Final Draft Status of the Epidemiology of Atrial Fibrillation

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Abstract

Atrial fibrillation (AF), a common and serious cardiac rhythm disturbance, is responsible for substantial morbidity and mortality in the population. Currently about 2.3 million people in the US are diagnosed with AF and, based of the US census, this number is expected to rise to 5.6 million by 2050. It doubles in prevalence with each decade of age, reaching almost 9% at age 80–89 years. It has increased in prevalence over the calendar decades, reaching 'epidemic' proportions. This alarming increase in prevalence is incompletely explained by an increase in the population prevalence of elderly individuals, valve disease, heart failure or myocardial infarction. New onset AF also doubles with each decade of age, independent of the prevalence of known predisposing conditions.

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

Adjusting for cardiovascular risk factors, heart failure, valvular heart disease and myocardial infarction substantially increase the likelihood of AF. Echocardiographic predictors of AF include left atrial enlargement, left ventricular fractional shortening, left ventricular wall thickness, and mitral annular calcification, offering prognostic information for AF beyond traditional clinical risk factors. Novel risk factors for AF include reduced vascular compliance, atherosclerosis, insulin resistance, environmental factors, inflammation and natriuretic peptides. There is emerging evidence that genetic variation also contributes to risk of atrial fibrillation.

The chief hazard of AF is a 4–5-fold increase in embolic stroke, assuming great importance in advanced age when it becomes a dominant factor. The attributable risk for stroke associated with AF increases steeply with age to 23.5% at age 80–89 years. AF is associated with a doubling of mortality in both sexes.

Synopsis—Atrial fibrillation (AF), an increasingly common dysrithmia, is responsible for substantial morbidity and mortality. Currently in the US about 2.3 million people are diagnosed with AF and, based on the US census, this number may rise to 5.6 million by 2050. Risk factors for AF include advancing age, cardiovascular disease and its risk factors. The chief hazard of AF is embolic

stroke which is increased 4–5-fold, assuming great importance in advanced age when it becomes a dominant factor. AF is associated with about a doubling of mortality.

Introduction

Before the Framingham study report in 1982 there were many misconceptions about AF (1). Its prognosis was believed to be dependent on the underlying cardiac condition, not AF per se. AF unassociated with overt cardiovascular disease was considered a benign condition. Risk of embolism was not considered excessive unless the 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 (1).

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 (2–4). 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 2–2.5-fold increase in hospitalization rates for AF between the 1980's and 1990's (5–7).

AF doubles in prevalence with each decade of age and is becoming increasingly prevalent in the population. The reason for the alarming increase is largely unexplained. There is a need for new strategies to prevent AF and improve its treatment. Although newer pharmacological and non-pharmacological therapies are being developed, more effective measures are needed to treat AF safely and prevent its occurrence and its cardiovascular consequences.

Incidence, Prevalence and Lifetime Risk

AF is a highly prevalent sustained dysrhythmia. It is the most common cardiac rhythm disturbance treated in clinical practice, accounting for approximately one-third of hospitalizations for cardiac dysrhythmias. It is estimated to currently affect over 6 million patients in Europe and approximately 2.3 million in the United States, and this number continues to grow rapidly because of the increasing proportion of the ageing population with and without underlying heart disease. Reports from the Cardiovascular Health Study and the Framingham Study indicate that the incidence of AF per 1000 person-years in subjects under 64 years is 3.1 in men and 1.9 in women, rising sharply to about 19.2 per 1000 person-years in those 65–74 years, and is as high as 31.4–38.0 in octogenarians (8,9).

The estimated prevalence of AF in the general population is 0.4% to 1%, increasing with advancing age (10,13). AF is uncommon before 60 years of age, but the prevalence increases markedly thereafter, afflicting about 10% of the population by 80 years of age (13). The median age of AF patients is about 75 years with approximately 70% between 65 and 85 years of age. About one-third of all patients with AF are aged 80 years or older and it is estimated that by 2050 half will be in this age group (13).

Multiple studies of the incidence and prevalence of AF in the US, Europe and Australia have produced reasonably consistent findings (10). For reasons that are largely unexplained, the age-adjusted prevalence of AF in the US is greater in men than in women, both in a large cross-sectional study of adults enrolled in the Kaiser Permanente health maintenance organization and in the Framingham Study. Likewise, in the large population-based Rotterdam study, the prevalence of AF increased with age and was higher in men than in women in each age group, but the high lifetime risk of AF differed little between the sexes. (11)

Because of the more than half century surveillance of the Framingham Study cohort it was possible to determine the lifetime risk of developing AF which is 1 in 4 for men and women

40 years of age and older (12). These lifetime risks for AF remain high (1 in 6), even in the absence of antecedent predisposing conditions such as heart failure or myocardial infarction (Table 1). Prospective data from the Rotterdam Study, also found a high lifetime AF risk (22–24% at age 40 years) similar to North American epidemiological data. (11) The substantial lifetime risks underscore the major public health burden posed by AF and the need for further investigation into predisposing conditions, preventive strategies, and more effective therapies.

