Epidemiology and Economic Burden of Atrial Fibrillation

a report by
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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is characterized by unco-ordinated atrial activation with consequent loss of atrial mechanical function. In developed nations, the number of men and women affected by AF is projected to more than double over the next two decades. Despite major advances in its management, AF remains a significant cause of cardiovascular morbidity and mortality, especially that arising from stroke and heart failure. This article reviews the epidemiology, cost of management, and future burden of AF.

Classification

In the past, AF has been classified inconsistently in various studies, which has led to difficulties in the comparison and collection of epidemiological data. The current guidelines of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology suggest a simple classification based on the temporal progression of the arrhythmia.[1] The classification has four categories:

- first detected episode of AF;
- paroxysmal AF (self-terminating episodes lasting no longer than seven days, commonly less than 24 hours);
- persistent AF (non-self-terminating episodes lasting more than seven days, requiring electrical or pharmacological cardioversion to terminate); and
- permanent AF (fails to terminate after cardioversion, or is accepted by the patient and the physician).

Paroxysmal and persistent AF may be recurrent and are often progressive. Using the above definitions, a recent general practice-based French study found that permanent AF accounted for 50% of cases, with 25% each for persistent and paroxysmal AF.[2] Data from the Canadian Registry of Atrial Fibrillation (CARAF) suggest that among 757 patients with new-onset paroxysmal AF, approximately 8–9% may progress to permanent AF by the end of one year, a figure that increases to 25% by five years.[3] Rates appear to be higher for those with persistent AF, with 40% developing permanent AF by the end of one year.[4]

Associated Cardiovascular Conditions

AF is common in patients with structural heart disease. While in developing countries rheumatic valvular disease remains a major etiological factor for AF, the spectrum in Western populations has shifted to hypertension, atherosclerotic heart disease, congestive heart failure, valvular heart disease (mainly mitral stenosis), and diabetes mellitus as the most common risk factors for the development and sustenance of AF (see *Table 1*).[5] As people begin to live longer with the background of the above risk factors, each decade of advancing age increases the likelihood of developing AF by 2.1-fold in men and 2.2-fold in women. Other modifiable risk factors and conditions include cigarette smoking, excessive alcohol consumption (>3 drinks/day[6]), pulmonary diseases, cardiothoracic surgery, and hyperthyroidism. A number of previously unrecognized or underappreciated risk factors—such as obesity, metabolic syndrome, diastolic dysfunction, sleep apnea, psychological stress, tall stature, and inflammatory conditions associated with raised levels of C-reactive protein—have emerged.[7] AF in the absence of the above risk factors or underlying heart disease, which is termed lone AF, accounts for 12–30% of all AF and between 20 and 45% of AF in younger patients.[1] Genetic predisposition to AF or specific genetically predetermined forms of the arrhythmia have also been described.[8]

Prevalence and Incidence

A recent report based on sub-analysis of Framingham data highlights the fact that AF poses a major public health burden, as the lifetime risk of developing AF from age 40 years onwards is approximately one in four for both men and women, and one in six even in the absence of congestive heart failure or myocardial infarction.[9] Large-scale population-based studies estimated an overall prevalence of 0.9% in the US, which increased steadily to 3–5% in people older than 65 years, and to 10% or higher in people over 80 years of age.[10] Similar prevalence has been reported in the UK.[11]

The incidence of AF follows a similar pattern and also appears to be on the rise. The Framingham study, over a 38-year follow-up period, found an overall incidence of 3/1,000 person-years in men and 2/1,000 person-years in women aged 55–64 years.[13] The Renfrew/Paisley cohort observed a 20-year incident rate of 2.1 and 1.7/1,000 person-years in men and women, respectively, in the same age range.[11] The Manitoba follow-up study in Canada (3,983 male aircrew recruits with average age of 31 years in 1948 followed up for 44 years) reported a similar overall incidence rate of 2/1,000 person-years.[13] The incidence of AF increases exponentially with advancing age to 20–30 per 1,000 patient-years in individuals 85 years of age and older. AF is 1.5 times more common in men than in women. However, the onset of AF in women occurs at a later age than in men (mean age 65 years versus 60 years).

