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Current Perceptions of the Epidemiology of Atrial Fibrillation

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Synopsis

Atrial fibrillation, an escalating dysrhythmia, is accountable for extensive population morbidity and mortality. In the United States, about 2.3 million people are presently diagnosed with AF and, it is estimated that this prevalence may increase to 5.6 million by 2050. Foremost predisposing risk factors for this dysrythmia include advanced age and cardiovascular disease and its risk factors. The chief hazard of atrial fibrillation is embolic stroke, which is increased 4–5 fold and in advanced age it becomes a dominant stroke risk factor. Atrial fibrillation also carries a doubled mortality rate.

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 2.3 million people in the United States with it is expected to rise to 5.6 million by 2050. Its prevalence doubles with each decade of age, reaching almost 9% at ages 80 to 89 years. Its population prevalence has reached epidemic proportions. This doubling with each decade of age, occurs independently of the known predisposing conditions. Cardiovascular Health Study and Framingham Study data indicate that the incidence of AF per 1000 person-years under age 64 is 3.1 in men and 1.9 in women, rising sharply to approximately 19.2 per 1000 person-years in those ages 65 to 74 and is 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 age 80 or older and it is estimated that by 2050 half will be in this age group [4].

There is a male preponderance of risk for reasons currently unknown [5]. The rise in incidence with age may involve age -related cardiac abnormalities, including gradual loss of nodal fibers and increased fibrous and adipose tissue in the sínoatrial 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], [7], [8]. There also appears 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 are clearly more vulnerable to its development than others.

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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 less than half of that of whites. AF also is less common in African American than in white heart failure patients. [1], [11], [12], [9].

Because of the more than 50 year surveillance of the Framingham Study cohort, enabled the determination of the lifetime risk of AF, which is 1 in 4 for men and women ages 40 and older [13]. These lifetime risks for AF are 1 in 6 even in the absence of predisposing cardiac conditions (Table 1). The prospective Rotterdam Study also found asimilarly high lifetime AF risk (22%–24% at age 40) [14]. These alarming lifetime risks highlight the important public health liability posed by AF and the urgent necessity continue investigation of predisposing conditions, preventive strategies, and more effective therapies.

The most credible explanation of 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 that only partially explaine the observed magnitude of the increased AF prevalence of [15].

Cardiovascular Risk Factors

Based on Framingham Study data, men have a 1.5-fold age and risk factor adjusted greater risk of 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. [2], (Table 2). Cigarette smoking was a significant risk factor in women adjusting only for age (OR 1.4) but was just short of significance on adjustment for other risk factors. Neither obesity nor alcohol intake appeared to be independently associated with short-term risk of AF incidence in either sex. However, in other studies with sufficient power and numbers of individuals who consume alcohol in large amounts, it appears 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 have reached major proportions worldwide. A retrospective analysis of AF incidence in relation to BMI in consecutive cardiac surgery patients 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, established predictors of AF.

Inter-relations AF risk factors like obesity, diabetes and the “metabolic syndrome” suggests an insulin-resistant state is operative. A prospective analysis of consecutive hospitalized 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 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/atrial flutter (OR 3.0, $P = .02$). It was concluded that

the metabolic syndrome is strongly associated with AF/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 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, potentially modifiable risk factor for AF, the excess risk of 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 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, but 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 non-cardioembolic 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 thrombo-embolism in patients who have AF. The reduction in stroke in warfarin-treated patients who had diabetes was below average in two studies [9].

Owing to its high prevalence, hypertension appears 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, increases AF risk [22]. Cumulative 20-year AF incidence rates were 5.6% for subjects who had a pulse pressure 40 mm Hg or less (25th percentile) and 23.3% for those who had a pulse pressure greater than 61 mm Hg (75th percentile). Even adjusting for age, sex, baseline and time-dependent change in mean arterial pressure, and clinical risk factors for AF including body mass index, smoking, valvular heart disease, diabetes, ECG left ventricular hypertrophy, hypertension treatment, and prevalent myocardial infarction or heart failure, *pulse pressure* was associated with 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% 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 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 increase AF occurrence. Echocardiographic predictors of AF include left atrial enlargement, left

ventricular (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, about a quarter of both sexes have heart failure, and 26% of men and 13% of women have myocardial infarctions. Prospectively, these overt cardiac conditions impose a substantial risk of AF. Adjusting for other relevant conditions, heart failure is associated with a 4.5- and 5.9-fold risk and valvular heart disease 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 1.6-fold increased risk for AF. This association was attenuated somewhat on further adjustment for left atrial size (HR 1.4; CI, 0.9–2.0), suggesting that the association between mitral annular calcification and AF is mediated only partially through left atrial enlargement [23].

