Atrial fibrillation (AF), the most prevalent sustained arrhythmia, is associated with substantial morbidity, reductions in functional status and quality of life (QOL), and increased mortality because of a combination of altered hemodynamics, atrioventricular dyssynchrony, progressive atrial and ventricular mechanical dysfunction, and thromboembolic
complications. Rarely a primary electric disorder, AF most commonly represents a final common pathway for a multitude of other predisposing cardiac and noncardiac conditions. Clinical presentations range from asymptomatic to debilitating reflecting, in part, the heterogeneity in associated comorbidities. The goal of this article is to review the epidemiological and clinical features of AF and then to relate them to the pathophysiology of the arrhythmia. Other articles in this compendium deal with specific pathophysiological entities in detail, but here we aim to provide a perspective on how different pathophysiological components operate to make AF a final common end point of a variety of cardiac conditions.

Incidence and Prevalence of AF

AF is a major burden to healthcare systems. Multiple studies of predominantly European and American populations have attempted to define precisely the contemporary incidence and prevalence of AF and project this information against demographic data to estimate anticipated AF-related healthcare delivery and resource allocation needs. The current evidence indicates that the overall prevalence of AF is in the range of 1% to 2% of the general population.1–12

Although the reported annual incidence rates for AF have varied widely depending on the populations studied (from 0.8 to 28.3 cases per 1000 person-years), time trend analyses reveal relatively stable incidence density rates over time (eg, 27.3 per 1000 life-years in 1993 compared with 28.3 per 1000 life-years in 2007).2,4,5,11–13 In contrast, the prevalence of AF continues to rise (eg, from 41 cases per 1000 in 1993 to 85 cases per 1000 in 2007).2 Some of the increasing prevalence may be attributable to a modest improvement in AF-related survival (eg, 3-year mortality rate reduction from 45% to 42% in 1993 versus 2005), which is related to better detection and treatment of underlying conditions such as hypertension, coronary artery disease (CAD), and heart failure (HF).2 However, the predominant demographic factor increasing the prevalence rates seems to be population-aging because both the incidence and the prevalence of AF are age dependent (Figures 1 and 2).2,4,5,11–13 Incidence rates increase from <0.5 to 2, to 3 to 9, and 10 to 39 cases per 1000 person-years at 50, 65, and 80 years, respectively.1–12 Corresponding prevalence rates increase from <0.5% to 1.0%, to 1% to 4%, and 6% to 15%, respectively.1–12 The lifetime risk of developing AF for individuals 40 to 55 years of age has been estimated to be 22% to 26%.5–9

It is important to note that the above-cited epidemiological studies likely underestimate the true disease burden. It is estimated that between a quarter and two thirds of the AF population has transient or paroxysmal AF, which would not be accounted for in the early epidemiological studies based on populations with permanent AF diagnosed by electrocardiography.5–8,14 Moreover, estimates of AF prevalence based on symptomatic presentations are problematic because AF is silent in ≤5% to 35% of patients.15–17 As such, when factoring in patients with paroxysmal and silent AF, the projected prevalence of AF in the United States in 2050 increases from 5.6 million (excluding paroxysmal and silent AF) to 12.1 to 15.9 million.9,13

Risk Factors for AF

AF is a multifaceted condition ranging from an isolated electrophysiological disorder to a manifestation or consequence of other cardiac and noncardiac pathologies. The former, so-called lone AF, is usually defined as paroxysmal, persistent, or permanent AF in individuals <60 to 65 years of age with no apparent cardiovascular disease. Established, emerging, and potential risk factors for AF are summarized in Table 1. Because risk factors are becoming increasingly defined and recognized, the term lone AF is applied to a dwindling proportion of patients.

Age and Sex

Age and sex are 2 of the most powerful predictors of incident AF. The role of age is discussed in detail above. Although the prevalence of AF doubles with each decade of age, after adjusting for age and other predisposing conditions, male sex is associated with a 1.5-fold risk of developing AF.1–12

Hypertension

The association between hypertension (blood pressure ≥140/90) and AF is well established.6,18–20 Although the increase in risk is relatively modest (relative risk, 1.2–1.5), the high prevalence of hypertension in the general population renders it the most significant population-attributable risk factor for AF beyond age and sex. It is estimated that hypertension is responsible for 14% of all cases of AF.20 Although overt systolic hypertension is strongly associated with incident AF, recent studies suggest that systolic blood pressure in the prehypertensive range (130–139 mm Hg) and widened pulse pressure are also associated with increased risk (adjusted hazard ratios [HRs], 1.28 versus systolic blood pressure <120 and 1.26 per 20 mm Hg increment, respectively).19,21 Interestingly, mean arterial pressure does not seem to be associated with incident AF.21