Most of the literature on the epidemiology of atrial fibrillation is based on white individuals residing in North American or Europe. (14) Based on limited data, the age-adjusted risk of developing AF in African-Americans is reported to be less than half of that in whites. AF is also less common among African-American than white patients with heart failure. (15–18)

Secular Trends

The prevalence of AF has increased over the past few decades, though studies have varied as to whether the increasing prevalence is restricted to men or both sexes. In the Copenhagen City Heart Study, the prevalence in men more than doubled from the 1970s to the 1990s, whereas the prevalence in women remained unchanged.(19) However, other studies show that it is increasing in both sexes (20,21). The alarming increase in numbers of patients with AF in the general population is not due to increasing use of the electrocardiogram in the community, because in the Framingham Study cohort electrocardiograms are routinely obtained on each examination; there was an age-adjusted secular increase in prevalence of AF on clinic electrocardiogram (5). Also in the Rochester population, utilization of the electrocardiogram increased by only 9–12%, over a 30-year period, whereas there was 2–3 fold increase in the prevalence of AF (22). In Denmark, standardizing by age and 10-year age group, the AF incidence rates approximately doubled for both men and women (197 per 100,000 in 1980 and 448 per 100,000 in 1999) (21)

A more credible explanation of the increasing prevalence of AF over time is that the elderly population of today has a higher prevalence of predisposing conditions for AF such as diabetes, obesity, heart failure, coronary and valvular heart disease, and prior cardiac surgery. This trend, brought about by advances in the treatment of cardiovascular disease, has produced a population of elderly survivors containing more candidates for AF than formerly. However, the Rochester study observed only modest increases in the prevalence of these predisposing conditions over a 3 decade period, that did not appear to more than partially explain the observed magnitude of the increase in prevalence of AF.(22)

US census projections for the next 50 years estimate that about 3 million Americans will have AF by the year 2020, increasing to 5.6 million by the year 2050, with more than half affected age 80 or older (13,23–25). The magnitude of these projections is may be underestimated because many episodes of AF go undetected.

Public Health Burden and Cost

AF, first described in 1909, has acquired increasing clinical and public health importance as a result of an expanding elderly population containing more vulnerable candidates (6). Data from a National Hospital Discharge Survey, indicate that hospital admissions resulting from AF increased two- to three fold from 1985 to 1999. During this period, hospitalizations listing AF increased from under 800 thousand to more than 2 million, predominantly in the elderly and men. Coyne et al assessing direct costs of treating AF in the US lists 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. (26)

Data from both the United States and the United Kingdom indicate that AF is a costly public health problem. (27). 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%). Globally, the annual cost per patient is close to $3600. Considering the prevalence of AF, the total economic burden is huge. (18)

Clinical Manifestations

AF may cause palpitations, fatigue, lightheadedness and dyspnea on exertion by precipitating cardiac failure. If there is underlying coronary artery disease it can initiate or aggravate angina from the associated rapid heart rate. However, AF often goes undetected because of lack of symptoms. It is frequently first detected by routine electrocardiographic examination, in the course of a myocardial infarction or stroke, on implanted pacemakers, or ambulatory ECG monitoring. AF was diagnosed incidentally in 12% of patients having an electrocardiogram for unrelated reasons in the Cardiovascular Health Study (16) and in 45% of patients in the Stroke Prevention in AF Trials (28) In a study of patients with paroxysmal AF, there were 12 times as many asymptomatic as symptomatic episodes of AF and 38% the patients with implanted pacemakers who experienced AF for more than 48 hrs were unaware of it (29). The low prevalence of AF in the absence of clinical and subclinical cardiovascular disease in the Cardiovascular Health Study of the elderly (1.6%) suggests that "lone atrial fibrillation" is fairly uncommon in the elderly (15).

Prognosis

AF is associated with an increased long-term risk of stroke, heart failure, and all-cause mortality, particularly in women.(30) The mortality rate of AF patients is about double that of patients in normal sinus rhythm and linked to the severity of underlying heart disease.(31–33) About two-thirds of the 3.7% mortality over 8.6 months in the ALFA Study was attributed to cardiovascular causes (34). However, AF independently predicts excess mortality and is associated with an increased incidence of embolic stroke, accounting for between 75,000 and 100,000 strokes per year in the USA (3). AF is in itself a powerful risk factor for stroke among patients of advanced age. The epidemic of AF in the 21st century is occurring in conjunction with a rising prevalence of heart failure, obesity, type-2 diabetes, and the prediabetic metabolic syndrome.(35)

The Framingham Study has shown that AF and heart failure often co-exist and that each may adversely impact the other (36). The decreased survival associated with AF occurs across a wide age range, partially attributable to the vulnerability of AF patients to development of heart failure. The differences in mortality reported among studies may be influenced by the proportion of deaths from heart failure as well as thromboembolism. In large heart failure trials 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.(37) In the Val-HeFT cohort of patients with chronic heart failure, development of AF was associated with significantly worse outcomes.(38) Heart failure promotes AF, AF aggravates failure, and persons with either share a poor prognosis. Thus, managing AF in conjunction with heart failure is a major challenge requiring more trial data to guide and optimize its management.