ECG-LVH appears 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 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. However, AF is often undetected because of *lack of symptoms* and first detected by routine ECG examination in the course of a myocardial infarction or stroke, or on implanted pacemakers, or ambulatory ECG monitoring.

AF was diagnosed incidentally in 12% of patients in the Cardiovascular Health Study [1] and in 45% of patients in the Stroke Prevention in Atrial Fibrillation Trials [26] having an 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 atrial fibrillation” is fairly uncommon in the elderly [11].

Prognosis

AF is associated with increased long-term risk for stroke, heart failure, and all-cause mortality, particularly in women [28]. The doubled mortality rate of AF patients is linked to the severity of underlying heart disease [29], [30], [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]. However, AF also independently predicts excess mortality as well as an increased incidence of embolic stroke, 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 appears to be occurring in conjunction with a rising prevalence of heart failure, obesity, type 2 diabetes mellitus, and the pre-diabetic 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 associated with AF occurs across a wide age range, is partially attributable to the vulnerability of AF patients to heart failure. Reported differences in AF mortality among studies may be influenced by the proportion of deaths from heart failure and thrombo-embolism. 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 4–5 fold [37]. AF assumes greater importance as a stroke hazard with advancing age and by the ninth decade becomes the dominant factor. The attributable risk for stroke associated with AF increases steeply from 1.5% at ages 50 to 59 to 23.5% at ages 80 to 89. The decreased survival associated with AF occurs across a wide age range.

AF is an established major independent risk factor for embolic stroke or TIA; AF but there also is evidence that a stroke may precipitate onset of AF because of its hemodynamic and autonomic consequences. About half of elderly patients with AF have hypertension as a concomitant major risk factor for stroke. Hypertension is both 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 5 major risk factors for stroke in AF patients: advanced age, prior stroke or TIA, a history of hypertension, heart failure, and diabetes (Table 6) [39]. Stroke risk increases at least 5-fold 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 AF patients. In patients 80 to 89 years old, 36% of strokes occur in those who have AF. The annual risk for stroke for 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 AF patients may be result from intrinsic cerebrovascular disease, other cardiac sources of embolism, or atherosclerotic pathology 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 appears to be a minor contributing factor [41], [42].

In the distant past, paroxysmal AF was considered more dangerous than persistent AF, the former postulated 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 [38]. However, several studies suggest higher mortality in persistent than chronic AF [39], [40], [41].

Before the Framingham Study report in 1982, there were many misconceptions about AF [43]. Its prognosis was believed to be entirely dependent on the underlying cardiac condition, not AF per se. AF unassociated with overt cardiovascular disease was considered 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 [44], [37], [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 United States, Scottish, and Danish studies reported a two- to 2.5-fold increase in hospitalization rates for AF between the 1980s and 1990s [46], [47], [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 2–3 fold from 1985 to 1999. During this period, hospitalizations listing AF increased from under 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

Hyperthyroidism has for decades been an undisputed condition predisposing to AF. The prevalence of AF reported in patients at time of diagnosis of overt hyperthyroidism varies from 2% to 30% [51], [52], [53],. About 10% to 15% of persons who have overt hyperthyroid disease with AF are reported to have an arterial embolic event [54], [55], [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 over age 60. A low-serum thyrotropin (<0.1 mU per liter) was found to be associated with a 3-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 ages 65 years or older [59]. Eighty-two percent of participants had normal thyroid function, 15% had subclinical hypothyroidism, 1.6% overt hypothyroidism, and 1.5% subclinical hyperthyroidism. Individuals with subclinical hyperthyroidism had a 2-fold 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 groups Vs. 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 non-modifiable 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 risk for AF.

An inflammatory contribution AF is supported by its frequent occurrence after cardiac surgery (25% to 40%), in genetic studies, and its association with pericarditis and myocarditis. The time course of AF after cardiac surgery parallels activation of the complement system and release of pro-inflammatory cytokines [60], [61]. C-reactive protein, a marker of inflammation, predicts adverse cardiac events linked to AF [60], [61] [62]. In the Cardiovascular Health Study, C-reactive protein was associated independently with AF at baseline and predicted increased risk for developing future AF [65]. It seems likely that indices of inflammation are markers for the underlying inflammatory atherosclerotic vascular disease [63] [64], [65].