Valvular Heart Disease

Valvular heart disease has been associated with a 1.8- and 3.4-fold increased risk for AF in men and women, respectively.20 Although any valvular pathology can be related to AF, stenotic left-sided valvular lesions (and in particular rheumatic heart disease) have the highest prevalence rates. Severity of obstruction follows a dose–response relationship: AF prevalence is 9.1% of patients with mild-to-moderate aortic stenosis and 33.7% among those with severe stenosis.22,23 Likewise, the prevalence of AF varies with the complexity of rheumatic heart disease: from 16% with isolated mitral regurgitation to 29% with isolated mitral stenosis, to 52% with coexisting mitral regurgitation and stenosis, and to 70% with mixed mitral and tricuspid valve disease.24

Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>APD</td>
<td>action potential duration</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>DAD</td>
<td>delayed afterdepolarization</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>OAC</td>
<td>oral anticoagulant</td>
</tr>
<tr>
<td>OSA</td>
<td>obstructive sleep apnea</td>
</tr>
<tr>
<td>QOL</td>
<td>quality of life</td>
</tr>
<tr>
<td>SR</td>
<td>sarcoplasmic reticulum</td>
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</tbody>
</table>
AF and HF often coexist, with a prevalence of AF that increases with the severity of HF symptomatology (eg, <5%–10% with New York Heart Association functional class I symptoms, 10%–26% in New York Heart Association class II–III, and 40%–50% for New York Heart Association class IV). HF is associated with a 4.5- to 5.9-fold adjusted risk for AF. The association is not limited to systolic left ventricular dysfunction. Isolated diastolic dysfunction is also associated with an increased AF incidence, possibly reflecting shared risk factors such as advancing age and hypertension. Similarly, a 10% to 28% prevalence of AF has been reported in hypertrophic cardiomyopathy, with an incidence 4× to 6× that of the general population.

**Congenital Heart Disease**

Atrial tachyarhythmias are highly prevalent in congenital heart disease, are the most common complication in adults with congenital heart disease, and are the leading cause of morbidity/hospitalizations. Potential contributors include surgical incisions, natural conduction barriers (eg, valve orifices, venous structures, septal defects, and crista terminalis), and sequelae of chronic hemodynamic or hypoxic stress (eg, fibrosis and hypertrophy). Whereas organized atrial macroreentrant arrhythmias are the most common supraventricular arrhythmia in patients with congenital heart disease, the prevalence of AF is rising, particularly with atrial/atrioventricular septal defects, Ebstein anomaly, tetralogy of Fallot, univentricular hearts, and left-sided obstructive lesions.

**HF and Cardiomyopathy**

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Pooled analysis of individual studies weighted by sample size.
A strong correlation between older age and congenital heart disease–related AF has been demonstrated; however, substantial AF onset rates appear in patients with congenital heart disease decades before their onset in the general population.9 For example, a multicenter study of patients with tetralogy of Fallot quantified a 7.4% AF prevalence that increased to >30% beyond age 55 years.39 Left-sided hemodynamic changes (eg, reduced left ventricular ejection fraction and increased left atrial dimensions) are important AF risk determinants.39 In contrast, right atrial enlargement is more closely linked to AF onset rates appear in patients with congenital heart disease decades before their onset in the general population.9

Table 1. AF Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Estimated Increased Risk</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>≥2</td>
<td>Per decade</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.2–1.5</td>
<td>BP &gt;140/90 mm Hg</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>1.8–3.4</td>
<td></td>
</tr>
<tr>
<td>LV systolic dysfunction</td>
<td>4.5–5.9</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>1.39–2.35</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>1.34–1.46</td>
<td>Heavy alcohol use (≥36 g/d)</td>
</tr>
<tr>
<td>Emerging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prehypertension</td>
<td>1.28</td>
<td>Systolic BP 130–139 mm Hg</td>
</tr>
<tr>
<td>Increased pulse pressure</td>
<td>1.26</td>
<td>Per 20-mm Hg increment</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>2.8–5.6</td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>2.87</td>
<td>Cumulative lifetime practice</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>3.33–5.26</td>
<td></td>
</tr>
<tr>
<td>Familial and genetic</td>
<td>1.85</td>
<td>AF in ≥1 parent</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>4–6</td>
<td></td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Potential</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>N/A</td>
<td>Data inconclusive</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.3–3.2</td>
<td>Graded risk</td>
</tr>
<tr>
<td>Inflammation</td>
<td>1.47–1.77</td>
<td>Independent predictive value unclear</td>
</tr>
<tr>
<td>Pericardial fat</td>
<td>1.28–5.30</td>
<td>Risk related to thickness and volume of pericardial fat</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>1.51–2.05</td>
<td></td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; BP, blood pressure; LV, left ventricular; and N/A, not available.

