Current Perceptions of the Epidemiology of Atrial Fibrillation

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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 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...
cardiac conditions (Table 1). The prospective Rotterdam Study also found a similarly high lifetime AF risk (22%–24% at the age of 40 years). 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

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**Table 1**

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<thead>
<tr>
<th>Index Age, Years</th>
<th>Men</th>
<th>Women</th>
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<tbody>
<tr>
<td>Lifetime risk for AF without antecedent or concurrent congestive heart failure</td>
<td></td>
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<tr>
<td>40</td>
<td>20.5</td>
<td>17.0</td>
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<td>80</td>
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<td>15.9</td>
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<tr>
<td>Lifetime risk for AF without antecedent or concurrent congestive heart failure or myocardial infarction</td>
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<tr>
<td>40</td>
<td>16.3</td>
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<tr>
<td>50</td>
<td>16.6</td>
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<tr>
<td>60</td>
<td>16.8</td>
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<tr>
<td>70</td>
<td>16.5</td>
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<tr>
<td>80</td>
<td>16.0</td>
<td>14.8</td>
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All values are percentages.

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.2,8 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

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<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Odds Ratios Age-Adjusted</th>
<th>Odds Ratios Risk Factor–Adjusted</th>
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<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.7**</td>
<td>2.1***</td>
</tr>
<tr>
<td>ECG LV hypertrophy</td>
<td>3.0**</td>
<td>3.8**</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.8**</td>
<td>1.7**</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>1.0</td>
<td>1.4*</td>
</tr>
<tr>
<td>BMI</td>
<td>1.03</td>
<td>1.02</td>
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<tr>
<td>Alcohol</td>
<td>1.01</td>
<td>0.95</td>
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Abbreviations: BMI, body mass index; ECG, electrocardiography; LV, left ventricular; —, not retained in the model.

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

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

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<th>Cardiac Conditions</th>
<th>Odds Ratios</th>
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<tr>
<td></td>
<td>Age-Adjusted</td>
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<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2.2**</td>
</tr>
<tr>
<td>Heart failure</td>
<td>6.1***</td>
</tr>
<tr>
<td>Valve disease</td>
<td>2.2***</td>
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</table>

*\( P < .05 \); **\( P < .01 \); ***\( P < .001 \).

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 Libérale 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 theValsartan 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

<table>
<thead>
<tr>
<th>Echocardiographic Feature</th>
<th>Atrial Fibrillation Risk</th>
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<tbody>
<tr>
<td>Left atrial diameter, mm</td>
<td>39% increase per 5 mm</td>
</tr>
<tr>
<td>Fractional shortening, %</td>
<td>34% increase per 5% decrease</td>
</tr>
<tr>
<td>LV wall thickness</td>
<td>28% increase per 4 mm</td>
</tr>
<tr>
<td>Two or more of previous features versus none</td>
<td>17% versus 3.7%</td>
</tr>
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</table>

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.  

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. 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. 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.

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. 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.

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. Analyses of pooled data from five randomized controlled trials suggest that paroxysmal and chronic AF have similar risks for stroke. Before the Framingham Study report in 1982, there were many misconceptions about AF. 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.

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. 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.

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. 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, 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. 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.

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%. Approximately 10% to 15% of persons who have overt hyperthyroid disease with AF are reported to have an arterial embolic event. Studies also suggest that subclinical abnormalities of thyroid-stimulating hormone have detrimental effects on the cardiovascular system. 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 threefold 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.50,61 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
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.

**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. 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. 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. 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. 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. 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. 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. They also may inhibit the proinflammatory and sympathetic effects of angiotensin and interfere with the triggers and substrate of AF.

Warfarin anticoagulant therapy is highly effective for prevention of stroke in patients who have AF. 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. 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


