the U.S.: an analysis of the national ambulatory medical care survey database. *J Am Coll Cardiol* 2007;49:1561–5.