Coronary Artery Disease

AF is a common complication of acute myocardial infarction.30,41 Although the prevalence of AF in patients with stable CAD does not seem to be substantially higher than in populations without CAD, recent work indicates that patients with AF have an increased prevalence of both nonobstructive and obstructive CAD compared with those without AF.42,43

Obesity

In comparison to people with a normal body mass index (<25 kg/m²), overweight (body mass index, 25–30 kg/m²) and obese (body mass index, >30 kg/m²) individuals are at increased AF risk (HR, 1.39–1.75 and 1.99–2.35, respectively).44,45 For each unit increase in body mass index, the corrected risk of incident AF increases 3% to 7%.44

Pericardial Fat

In addition to sharing blood supply with the cardiac microcirculation, pericardial fat is metabolically active and produces cytokines with inflammatory properties. The presence, thickness, and volume of pericardial fat have been independently associated with the prevalence and severity of AF (ie, symptom burden, AF chronicity, AF subtype, and AF burden).36–46

Sleep Apnea

Obstructive sleep apnea (OSA), characterized by periodic reduction or cessation of breathing during sleep, often coexists with AF. Patients with OSA have a 4-fold increased risk of developing AF, with an adjusted odds estimate controlled for concomitant risk factors ranging from 2.8 to 5.6.49–51 Patients with AF have a high prevalence of OSA (32%–49%), approximately double that of the general cardiology population (adjusted odds ratio, 2.19).52,53 OSA is also associated with recurrent AF after cardioversion and ablation.53–59 Although it remains unclear whether OSA is independently and pathogenetically linked to AF or merely reflects a shared risk factor profile, the observation that continuous positive pressure ventilation reduces the risk of recurrent AF supports a causal role of OSA in AF pathogenesis.53,55,56,59

Chronic Kidney Disease

AF is more prevalent in patients with chronic renal dysfunction, even after accounting for associated factors (coronary heart disease, HF, hypertension, left ventricular hypertrophy, and systemic inflammation). AF risk increases with severity of renal dysfunction (eg, HR of 1.3–1.6 and 1.6–3.2 with an estimated glomerular filtration rate of 30–59 and <30 mL/min per 1.73 m², respectively, versus estimated glomerular filtration rate ≥60 mL/min per 1.73 m²).60,61 Incident AF is associated with an increased incidence of end-stage renal disease (adjusted HR, 1.67–1.77).60,62

Alcohol

The relationship between ethanol consumption and AF has long been known, with acute AF paroxysms associated with binge drinking (holiday heart syndrome). Although moderate alcohol intake does not seem to increase risk, heavy alcohol consumption (≥236 g/d) is associated with an adjusted HR of 1.34 to 1.46 for new-onset AF.63–65 It has been postulated that the consumption of and subsequent withdrawal from alcohol result in a hyperadrenergic state, impaired vagal tone, and changes in atrial conduction properties, the sum of which predispose to AF.63–65

Smoking

Tobacco use has recently been linked to AF development (HR, 1.51–2.05), with a dose–response effect (greatest risk in the highest tertile, >675 cigarette-years).66,67 Continued tobacco use is also associated with AF recurrence after catheter ablation.68

Diabetes Mellitus

Diabetes mellitus has been associated with a 1.4- to 1.6-fold increased risk of AF.69–71 Although a shared risk factor profile
exists (diabetes mellitus being associated with systemic inflammation, autonomic dysfunction, obesity, OSA, CAD, and HF), a longer duration of treated diabetes mellitus and worse glycemic control has been independently associated with increased risk of AF.99,72

**Thyroid Dysfunction**

The risk of AF is closely associated with underlying thyroid function. Although overt hyperthyroidism has long been associated with an increased risk of AF (3- to 6-fold increased incidence versus those with normal thyroid function), an apparent linear relationship between thyroid function and AF risk has been noted with the risk of AF increasing with decreasing levels of thyroid-stimulating hormone (relative risk 1.1 with high normal euthyroidism to 1.2 with subclinical hyperthyroidism, to 1.4 with subclinical hyperthyroidism and suppressed thyroid-stimulating hormone compared with those with normal thyroid function).73-76 This is postulated to reflect increases in β-adrenergic tone, as well as the direct effects of thyroid hormone on pulmonary vein cardiomyocytes (increased automaticity and enhanced triggered activity).77

**Physical Activity/Exercise**

Regular moderate physical activity beneficially affects multiple cardiovascular risk factors and may decrease the incidence of AF.78-80 Conversely, excessive or vigorous sports practices (eg, endurance or high-performance athletes) are linked to a higher AF prevalence. A cumulative lifetime practice >1500 hours is associated with a 3-fold risk of developing AF (HR, 2.87) and greater AF recurrence rates after catheter ablation (multivariate HR, 1.81).80-83 In this population, AF paroxysms are >3× as likely to occur in vagal contexts (postprandial, sleep, at rest) compared with healthy controls (57% versus 18% in non–high-performance athletes).84