Moreover, the incidence pattern of AF may show racial and geographical variations. The Cardiovascular Health Study reported that incidence of AF

among white subjects was twice that among African-Americans.[14] The incidence and prevalence of AF appear to be similar in the US and Europe, but possibly lower in Asia.[15]

Projected data from population-based studies, such as the Anticoagulation and Risk Factors In Atrial Fibrillation (ATRIA) study in California and analysis from the Mayo Clinic in the Midwest, suggest that the number of adults with AF may reach 5.6–12.1 million by 2050 (see *Figure 1*).[16,17] In fact, this number could be as high as 15.9 million, if a continuous raise in the incidence of AF is present.[17]

However, even these projections may represent conservative estimates because of silent AF. The prevalence of sustained silent AF in people over the age of 65 is believed to be 25–30%, but modern implantable rhythm control devices—such as pacemakers and cardioverter defibrillators—have revealed that up to 50–60% may have unsuspected episodes of the arrhythmia, with almost half of these lasting more than 48 hours.[18] Pharmacological therapy and catheter ablation have been shown to convert symptomatic into asymptomatic AF.

Morbidity and Mortality

AF is a significant marker of future morbidity with major consequences for the healthcare delivery system. All large-scale studies have shown increased risk of all-cause mortality and death from cardiovascular causes, ranging from 1.3- to 1.8-fold for men and 1.9- to 2.8-fold for women.[11–13] A four-year follow-up of patients in the Marshfield Clinic Epidemiologic Study Area population also showed a 2.4-fold increased risk of death even after adjustments for sex, age, and other cardiovascular risk factors in patients with AF or atrial flutter.[19]

Thromboembolic stroke is the most serious and debilitating of all complications, the risk of which is increased three to five times in patients with non-valvular AF.[12] In the Framingham Study, the annual risk of stroke attributable to AF was 1.5% among patients aged 50–59 years and increased to 23.5% in those over 80 years. Strokes in AF are typically more severe and are associated with greater disability. The risk of AF-related stroke mortality increases from 1.5% in those aged 50–59 years to 24% in those aged 80–89 years. Patients with AF also appear to have more recurrent and fatal strokes independent of age and other risk factors for stroke. In addition to stroke, chronic AF also increases the risk of developing congestive heart failure. In the Manitoba Study and the Renfrew/Paisley cohort, AF was associated with a 3- and 3.4-fold increase, respectively, in risk of heart failure.[11,13] Nevertheless, the overall prognosis of AF is likely to be influenced by an appropriate treatment strategy, such as increased use of anticoagulation in high-risk individuals (e.g. those aged >75 years) or improved rate of rhythm control to prevent tachycardia-induced cardiomyopathy and heart failure.

AF affects quality of life across areas of physical, mental, social, and functional statuses. Even patients with asymptomatic AF have lower global life satisfaction compared with healthy subjects.[20] Women and younger individuals with AF appear to experience more symptoms than men and elderly patients, regardless of associated comorbid conditions.[21]

Economic Burden

AF imposes a substantial cost burden on the healthcare system due to its increased morbidity- and mortality-associated therapeutic interventions. Based on data from the National Hospital Discharge Survey, the number of AF-related hospitalizations almost tripled in 2000 compared with two decades ago.[22] Few studies have been performed to evaluate the cost of care and health resource utilization for AF (see *Figure 2*). A good estimate of the involved costs was provided by a large UK-based survey that revealed that the direct cost of managing AF increased from 0.6–1.2% of the total National Health Service (NHS) budget in 1995 to 0.9–2.4% by 2000.[23] A study from France showed similar figures, with a significantly higher number of hospitalizations and deaths in patients with persistent or permanent AF compared with those with paroxysmal AF.[24] AF-associated heart failure, coronary disease, use of class III antiarrhythmic drugs, hypertension, and metabolic disease were significantly associated with higher costs. Based on retrospective analyses of three federally funded databases in the US (2001 data), total annual costs for treatment of AF were estimated at US$6.65 billion, including US$2.93 billion (44%) for hospitalizations for AF, US$1.95 billion (29%) for the incremental inpatient cost of AF as a comorbid diagnosis, US$1.53 billion (23%) for outpatient treatment of AF, and US$235 million (4%) for prescription drugs.[25]