The most feared consequence of AF is stroke, the risk of which is increased 4–5-fold. AF assumes greater importance as a stroke hazard with advancing and by the ninth decade becomes a dominant factor. The attributable risk for stroke associated with AF increases steeply from 1.5% at age 50–59 years to 23.5% at age 80–89 years. AF is associated with a doubling of mortality in both sexes, which is decreased to 1.5–1.9-fold after adjusting for associated

cardiovascular conditions. The decreased survival associated with AF occurs across a wide age range.

In the distant past, paroxysmal AF was considered more dangerous than persistent, chronic AF postulating that the former was more likely to embolize. The Framingham Study found chronic sustained AF to be at least as dangerous (1). Analysis of pooled data from five randomized controlled trials suggested that paroxysmal and chronic AF have similar risks for stroke (39). However, several studies have suggested higher mortality in persistent versus chronic AF (40,41,42).

Risk Factors

Age and sex

As noted above AF increases with age, doubling in prevalence and incidence with each decade of age, even accounting for known predisposing conditions. Based on 38-year follow-up data from the Framingham Study, men had a 1.5-fold greater risk of developing AF than women after adjustment for age and predisposing conditions. The reason for the male preponderance of risk is currently unexplained (43).

Aging is accompanied by multiple cardiac abnormalities including: gradual loss of nodal fibers and increased fibrous and adipose tissue in the síno-atrial node, decreased ventricular compliance from myocardial fibrosis resulting in atrial dilatation that predisposes to AF, and extensive senile amyloid infiltration of the sinoatrial node may occur (44–46). In patients with AF, aging is associated with left atrial enlargement, reduced left atrial appendage flow velocity, all of which predispose to left atrial thrombus formation.(18). Prothrombin activation fragment and thrombin generation also increase with age, both in the general population and in persons with AF suggesting an age-related prothrombotic diathesis. Age appears to be a more potent risk factor for AF if it is combined with other risk factors (18). Also, aging also reflects longer exposure to predisposing conditions for AF, and even in advanced age some are clearly more vulnerable to the development of AF than others.

Cardiovascular Risk Factors

Of the major cardiovascular risk factors investigated by the Framingham study (9), hypertension and diabetes were significant *independent* predictors of AF, adjusting for age and other predisposing conditions (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 (pooled logistic regression) of AF incidence in either sex. However, in other studies with sufficient power and individuals who consume alcohol at sufficiently high amounts, it appears that alcohol abuse is related to occurrence of AF.(47,48). As will be discussed below, obesity has been associated with long-term risk of atrial fibrillation (Cox model), which appears to be partially mediated by left atrial enlargement.

For men and women, respectively, diabetes conferred a 1.4- and 1.6-fold risk, and hypertension a 1.5- and 1.4-fold risk, after adjusting for other associated conditions. Because of its high prevalence, hypertension was responsible for more AF in the population (14%) than any other risk factor (9, 43).

Increased pulse pressure, a reflection of aortic stiffness, increases the cardiac load and has been shown to increase AF risk in the Framingham Study (49). Cumulative 20-year AF incidence rates were 5.6% for subjects with a pulse pressure 40 mm Hg or less (25th percentile) and 23.3% for those with a pulse pressure greater than 61 mm Hg (75th percentile). In models adjusted for age, sex, baseline and time dependent change in mean arterial pressure, and clinical

risk factors for AF (body mass index, smoking, valvular disease, diabetes, electrocardiographic left ventricular hypertrophy, hypertension treatment, and prevalent myocardial infarction or heart failure), pulse pressure was associated with increased risk for AF (adjusted hazard ratio [HR], 1.26 per 20-mm Hg increment; 95% confidence interval [CI], 1.12–1.43; P=0.001).

In contrast, mean arterial pressure was unrelated to incident AF. Systolic pressure was related to AF (HR, 1.14 per 20-mm Hg increment; 95% CI, 1.04–1.25; P=0.006). However, 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 with a pulse pressure effect. Furthermore, the association between pulse pressure and AF persisted in models that adjusted for baseline left atrial dimension, left ventricular mass, and left ventricular fractional shortening (adjusted HR, 1.23; 95% CI, 1.09–1.39; P=.001). It appears that pulse pressure is an important risk factor for incident AF. Further research is needed to determine whether interventions that reduce pulse pressure can help retard the growing incidence of AF.

Diabetes was also a significant independent predictor of AF in 4 other studies, associated with an average relative risk of 1.8, but in 2 other studies it was not (18). Because the strength of diabetes as a predictor appears to be greater in lower-risk patients with AF, it is speculated that it may also be associated with non-cardioembolic strokes. Diabetes is a less powerful independent predictor than prior stroke/TIA, hypertension, or age, but further analysis is needed to refine its predictive value for thrombo-embolism in patients with AF. The reduction in stroke in warfarin-treated patients with diabetes was below average in 2 studies (18).

Thyroid Disease

Hyperthyroidism has long been implicated as a condition predisposing to AF. The prevalence of AF reported in patients at time of diagnosis of overt hyperthyroidism varies widely from 2–30 % (50–53). About 10–15% of persons with overt hyperthyroid disease and AF have been reported to have an arterial embolic event (53,54,55). Studies have also suggested that subclinical abnormalities in thyroid stimulating hormone levels have detrimental effects on the cardiovascular system. In one small study based on samples from a central reference laboratory, AF developed in 3 of 32 subjects with subclinical hyperthyroidism over 2 years of follow-up, compared to none in 35 with normal thyrotropins (56).