**Inflammation**

Multiple studies have noted an association between circulating inflammatory markers (C-reactive protein and interleukins) and AF severity (chronicity, type, and burden).85,86 Although elevated inflammatory markers predict incident AF and recurrence after cardioversion, sinus rhythm restoration alone reduces inflammatory markers.87-89 Despite these observations, the inclusion of inflammatory biomarkers (C-reactive protein and fibrinogen) does not improve predictive ability beyond well-established clinical risk factors.84

**Familial and Genetic**

Genetic contributions are increasingly recognized. A family history of AF in a first-degree relative independently increases AF risk 2-fold.91-93 Although polygenic inheritance is more common, monogenic inheritance has been described for a variety of genes, principally affecting ion channels.94-98 Genetic linkage analyses have identified a range of potentially pathogenic loci.94,95,99-102 In particular, multiple susceptibility signals have been identified at the chromosome 4q25 locus, which is thought to alter the expression of transcription factor PITX2.102,103

**Associated Morbidity and Mortality**

The clinical consequences of AF can be highly variable, from incapacitating symptoms to an asymptomatic dysrhythmia. Similarly, the prognosis associated with AF depends on whether the arrhythmia is isolated or is a consequence of other pathologies. On the whole, AF is associated with impaired QOL, increased mortality, thromboembolic events, left ventricular dysfunction, and HF.

**Symptoms and QOL**

The QOL in individuals with AF is significantly impaired across areas of physical and social functioning, mental and general health, as well as metrics of illness intrusiveness, activity limitation, and symptom status.104-106 In addition, AF is associated with a significantly reduced exercise capacity.106 Even in the perceived absence of symptoms, patients with AF express reduced global life satisfaction.106 These impairments are comparable or worse than those in patients with HF or coronary heart disease (postcoronary angioplasty and postmyocardial infarction cohorts).101 Although studies have demonstrated significantly improved QOL after therapeutic intervention, in general there does not seem to be a significant difference between a management strategy aiming to control ventricular rate and a strategy of rhythm control (ie, interventions to convert AF and maintain sinus rhythm).107,109,110 This is despite the observations that (1) restoration of sinus rhythm increases scores for physical functioning, vitality, mental health, and role-emotional104,106,111,112 and (2) AF recurrences have a significant and negative effect on global well-being.104,106,108,111,112 thus suggesting that the lack of observed QOL benefit may reflect deficiencies of the contemporary rhythm-control toolset rather than the strategy itself.

**Mortality**

Incident AF is associated with age-adjusted 1-year mortality rates of 23% to 27%, significantly greater (HR, 1.41) than patients without AF.2,113-114 Although AF has been associated with increased mortality in diverse populations, it remains unclear whether well-controlled AF independently predicts death or whether residual confounding may be at play.2,18,42,113-119 In particular, increases in mortality rates are highest with an inpatient diagnosis of AF, suggesting that a portion of the excess mortality may reflect underlying comorbidities.2 Moreover, despite improved treatment strategies, the AF-related mortality has remained relatively static. Although observational studies have suggested that a long-term strategy of rhythm control may be associated with improved long-term mortality (HR 0.89 at 5 years and 0.77 at 8 years of follow-up), to date only anticoagulation therapy has been definitively shown to improve survival.120,121 Large-scale randomized trials have not shown mortality benefits of rhythm-control over rate-control therapy.122-124 It has been suggested that failure to improve outcomes may have been because of inefficacy of available rhythm-control therapies or application too late in the natural history of the disease.125 Ongoing trials including the Catheter ABlation vs ANti-Arrhythmic drug therapy for atrial fibrillation (CABANA) trial and the Early treatment of Atrial fibrillation for Stroke prevention Trial (EAST) should address this issue.125

**Stroke and Thromboembolism**

AF is associated with a 3- to 5-fold increased risk of stroke,5,15,20,126 accounting for ≈20% of all strokes.17 Importantly, the annual stroke risk increases significantly by
age category (from 1.5% for patients aged 50–59 years to >23% for those >80 years). AF-associated strokes are often recurrent and relatively more severe, causing significantly greater resource use, long-term disability, and mortality compared with non-AF stroke.129–132

The absolute risk of stroke associated with AF is variable and reflects other clinical characteristics and comorbidities. A high risk is observed in AF associated with rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves. Conversely, the risk of stroke with lone AF is low and comparable with that in the general population. Because of this heterogeneity, risk prediction systems have been developed to inform decision making on stroke risk and antithrombotic therapy. These scores were initially derived from control populations in AF stroke prevention trials. The Atrial Fibrillation Investigators pooled data from several trials to form a unified stroke classification scheme that included age, hypertension, prior cerebral ischemia (either stroke or transient ischemic attack), and diabetes mellitus, as well as CAD and congestive HF (equivocal stroke risk factors).133 Similarly, the Stroke Prevention and Atrial Fibrillation investigators identified hypertension (blood pressure >160 mmHg), prior cerebral ischemia, recent HF (within 100 days) or left ventricular dysfunction, or the combination of age >75 years and female sex.134 Combinations of these risk-scoring systems led to the development of the CHADS2 score (Table 2).135 Although CHADS2 is elegant in its simplicity, it is weak in identifying truly low-risk individuals. The expanded CHA2DS2-VASc scoring system was developed to identify low-risk patients for whom oral anticoagulant (OAC) therapy would not be beneficial (Table 2).136