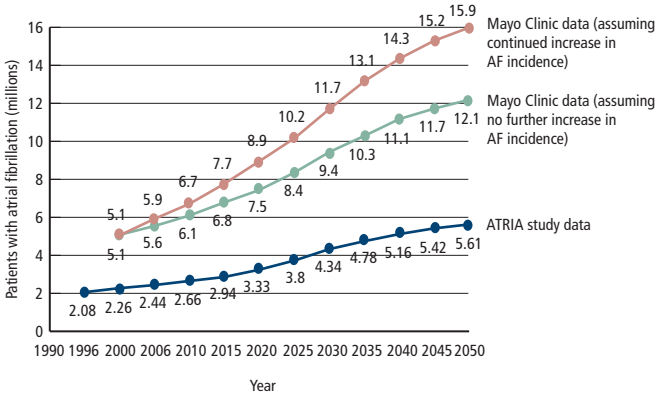
These figures may be an underestimate as they do not comprehensively include other costs in the community (e.g. monitoring of anticoagulation

Table 1: Increases in Risk of Atrial Fibrillation in the Presence of Risk Factors

Risk Factor	Men	Women
Age per decade	2.1	2.2
Hypertension	1.5	1.4
Myocardial infarction	1.4	–
Heart failure	4.5	5.9
Mitral valve disease	1.8	3.4
Diabetes mellitus	1.4	1.6
BMI per 1 unit increase	1.52	1.46
Alcohol >36g/day	1.33	1.25
≥1 parent with AF	1.85	1.85

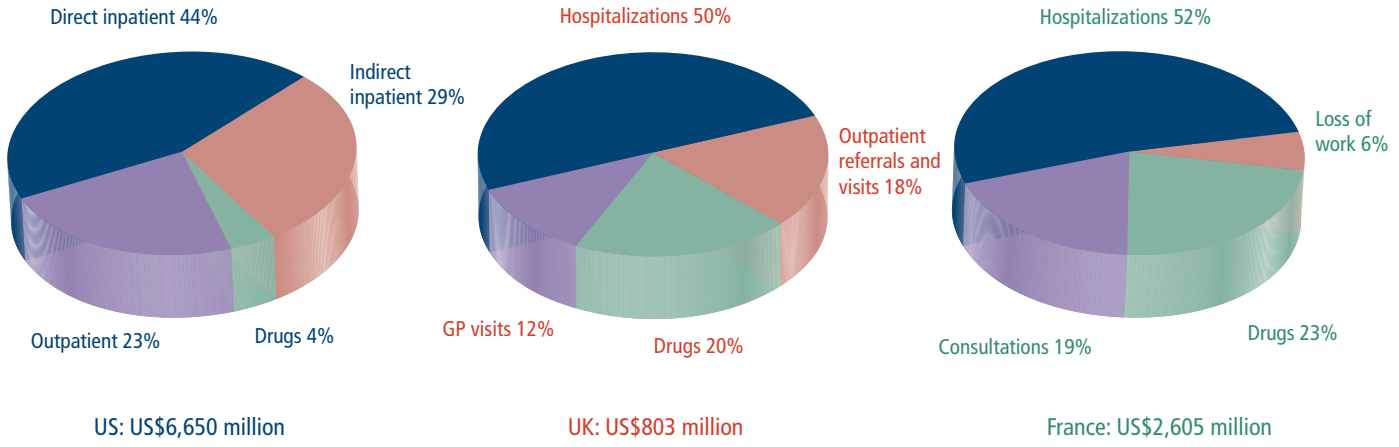
AF = atrial fibrillation; BMI = body mass index.
Source: Framingham Study.