Although AF is an acknowledged manifestation of hyperthyroidism, older people in whom AF is common, do not often have clinically *overt* hyperthyroidism but subclinical hyperthyroidism signified by a low serum thyrotropin is more common. It was not firmly established that subclinical hyperthyroidism imposed a risk for AF until the Framingham Study investigated this hypothesis. The Framingham Study examined prospectively the incidence of AF in relation to serum thyrotropin concentrations over 10-years in study participants over 60 years of age. A low serum thyrotropin (<0.1 mU per liter) was found to be associated with a threefold higher risk of developing AF over a decade after adjusting for other known risk factors.(57).

The increased AF risk of hyperthyroidism was confirmed in the Cardiovascular Health Study of community-dwellers aged 65 years or older for whom baseline serum thyroid-stimulating hormone levels were measured and the relationship between baseline thyroid status and incident AF, incident cardiovascular disease, and mortality in older men and women not taking thyroid medication was determined (58). Eighty-two percent of participants (n = 2639) had normal thyroid function, 15% (n = 496) had subclinical hypothyroidism, 1.6% (n = 51) had overt hypothyroidism, and 1.5% (n = 47) had subclinical hyperthyroidism. After exclusion of those with prevalent AF, individuals with subclinical hyperthyroidism had a greater incidence of AF compared with those with normal thyroid function (67 events versus 31 events per 1000 person-years; (adjusted HR, 1.98; CI 1.29–3.03). No differences were seen between the subclinical hyperthyroidism and euthyroidism groups for incident coronary heart disease,

stroke, cardiovascular death, or all-cause mortality. Likewise, there were no differences between the subclinical hypothyroidism or overt hypothyroidism groups and 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.

Cardiovascular Conditions

Persons who develop AF are usually elderly and more likely than persons of the same age to have coronary disease, valvular heart disease, heart failure, echocardiographic abnormalities, or left ventricular hypertrophy (9,43). About 20% of men and a third of women have valvular heart disease, about a quarter of both sexes have heart failure and 28% of men and 14% of women have myocardial infarctions. These overt cardiac conditions impose a substantial risk. Adjusting for other relevant conditions, heart failure was 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).

Echocardiographic Abnormalities

Valvular heart disease, echocardiographic enlargement of the left atrial dimension, and abnormal mitral or aortic valve function were independently associated with increased prevalence and incidence of AF in the Cardiovascular Health Study (8,15). Based on Framingham Study data, echocardiographic predictors of AF include left atrial enlargement (39% increase in risk per 5-mm increment), left ventricular fractional shortening (34% per 5% decrement), and left ventricular wall thickness (28% per 4-mm increment). (Table 4) These echocardiographic features offer prognostic information for AF beyond the traditional clinical risk factors (43,59).

Mitral annular calcification is associated with adverse cardiovascular disease outcomes and stroke in longitudinal and community-based cohorts. Prospective data are limited on its association with AF. The Framingham study investigated the association between mitral annular calcification and long-term risk of AF (over 16 years of follow-up) in participants in the original cohort attending routine examinations between 1979 and 1981 (60). The age- and sex-adjusted incidence rate the condition was 362 per 10,000 person-years in subjects with mitral annular calcification compared with 185 per 10,000 person-years in those without it. In multivariable-adjusted analyses, mitral annular calcification was associated with 1.6 fold increased risk of AF. This association was attenuated somewhat upon further adjustment for left atrial size (HR 1.4, 95% CI 0.9–2.0) suggesting that the association between mitral annular calcification and incident AF is only partially mediated through left atrial enlargement (60).

In a double-blind randomized parallel-group study of 8831 men and women with hypertension and ECG left ventricular hypertrophy enrolled in the Losartan Intervention for Endpoint Reduction in hypertension Study, the occurrence of new onset AF was investigated in relation to in-treatment regression or continued absence of ECG left ventricular hypertrophy (61). Quantified regression of ECG left ventricular hypertrophy was found to be associated with a reduced likelihood of new onset AF, independent of blood pressure lowering and treatment.

Novel Risk Factors

A large number of novel risk factors for AF that have been identified, some modifiable, and some not. These include: inflammatory markers, the obesity-induced metabolic syndrome,

insulin resistance, thrombogenic tendencies, sleep apnea, decreased arterial compliance, left atrial volume and diastolic dysfunction.

Inflammation

The suspicion that inflammation contributes to some types of AF is supported by the frequent occurrence of AF after cardiac surgery (25% to 40%), genetic studies and the association of AF with pericarditis and myocarditis. The time course of AF following cardiac surgery parallels activation of the complement system and release of proinflammatory cytokines.(62,63)

C-reactive protein, a sensitive marker of inflammation, is a predictor of adverse cardiac events that has recently been linked to AF (64,65). In the Cardiovascular Health Study a large, population-based study of cardiovascular disease in the elderly, C-reactive protein was independently associated with the presence of AF at baseline and also predicted patients at increased risk for developing future AF.(67). It is not clear whether indices of inflammation should be regarded as direct *risk factors* for AF by causing an atrial inflammatory state, or whether these are markers for the underlying atherosclerotic vascular disease.