### Cognitive Dysfunction

Independent of stroke, AF has been linked to a more rapid decline in cognitive function, resulting in a 1.7- to 3.3-fold increased risk of cognitive impairment, and a 2.3-fold increased risk of dementia, compared with patients in sinus rhythm. Although shared risk factors have been proposed as a potential mechanism, the association between AF and cognitive impairment persists after risk factor adjustment.140,141 In a meta-analysis including 77,668 patients, of whom 11,700 had AF, AF was associated with a 42% greater risk of dementia after adjustment for other known stroke-promoting conditions.142 Hypothesized pathophysiological mechanisms include cerebral hypoperfusion, microembolization, inflammation, and platelet dysfunction.143 Unfortunately, although the Atrial fibrillation Clopidogrel Trial with Ibesartan for Prevention of Vascular Events (ACTIVE) trial correled low Mini-Mental State Examination scores with nontherapeutic anticoagulation, these results were not reproduced in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized Assessment Study in ACE-intolerant Subjects with Cardiovascular Disease (TRANSCEND) studies. Consequently, the pathogenetic role of microemboli is uncertain, given the observation that antithrombotic therapy did not modify the association between AF and cognitive decline in these studies.

### Heart Failure

Although the association between AF and HF is well established, the causative relationship between the 2 has not been fully elucidated. AF can cause reductions in cardiac output (because of shorter diastolic filling time, loss of atrial contractile function, and elevated filling pressures) and tachycardia-induced myocardial dysfunction. In turn, HF results in structural and electric remodeling changes that enhance susceptibility to AF (see below).

### Healthcare Resource Use

Contemporary costs of managing AF have been estimated to account for 1.0% to 2.7% of total annual healthcare expenditures (United States, $6.65 billion in 2001; United Kingdom, £459 million in 2000). A sizeable proportion of these expenses is attributed to direct costs associated with hospitalization and acute care (40%–50% if AF is the primary diagnosis; ≤75% if AF is a comorbid diagnosis), with outpatient care and pharmacotherapy accounting for the remainder. On a per-patient basis, the adjusted excess annual direct and indirect cost of AF has been estimated to be $12,349 and $14,875, respectively.

<table>
<thead>
<tr>
<th>Scoring System</th>
<th>CHADS2</th>
<th>CHA2DS2-VASc</th>
<th>Total Points</th>
<th>CHADS2</th>
<th>CHA2DS2-VASc</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF or LVEF &lt;40%</td>
<td>1 point</td>
<td>1 point</td>
<td>0</td>
<td>1.9%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 point</td>
<td>1 point</td>
<td>1</td>
<td>2.8%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>1 point</td>
<td>2 points</td>
<td>2</td>
<td>4%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 point</td>
<td>1 point</td>
<td>3</td>
<td>5.9%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Stroke/TIA/thromboembolism</td>
<td>2 points</td>
<td>2 points</td>
<td>4</td>
<td>8.5%</td>
<td>4%</td>
</tr>
<tr>
<td>Vascular disease (MI, PVD)</td>
<td>…</td>
<td>1 point</td>
<td>5</td>
<td>12.5%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Age 65–74 y</td>
<td>…</td>
<td>1 point</td>
<td>6</td>
<td>18.2%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>…</td>
<td>1 point</td>
<td>7</td>
<td>N/A</td>
<td>9.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td>N/A</td>
<td>6.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td>N/A</td>
<td>15.2%</td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not applicable; PVD, peripheral vascular disease; and TIA, transient ischemic attack.
respectively, with patients with AF proving 5× more costly than non-AF individuals.150 A rate-control strategy has been associated with lower resource use and costs compared with a rhythm-control strategy but not consistently so.151–154 Among patients with paroxysmal AF, the frequency of recurrences is strongly linked to higher resource use, with each recurrence averaging an additional $1600 dollars/y.154

Although the current clinical and economic burden of AF is substantial, AF is poised to become a public health crisis. Between 1995 and 2000,148 the cost of caring for AF nearly doubled and is expected to continue to increase with aging of the population.

**Hospitalization and Acute Care**
AF accounts for the majority of arrhythmia-related emergency room visits and hospital admissions (eg, 350,000 hospitalizations in the United States each year),155,156 with an increasing burden over time.157 Costs associated with AF-related hospitalizations are substantial. Emergency room patients in the United States with a primary diagnosis of AF had an average hospital stay of 3.9±5.2 (mean±SD) days, despite a spontaneous conversion rate of ≈50%.158 The average cost of hospitalization was $6692±4928 (mean±SD)/patient.