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 with 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 [0.5–3.1]) suggesting that AF may be associated with the diabetes-hypertension combination because of insulin resistance [66]. The insulin resistant “metabolic syndrome” is considered to be pro-inflammatory 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, also a major determinant of AF [67].

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 pro-atrial natriuretic indicates that these natriuretic peptides are linked with increased risk for AF and its predisposing cardiovascular conditions, such as heart failure and stroke (Table 5) [68].

There is a well-documented relationship between obesity and sleep apnea. A high recurrence of AF after cardioversion and AF recurrences in general, are 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 other predisposing conditions [69], [70]. Postulated mechanisms include hypoxia, hypercarbia, autonomic imbalance, atrial stretching, and LV wall stress. Increased right-sided cardiac pressure stimulates atrial natriuretic peptide release that is encountered in AF. However, prospective studies of the relationship of sleep-disordered breathing with AF are needed, taking into account its relationship to obesity, metabolic syndrome, coronary artery disease, heart failure, and stroke [71], [72].

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 Elderly patients in on echocardiographic examination 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 development of AF over that obtained from clinical risk factors. As left atrial volumes increase, diastolic function deteriorates, providing predictive information for 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 [73, [74].

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 was considered uncommon. The Framingham Study confirmed that observed parental AF increases its risk for offspring 2–3 fold after excluding persons with predisposing conditions. This observation supports a genetic susceptibility for this dysrhythmia [75]. In such AF families familial linkage studies are beginning to explore the genetics of AF, particularly in younger persons [76], [77], [78]. 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 [77], [79]., However, the majority of patients with AF in these families are younger than age 65, 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 will genotype 1000s of candidate genes (Candidate gene Association Resource project) and a 550K 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 will be available for analysis by investigators who have approved projects and ethical oversight. The aggregate results of these studies will be posted on the Web (http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?id=phs000007). 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 so estimating the risk for stroke for individual patients with AF is crucial for the decision to prescribe anticoagulation therapy. However, the threshold risk warranting anticoagulation remains controversial. Patients who have a stroke risk of ≤ 2% 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 3% to 5%), opinion about routine anticoagulation remains divided.

AF is a major component of the Framingham stroke risk prediction algorithm [3]. 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, appear to reduce the rate of recurrence of AF after cardioversion and protect against development of AF in patients with LV dysfunction [81], [82], [83]. They also may inhibit the pro-inflammatory 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 AF patients [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 [38]. Using "on-treatment analysis" the preventive efficacy of oral anticoagulation exceeds 80%. Despite this, a survey of treatment for patients having cerbrovascular 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 AF in particular poses serious threats to the health of the population. Strategies to reduce these deficits in care are urgently needed.

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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 The Framingham Heart Study. Circulation 2004;110:1042–6.

Table 2

Cardiovascular risk factors for atrial fibrillation; 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**	1.5*	1.4***
Cigarettes	1.0	1.4***	1.1	1.4
BMI	1.03	1.02	d	d
Alcohol	1.01	0.95	d	d

* P!.01;

** P!.001;

*** P!.05.

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

Table 3

Risk of Atrial Fibrillation by Specified Cardiac Conditions. Subjects Ages 55–94 Years. Framingham Study

	Odds Ratios			
	Age adjusted		Risk Factor Adjusted	
Cardiac Conditions	**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< 0.05,

** P,0.01,

*** P, 0.001

EJ Benjamin et al. JAMA 1994; 271: 840–844

Table 4

Echocardiographic predictors of atrial fibrillation: Framingham study; subjects ages 50 to 59 years

Echocardiographic features	Atrial fibrillation risk
Left atrial diameter, mm	39% increase per 5 mm
Fractional shortening, %	34% increase per _5%
Left ventricular wall thickness	28% increase per 4 mm
Two or more of above 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.

Table 5

Plasma B-type natriuretic peptides and risk for cerebrovascular disease and atrial fibrillation: Framingham Study

Cardiovascular disease event	Percent increase in CVD per SD increment	Multivariable Hazaed Ratio per BNP > 80th Percentile
Heart failure	77%	3.1*
Atrial fibrillation	66%	1.9**
Stroke/TIA	53%	2.0**
First CV event	28%	1.8**
Death	27%	1.6**
A		

Adjusted for age, diabetes, blood pressure, smoking, creatinine, LV mass, and systolic function; 80th percentile B-type natriuretic peptide (BNP): women 23.3 pg/mL, men 20 pg/mL.

Peptide levels not significantly related to coronary heart disease.

* P!.01;

** P!.05.

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.