Insulin risistance and the metabolic syndrome

Concurrently, the prevalence of obesity, diabetes, and the metabolic syndrome have reached major proportions around the world. In a retrospective analysis of the incidence of AF in relation to body mass index in consecutive cardiac surgery patients obesity was reported to be an important determinant of new-onset AF after cardiac surgery (68). It has been unclear as to what extent cardiovascular risk factors mediate the association between obesity and AF. In a population-based Veterans Administration case-control study of subjects with new-onset AF and controls identified through medical record review of inpatient and outpatient visits, the association of AF with BMI appeared to be partially mediated by diabetes mellitus but minimally through other cardiovascular risk factors (69)

Obesity is associated with atrial enlargement and ventricular diastolic dysfunction, which are established predictors of AF. The Framingham Study investigated the association between body mass index and the long-term risk of developing new onset of AF in a prospective, community-based observational cohort (70). During a mean follow-up of 13.7 years, age-adjusted incidence rates for AF were found to increase across the 3 body mass index 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). In multivariable models adjusted for cardiovascular risk factors and interim myocardial infarction or heart failure, a 4% increase in AF risk per 1-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 individuals with normal BMI. After adjustment for echocardiographic left atrial diameter in addition to clinical risk factors, BMI was no longer associated with AF risk. It was concluded that obesity is an important, potentially modifiable risk factor for AF, the excess risk of which appears to be mediated chiefly by left atrial dilatation. These prospective data suggest that interventions to promote normal weight may reduce the population burden of AF.

The inter-relationship between obesity, diabetes and the metabolic syndrome strongly suggests an insulin resistant state. In a prospective analysis of consecutive hospitalized patients in sinus rhythm and without obvious structural heart disease, paroxysmal AF or flutter occurred in 9% of the patients with metabolic syndrome, but only 4% of patients without the syndrome (p=0.02). Multivariate logistic regression analysis indicated that the metabolic syndrome was a significant risk factor that was independent of left atrial diameter or age (odds ratio 2.8 p<0.01). Among the 5 components of the metabolic syndrome, body mass index was the most strongly associated with AF/Flutter (OR; 3.0, p=0.02). It was concluded that the metabolic

syndrome is strongly associated with AF/Flutter in patients without structural heart diseases and that obesity may be an important underlying mechanism. (71)

A community-based, cross-sectional observational study conducted in a primary health care facility in Sweden explored the prevalence of AF in patients with hypertension and type 2 diabetes seeking possible mechanisms for its development. An association of AF with combined hypertension and type-2 diabetes was found that remained significant when adjusted for other cardiovascular disease risk factors. Body mass index AF risk was attenuated by adjustment for ischemic ECG findings and lost significance with adjustment for insulin resistance, OR 1.3 (0.5–3.1). It was suggested that AF may be associated with the combined occurrence of type 2 diabetes and hypertension because of insulin (72).

Given the evidence that the metabolic syndrome is pro-inflammatory and that AF has been linked to inflammation, the relationship of these risk factors to incident AF merits further investigation. The finding that new onset AF is significantly related to BMI in multivariate analysis, adjusting for age and sex also has some credibility because obesity is an independent predictor of diastolic dysfunction, also a major determinant of AF (73).

Stature—Data from, a multicenter registry of patients with impaired left ventricular function (ADVANCENT) were used to investigate the influence of stature on AF in high-risk patients with reduced left ventricular systolic function (74). Because left atrial size is strongly associated with stature it was hypothesized that height and body surface area are risk factors for AF, independent of other known associations. The study was based on 25,268 patients (mean age of 66 years) consisting mostly of white men (72%) with ischemic cardiomyopathy (72%), and with a mean left ventricular ejection fraction of 31%.

A history of AF was present in 7,027 patients (27.8%). AF prevalence was found to increase significantly between the lowest and highest height quartiles (32% relative increase, p<0.0001). In multivariable analysis, the effect of height on AF risk persisted after adjusting for age, sex, race, left ventricular ejection fraction, heart failure class and etiology, hypertension, diabetes, and medication use. In patients with LV dysfunction, increasing stature appears to portend a higher risk of AF after accounting for other traditional risk factors for the arrhythmia. This association may account for some of the higher prevalence of AF in men (74) Height has also been observed to be associated with an increased risk of incident AF in the community (hazard ratio 1.03 per cm [1.02–1.05]).(8).

Plasma Natriuretic Peptides

Obesity-promoted natriuretic peptides are secreted from cardiomyocytes. They play a fundamental role in cardiovascular remodeling, volume homeostasis, and response to ischemia. Investigation of the relation of B-type natriuretic peptide and N-terminal pro-atrial natriuretic peptide by the Framingham Study has shown these natriuretic peptides to be associated with an increased risk of AF and its predisposing cardiovascular conditions such as heart failure and stroke (75) (Table 5).