**Stroke Prevention and Care**
OACs are paramount in preventing AF-associated thromboembolism. OACs (and their attendant monitoring) account for a large portion of AF-related costs.148 Nevertheless, despite strong evidence of efficacy, OAC use is limited by nonprescription (≈50% patients do not receive OAC, despite an appropriate indication),159,160 nonadherence (30% 1-year discontinuation for warfarin),161 and subtherapeutic dosing (≈25%–38% of warfarin-treated patients).162,163 Suboptimal therapy is costly as a result of the economic burden associated with excess stroke, an observation that is particularly relevant in the case of AF-associated strokes.148,164 Although the mean lifetime cost of stroke (including inpatient care, rehabilitation, and follow-up) is estimated at $140,000/patient, the cost of caring for patients with AF-associated strokes is substantially higher because AF-associated strokes are more severe.129,130 As a result of the increased disability associated with AF-related strokes, the nursing home costs associated with AF more than doubled from $73.3 million in 1995 to $167.8 million in 2000.148

**Pathophysiological Links Between AF Risk Factors and Arrhythmia Occurrence**

**Overview of AF Pathophysiology**
The pathophysiology of AF is complex. A general overview is provided here; for more information, see detailed reviews.165–167 Figure 3 provides a schematic representation of AF pathophysiology. AF can be maintained by a rapidly firing focus, by complex multiple-circuit re-entry, or by ≥1 discrete rotors.168 Ectopic atrial foci are thought to arise via triggered activity, most typically caused by delayed afterdepolarizations (DADs),168 but in some cases by early afterdepolarizations.169 Ca2+-handling abnormalities are central to DADs and can also contribute to early afterdepolarizations, particularly in the presence of sympathovagal activation.169 In addition to maintaining AF by rapid focal firing, ectopic activity can act on a vulnerable substrate to induce AF-sustaining re-entry. Re-entry requires specific conditions for initiation and maintenance and is favored by brief refractoriness, slow conduction, and conduction barriers that can stabilize re-entry circuits.165–168,170 Structural remodeling, consisting primarily of atrial fibrosis,171 causes localized conduction slowing and conduction barriers that can induce unidirectional block.171–173 Fibrosis may also increase the number of fibroblasts and alter their properties, promoting AF by altering the electrophysiological behavior of cardiomyocytes coupled to fibroblasts through cardiomyocyte–fibroblast interactions.173 Ion channel dysfunction that either increases plateau outward K+ currents or decreases inward L-type Ca2+ current accelerates repolarization, abbreviating atrial action potential duration (APD) and atrial refractoriness, and thereby facilitating re-entry.165–167 Altered autonomic function can also promote AF by several mechanisms, including vagally mediated APD shortening in adrenergically mediated Ca2+ loading and DAD promotion, and early afterdepolarization induction through combined sympatoadrenal discharge.169 In addition to enhancing cellular Ca2+ load by increasing the open probability of L-type Ca2+ channels and thereby enhancing transmembrane Ca2+ entry, β-adrenergic stimulation favors abnormal diastolic Ca2+ release from the sarcoplasmic reticulum (SR) Ca2+ stores, which causes DAD formation by enhancing phosphorylation of several important Ca2+-handling proteins. Adrenergically induced hyperphosphorylation of phospholamban removes phospholamban-induced suppression of the cardiac SR Ca2+ uptake pump, SR Ca2+ ATPase, increasing SR Ca2+ load. In addition, hyperphosphorylation of the ryanodine receptor (the SR Ca2+ release channel) by adrenergically activated protein kinases (protein kinase A and Ca2+/calmodulin-dependent kinase type 2) increases ryanodine receptor 2 sensitivity to SR Ca2+ load and favors aberrant diastolic Ca2+ releases.167 Abnormalities in Ca2+ signaling also contribute to the development of AF-related ion channel dysfunction and structural remodeling.172 Each of the principal mechanisms in blue boxes in Figure 3 have been implicated in the association of AF with risk factors; all of them also occur as a result of AF-induced remodeling and contribute to the “AF begets AF” phenomenon.165,166

**Nature and Role of Structural Remodeling**
Other articles in this compendium deal in detail with AF-related remodeling of atrial ion channel properties,174 Ca2+ handling,174 and autonomic innervation.175 Structural remodeling is not a primary focus of any other article in the compendium and so will be discussed in somewhat greater depth here. Structural remodeling has emerged as an important motif in AF. The term structural remodeling includes changes in atrial tissue properties (most notably fibrosis), size, and cellular ultrastructure. Atrial cardiomyocyte ultrastructure is changed in AF, with alterations including myolysis, glycogen accumulation, gap junction disturbances, changes in nuclear chromatin, mitochondrial disruption and redistribution, and SR alterations.176,177 Ca2+-dependent calpain activation and
resulting proteolysis play a major role in remodeling of cell ultrastructure.\textsuperscript{177} Cell ultrastructure changes likely contribute to the atrial hypocontractility that characterizes AF,\textsuperscript{179–180} thereby contributing to atrial dilation.\textsuperscript{179} Whether, and if so how, cellular ultrastructural remodeling also plays a role in the AF-initiating or AF-maintaining substrate remains unclear.