Sleep apnea

There is a well documented relationship between obesity and sleep apnea, but the prevalence of sleep disordered breathing is also substantial in the non-obese. A high recurrence of AF in patients undergoing cardioversion is reported and AF recurrences are found to be 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, which is not attributable other predisposing conditions. (76,77) Mechanisms postulated include: hypoxia, hypercarbia, autonomic imbalance,

stretching of the atrium and left ventricular wall stress. Increased right-sided cardiac pressure stimulates atrial natriuretic peptide release that is noted in AF. Prospective studies of the relationship of sleep-disordered breathing with AF are needed, taking into account the sleep apnea relationship to obesity, the metabolic syndrome, coronary artery disease, heart failure, and stroke (78,79).

Diastolic dysfunction

Diastolic dysfunction, is a common accompaniment of ageing, hypertension, obesity, diabetes, heart failure and coronary artery disease in the elderly. Elderly patients in sinus rhythm at the time of an echocardiographic examination, were found to develop of AF at a 1% rate with mild diastolic dysfunction compared with 12% with moderate diastolic dysfunction, and 20% severe diastolic dysfunction. Diastolic dysfunction provides additional predictive information, for development of AF over that obtained from the clinical risk factors. As left atrial volumes increase diastolic function deteriorates providing predictive information for the development of AF and stroke (80,81). Furthermore, left atrial volume is a predictor of other cardiovascular events including myocardial infarction, stroke, and coronary revascularization all of which predispose to AF. (82,83)

AF as a Stroke Risk Factor

AF is an established major independent risk factor for embolic stroke or transient ischemic attack; AF is associated with a 4–5-fold greater risk than in the unaffected population (3). However, there is also evidence that a stroke may precipitate the occurrence of AF, because of its hemodynamic and autonomic consequences. About half of all elderly AF patients have hypertension as a 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, left ventricular hypertrophy, diastolic dysfunction, and left atrial dilatation, giving rise to stasis and thrombus formation.(28,84,85).

AF accounts for about 45% of all embolic strokes. The risk of stroke in placebo-treated patients in randomized warfarin trials is reported as 4.5% per year (84,86). A collaborative analysis of five randomized trials, by the AF Investigators identified five major risk factors for stroke in AF patients; namely, prior stroke or transient ischemic attack, a history of hypertension, advanced age, a history of heart failure, and diabetes (85) (Table 6). The risk of stroke increases at least five-fold in patients with clinical risk factors, and this is in marked contrast to the low risk of stroke in younger patients without clinical risk factors. Other factors, such as female sex, systolic blood pressure over 160 mm Hg, and left ventricular dysfunction, have been variably linked to stroke.

In patients 80 to 89 years old, 36% of strokes occur in those with AF. The annual risk of stroke for octogenarians with AF is in the range of 3% to 8% per year, depending on associated stroke risk factors.(3) The powerful impact of age and clinical risk factors on the risk of stroke in patients with AF suggests that vigorous control of accompanying risk factors should be undertaken to lower the risk.

Ischemic stroke and systemic arterial occlusion in AF are generally attributed to embolism of thrombus from the left atrium, however, up to 25% of strokes in patients with AF may be due to intrinsic cerebrovascular diseases, other cardiac sources of embolism, or atherosclerotic pathology in the proximal aorta (18,84). Although 12% harbor carotid artery stenosis, carotid atherosclerosis is not substantially more prevalent in AF patients with stroke and appears to be a relatively minor contributing factor.(87,88)

Genetic Influences

Familial occurrence of AF has been recognized for many years, but was considered uncommon. The Framingham Study found that parental AF increases the future risk for offspring AF about 2–3-fold after excluding persons with predisposing conditions, an observation supporting a genetic susceptibility to developing this dysrhythmia (89). (Figure 1). In such families with AF, familial linkage studies are beginning to explore the genetics of AF, particularly in younger persons. (90,91)

Purported genetically determined constitutional factors such as blood pressure, obesity and greater stature, have been found to predispose to AF. It is uncertain how these constitutional factors promote AF, but metabolic disorders and genetic factors seem to be implicated.

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 (91,93). However, the majority of patients with AF in these families are younger, than age 65 years suggesting that the postulated genes causing AF may not be directly involved in the elderly

The National Heart Lung and Blood Institute is sponsoring several projects that will examine the genetic contribution to AF and other cardiovascular phenotypes in the community. Two studies in particular will genotype 1000s of candidate genes (**C**andidate gene **A**ssociation **RE**source, "CARE" project) and a 550K genome wide scan of genetic polymorphisms (SNP Health Association Resource, SHARe) with 1000s of participants across many of the NHLBI's cohort studies. The data from these studies will be available for analysis to investigators with approved projects and ethnical oversight. The aggregate results of these studies will be web-posted (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 will undoubtedly lead to major advances in understanding the contribution of common complex genetic variation to AF in the community.

Multivariable Risk Assessment

Multivariable risk assessment of the stroke risk of patients with 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. Estimating the risk of stroke for individual AF patients is crucial for the decision to prescribe anticoagulation therapy, but the threshold risk warranting anticoagulation is controversial. Patients with a stroke risk of 2% per year or less do not benefit substantially from oral anticoagulation, and it would require treating 100 or more patients for 1 year to prevent a single stroke (18). For high-risk AF patients, with stroke rates of 6% per year or greater, the comparable number needed-to-treat is 25 or fewer, 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 further risk stratify and elucidate which individuals with AF were at particularly increased risk of stroke or stroke and death (94). Their multivariable analysis examined risk factors for stroke among 705 patients with recently detected AF, excluding those who had sustained ischemic stroke, TIA, or death within 30 days of diagnosis (Figure 2). The significant predictors of ischemic stroke in subjects with AF were age (RR = 1.3 per decade), female sex (RR = 1.9), prior stroke or TIA (RR = 1.9), and diabetes mellitus (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 upon whether selected stroke rate thresholds were less than 1.5% per year or less than 2% per year.