Atrial size is a long-recognized determinant of AF likelihood, both at the experimental\textsuperscript{181} and clinical\textsuperscript{182} levels. This relationship has been attributed to a critical mass needed to maintain multiple-circuit re-entry.\textsuperscript{181} More recent computational modeling suggests that larger atrial substrates have a greater ability to maintain a critical balance between rotor formation and rotor annihilation in the absence of rotor-stabilizing properties such as functional or anatomic pinning.\textsuperscript{183} In addition, greater atrial enlargement likely reflects greater atrial stretch, a known profibrillatory phenomenon,\textsuperscript{184} as well as atrial damage/remodeling in general.

Ever since its pathophysiological importance in AF substrate development was first identified,\textsuperscript{173} atrial fibrosis has emerged as a significant contributor to AF in many paradigms. Fibrosis results from a broad range of factors related to AF-inducing pathologies, including cell stretch, neurohumoral activation, oxidative stress, and possibly even AF itself.\textsuperscript{184–187} For a full discussion of the complex signaling mechanisms that lead to atrial fibrosis, please see detailed reviews.\textsuperscript{167,185,188} Fibrosis can favor atrial arrhythmogenesis in several ways (Figure 4). First, fibrous tissue can physically separate atrial muscle fibers in the longitudinal direction (Figure 4A), interrupting muscle continuity and creating a physical barrier to conduction.\textsuperscript{189} This type of conduction barrier has been implicated in local conduction disturbances and block that induce re-entry (Figure 5).\textsuperscript{171,189,190} Second, fibrosis is associated with proliferation of fibroblasts and their differentiation into a myofibroblast phenotype,\textsuperscript{173} increasing the likelihood and significance of fibroblast–cardiomyocyte interaction. Extensive cardiomyocyte–fibroblast electric interaction, with the induction of re-entry and spontaneous ectopic activity, is well documented in cardiomyocyte–fibroblast coculture systems.\textsuperscript{191,192} Interactions between cardiomyocytes and fibroblasts via cell-coupling connexin hemichannels make fibroblasts (which are inexcitable but can carry currents) act as an electric sink for cardiomyocyte bioelectricity.\textsuperscript{173} This results in slowing of conduction, depolarization of cardiomyocyte resting potential, \textsuperscript{169} variable effects on APD, and the induction of spontaneous phase-4 depolarization.\textsuperscript{169} Spontaneous depolarization causes focal ectopy and both conduction slowing and APD abbreviation favor the induction and maintenance of re-entry. In addition to direct electric interactions, fibroblasts can affect cardiomyocyte bioelectricity by secreting biologically active substances that cause paracrine effects.\textsuperscript{193} Whether fibroblast–cardiomyocyte interactions promote arrhythmogenesis depends on the number of fibroblasts, their size, and (for electric interactions) the extent of electric coupling between the 2 cell types.\textsuperscript{194,195} Thus, although fibroblasts can directly induce cardiomyocyte arrhythmic activity in cocultured in vitro systems, whether this happens in vivo is still unclear. However,
the contribution of fibrosis per se to the AF substrate is fairly well established based on the close association between fibrosis and AF promotion over a wide range of paradigms, as well as observations that under conditions in which atrial fibrosis seems to be the only fibrosis-promoting derangement a strong AF-supporting substrate can be demonstrated. Atrial fibrosis can now be imaged quantitatively in vivo in man, and the combination of quantitative imaging and mathematical modeling promises to provide new insights into the mechanisms by which fibrosis contributes to clinical AF.

**Pathophysiological Mechanisms by Which Specific Risk Factors Promote AF**
The recognition of AF risk factors has led to extensive research into the pathophysiological mechanisms through which risk factors operate to make AF more likely. In turn, this research has provided central insights into key pathophysiological paradigms underlying AF.