Preventive Measures

AF remains a substantial global health burden requiring detection of candidates likely to develop it for preventive management. The disappointing results of anti-dysrhythmic therapy for AF require a therapeutic approach that focuses treatment on the underlying myocardial pathology leading to the occurrence of the AF. Many risk factors for AF are shared by other cardiac conditions that in turn predispose to the occurrence of AF. The premordial prevention of the risk factors would jointly prevent their emergence and in turn the AF they promote. Identification of modifiable risk factors specific for AF enables intervention early in the course of the disease when preventative or corrective strategies are most efficient. Improvement of the multivariable risk profile to prevent a stroke, coronary disease or cardiovascular disease in general should carry a bonus of prevention of AF

For example, ACE-inhibitors and angiotensin receptor blockers, which are 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 left ventricular dysfunction.(95,96). They may also inhibit the pro-inflammatory and sympathetic effects of angiotensin and interfere with the triggers and substrate of AF (18).

Warfarin anticoagulant therapy is highly effective for prevention of strokes in patients with AF, reducing the risk by 62% (28,84). Meta-analysis according to the principle of intention to treat showed that adjusted-dose oral anticoagulation is highly efficacious for prevention of all stroke (both ischemic and hemorrhagic), with a risk reduction of 62% (95% CI 48% to 72%) versus placebo (84). This reduction was similar for both primary and secondary prevention and for both disabling and non-disabling strokes. Using "on-treatment analysis" (excluding patients not on oral anticoagulation at the time of stroke) the preventive efficacy of oral anticoagulation exceeded 80%. Despite this a survey of treatment for patients with CVD 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 pose serious threats to the health of the American public. Strategies to reduce these deficits in care are urgently needed.

Summary

We are confronted with a rapidly growing epidemic of AF, the scope of which urgently demands improved prevention and treatment of this condition and its predisposing cardiovascular substrate. The cardiovascular conditions associated with AF are justifiably considered risk factors rather than risk markers. It is also likely that AF and the left atrial enlargement associated with it are direct causes of embolic stroke requiring, early detection and treatment. AF is now a global health burden requiring targeted screening to detect persons likely to develop this condition.

The disappointing results of therapy to suppress or eliminate the rhythm disturbance have focused greater attention on treatment to prevent or delay myocardial changes leading to the occurrence of the AF. Many risk factors associated with AF also predispose to cardiovascular diseases that beget the development of AF so that their eradication should theoretically confer a substantial public health and healthcare benefit. Identification and treatment of modifiable risk factors specific for AF in high-risk candidates for the condition would enable early intervention when preventative or corrective measures are most effective. In addition, advances in identifying genetic and biological markers of risk for AF and its complications will provide

pathophysiological insights and enable better risk stratification for more personalized and targeted therapy.

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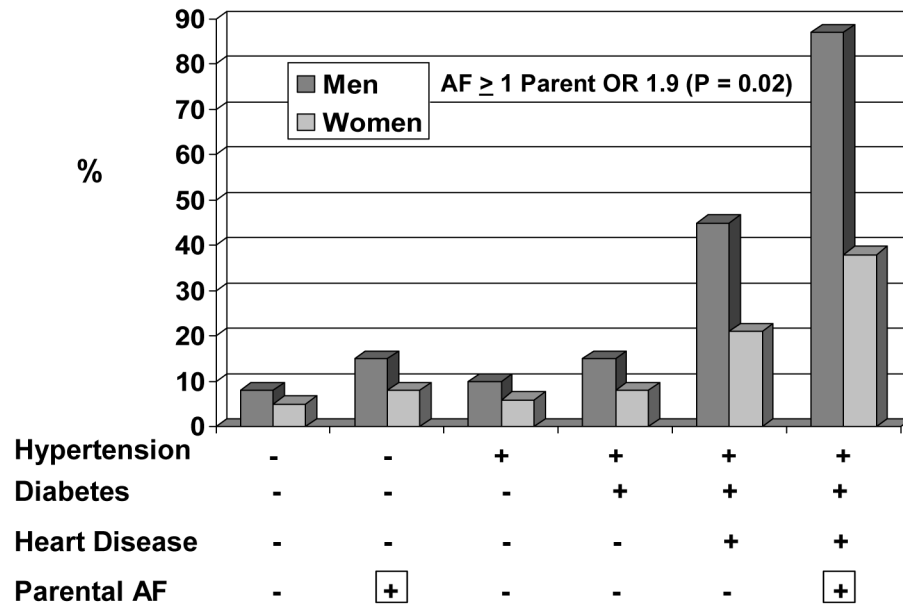
C Fox et al. JAMA 2004; 291:2851