The risk factors (other than genetic) for which mechanisms have been identified are summarized in Table 3. Aging is accompanied by atrial structural remodeling associated with substantial conduction abnormalities. The precise basis for sex-dependent differences in AF risk is unclear. Men have greater expression of important repolarizing ion channel subunits, which could accelerate atrial repolarization, abbreviate atrial refractoriness, and favor re-entry; however, atrial refractoriness does not seem to be sex dependent, and men have greater atrial dimensions that could promote AF maintenance. Hypertension causes significant atrial structural remodeling, and in particular atrial fibrosis, which seems to underlie an enhanced susceptibility to AF. Cardiac valve disease, for which mitral regurgitation is a paradigm that has been studied experimentally, also promotes AF via structural remodeling. Congestive HF produces major atrial structural remodeling and was the context in which the important contribution of structural remodeling to AF pathophysiology was first identified. In addition, HF causes substantial alterations in atrial cardiomyocyte Ca\(^{2+}\) handling, increasing cell Ca\(^{2+}\) load via increased APD and phospholamban hyperphosphorylation, and thereby promoting DAD-related triggered activity. CAD can promote AF via multiple mechanisms. Myocardial infarction often causes substantial left ventricular dysfunction and HF, resulting in HF-related AF promotion. In addition, atrial ischemia has significant AF-promoting properties. Acute atrial ischemia/injury enhances AF sustainability by causing important atrial conduction disturbances, likely related to impaired cell-to-cell coupling. Healed atrial infarctions/persistent ischemia favor AF occurrence by causing Ca\(^{2+}\)-handling abnormalities, resulting in DADs and triggered activity that underlie ectopic firing, along with structural remodeling that creates a reentrant substrate. Autonomic activity is required to elicit ectopic firing in the setting of chronic atrial coronary artery obstruction. Obesity causes atrial structural remodeling, as well as left ventricular diastolic dysfunction that induces acute left atrial dilation and stretch on volume loading. Acute OSA is associated with strongly negative intrathoracic pressures that increase venous return and thereby induce AF-promoting left atrial volume loading. Repetitive OSA over prolonged periods induces atrial structural remodeling. Chronic nicotine exposure also leads to atrial structural remodeling, possibly caused by downregulation of microRNAs 133 and 590. Long-term endurance exercise causes a combination of structural remodeling and vagal enhancement. Enhanced vagal tone promotes AF by causing spatially heterogeneous abbreviations in atrial refractoriness. Autonomic changes, due both to baroreflex enhancement and sensitization to acetylcholine resulting from downregulation of regulators of G-protein signaling proteins, seem to be particularly important for the AF-maintaining substrate caused by endurance exercise training. Diabetes mellitus promotes AF via both structural remodeling, possibly mediated by advanced glycosylation end products, and autonomic remodeling. Thyroid dysfunction seems to promote arrhythmic activity of pulmonary vein cardiomyocytes, to cause ion current remodeling, and to promote atrial structural remodeling.
Genetic risk factors for AF can be separated into monogenic (usually rare disease-causing mutations) and polygenic (generally common gene variants). The pathophysiology underlying most monogenic causes of AF is reasonably understood. Most monogenic AF-causing mutations occur in genes encoding cardiac ion channels. Gain-of-function K⁺ channel mutations accelerate repolarization and thereby promote atrial re-entry. Loss-of-function K⁺ channel mutations and other long-QT syndrome mutations paradoxically also predispose to AF, probably by inducing atrial early afterdepolarization–related ectopic activity. Mutations altering connexin expression or function lead to AF by altering cell-to-cell coupling and causing conduction abnormalities. Catecholaminergic polymorphic ventricular tachycardia mutations alter cellular Ca²⁺ handling and induce DADs; although they are typically associated with ventricular arrhythmias, they can also cause AF likely by inducing DAD-related rapid atrial ectopic firing. Common gene variants, generally manifesting as single nucleotide polymorphisms, contribute to AF susceptibility in a quantitative fashion, with much lower penetrance than monogenic causes. It is likely that they predispose individuals to develop AF in association with acquired risk factors. The mechanisms linking single nucleotide polymorphisms to AF are much less clear than for monogenic causes. For a detailed discussion, readers are referred to the review by Ellinor in this Compendium.

Significance of Understanding Pathophysiological Links Between Risk Factors and AF
Understanding the mechanisms linking risk factors to AF provides better insights into the pathophysiology of the arrhythmia. More importantly, such understanding may be the key to improve AF prevention measures. By appreciating the fundamental mechanisms through which risk factors promote AF, we may be able to develop innovative therapeutic approaches that are directed toward preventing the development.
of tissue substrates that lead to AF. To apply preventive interventions effectively, we will also need improved methods for estimating individual patient risk and pathophysiological mechanisms. Ongoing efforts to develop new biomarkers and for estimating individual patient risk and pathophysiological interventions effectively, we will also need improved methods.

Acknowledgments

We thank France Thériault for expert secretarial assistance.

Sources of Funding

This work was supported by Canadian Institutes of Health Research (S. Nattel: grant Nos. 6957 and 44365), Quebec Heart and Stroke Foundation (S. Nattel), Fondation Leducq (D. Dobrev, S. Nattel: European North-American Atrial Fibrillation Research Alliance), and the European Network for Translational Research in Atrial Fibrillation (D. Dobrev: No. 261057).

Disclosures

None.

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_Circ Res._ 2014;114:1453-1468
doi: 10.1161/CIRCRESAHA.114.303211

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/114/9/1453

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