Figure 1.
Risk of Atrial Fibrillation by Parental Atrial Fibrillation Status: Framingham Offspring Cohort
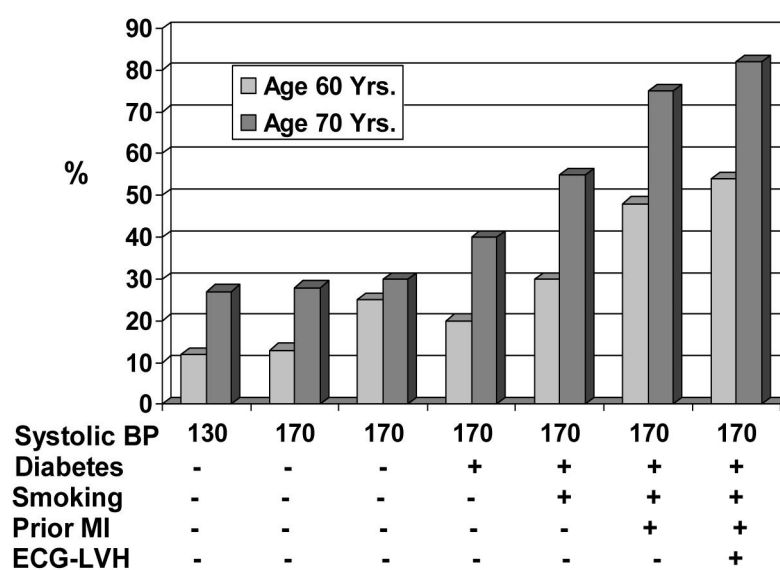
T Wang et al. JAMA 2003; 290:1049

Figure 2.
5-Year Stroke/Death Risk in Atrial Fibrillation Framingham Study

TABLE 1

Lifetime Risk for AF in the Absence of Antecedent or Concurrent Diagnosis of CHF or Myocardial Infarction

Index Age, y	Men	Women
Lifetime risk for AF without antecedent or concurrent CHF		
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 CHF 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.

From: DM Lloyd-Jones et al. *Circulation.* 2004;110:1042–1046.

TABLE 2

Cardiovascular Risk Factors for AF 38-Year Follow-up: Framingham Study

| Risk Factors | Odds Ratios | | | |
| | Age-Adjusted | | RF-Adjusted | |
	Men	Women	Men	Women
Diabetes	$1.7^{\dagger}$	$2.1^{\ddagger}$	1.4^{*}	$1.6^{\dagger}$
ECG-LVH	$3.0^{\ddagger}$	$3.8^{\ddagger}$	1.4	1.3
Hypertension	$1.8^{\ddagger}$	$1.7^{\ddagger}$	$1.5^{\dagger}$	1.4^{*}
Cigarettes	1.0	1.4^{*}	1.1	1.4
BMI	1.03	1.02	—	—
Alcohol	1.01	0.95	—	—

*
$p<0.05$,

†
$p<0.01$,

‡
$p<0.001$.

TABLE 3

Odds of Developing AF for Specified Cardiac Conditions: Framingham Study Subjects Ages 55–94 Yr 38-Yr Follow-up

	Odds Ratios			
	Age-Adjusted		RF-Adjusted	
Cardiac Conditions	Men	Women	Men	Women
MI	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[‡]

[*] $p < 0.05$,

[†] $p < 0.01$,

[‡] $p < 0.001$

Table 4

Echocardiographic Predictors of Atrial Fibrillation: Framingham Study Subjects ages 50–59 Years

Echocardiographic Features	Atrial Fibrillation Risk
Left Atrial Size	29% incr. per 5mm
Left Ventricular Fractional Shortening	34% incr. per 5%
Left Ventricular wall thickness	28% incr. per 4 mm
Two or more of above vs none	17% vs 3.7%

Vazirí SM, et al Circulation 1994; 89:724–730.

Table 5

Plasma B-Type Natriuretic Peptides and Risk of CVD: Framingham Study

CVD Event	% increase in CVD Per SD Increment	M-V H.R[#] > 80th Percentile
Heart Failure	77%	3.1[**]
Arial Fibrillation	66%	1.9[*]
Stroke/TIA	53%	2.0[*]
First CV Event	28%	1.8[*]
Death	27%	1.6[*]

Peptide Levels not significantly related to CHD

[#]Adjusted for: age, diabetes, BP, smoking, creatinine, LV mass and systolic function. 80th percentile BNP: women 23.3 pg/ml, men 20 pg/ml

[*]$P<.05$,

[**]$P<.01$

Wang TJ, et al. N Engl J Med 2004: 350:655-663.

TABLE 6

Risk Factors for Ischemic Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

Risk Factors	Relative Risk
Previous stroke or TIA	2.5
Diabetes mellitus	1.7
History of hypertension	1.6
Heart failure	1.4
Advanced age (continuous, per decade)	1.4

Data derived from collaborative analysis of 5 untreated control groups in primary prevention trials.47 As a group, patients with AF carry about a 6-fold increased risk of thromboembolism compared with patients in sinus rhythm. Relative risk refers to comparison of patients with AF to patients without these risk factors.

TIA indicates transient ischemic attack.

Source:. Analysis of pooled data from five randomized controlled trials *Arch Intern Med.* 1994; 154: 1449–57.