Figure 1: Projected Number of Adults with Atrial Fibrillation in the US by 2050



ATRIA = AnTicoagulation and Risk Factors In Atrial Fibrillation.
Source: Go AS et al.[16] and Miyasaka Y et al.[17]

Figure 2: Costs of Atrial Fibrillation



Source: Stewart S et al.,[23] Le Heuzy JY et al.,[24] and Coyne KS et al.[25]

Table 2: Incremental Cost-effectiveness Ratios of Different Treatment Strategies for Atrial Fibrillation Stratified by Ischemic Stroke Risk (Markov Model)

Stroke Risk	Strategy	Cost	QALYs	ICER (US$/QALY)
Moderate, age 65 years	Rate control + warfarin	US$39,391	10.81	Reference
	Amiodarone + warfarin	US$43,358	10.75	Dominated
	LACA + warfarin	US$52,369	11.06	US$51,800
Moderate, age 55 years	Rate control + warfarin	US$50,509	14.80	Reference
	Amiodarone + warfarin	US$55,795	14.75	Dominated
	LACA + warfarin	US$59,380	14.88	US$28,700
Low	Rate control + aspirin	US$25,540	11.21	Reference
	Amiodarone + aspirin	US$38,425	11.02	Dominated
	LACA + aspirin	US$43,036	11.40	US$98,900

An ICER of US$50,000 per QALY is used to determine whether therapies are considered cost-effective.
ICER = incremental cost-effectiveness ratio; LACA = left atrial catheter ablation; QALY = quality-adjusted life years.
Modified from Chan PS et al.[33]

status), costs of AF-related complications (e.g. side effects from drug therapy), and costs of managing conditions when AF was a secondary diagnosis during admission (e.g. hemorrhagic strokes, cardiac surgery). In a prospective cohort study of hospitalized Medicare patients, adjusted total Medicare spending in one year was 8.6- to 22.6-fold greater in men and 9.8- to 11.2-fold greater in women with AF compared with a matched group without AF.[26] The cost of caring for patients with stroke associated with AF is significantly higher than for those whose stroke was not caused by AF. In the Berlin Acute Stroke Study, mean direct costs per patient were approximately 33% greater for AF-related stroke, driven by costs incurred by initial hospital stay (49%) and rehabilitation (16%).[27] A study relating to the cost of managing AF following coronary artery bypass surgery showed that 33% of patients developed post-operative AF as the first ever episode and incurred an additional cost of US$6,356 compared with those without AF.[28]

Cost-effectiveness of Current Management Strategies

It is important to consider costs attributable to AF in the context of different treatment strategies. Although few formal economic analyses have been conducted, anticoagulation in AF patients at high risk of stroke is highly cost-effective. However, a Medicare-based project measuring the national economic burden of stroke in AF in the US in 2003 has suggested that only a small proportion of the potential anticoagulation benefit is currently attained because of substantial underprescription of warfarin.[29] According to one economic model of stroke in AF, approximately 1.265 million patients (55%) not receiving antithrombotic prophylaxis suffer 58,382 strokes annually with an associated total direct cost to Medicare of US$4.8 billion. For the 1.035 million receiving warfarin, 38,468 strokes are predicted every year, costing an estimated US$3.1 billion.[29]

Recent studies comparing the effectiveness of rate control versus rhythm control strategies were consistent in their results that rate control is at least as effective as rhythm control in relatively asymptomatic patients over 65 years of age.[30] There is evidence that in this category of patients, a strategy of rhythm control using currently available antiarrhythmic drugs is more expensive and less effective than rate control strategy in the prevention of major adverse events. Cost-effectiveness analysis from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study convincingly demonstrated that patients randomized to pharmacological rhythm control had greater resource utilization and higher costs than patients randomized to rate control (US$25,600 versus US$20,500 over 4.6 years).[31]

An economic analysis from the Fibrillation Registry Assessing Costs, Therapies, Adverse events, and Lifestyle (FRACTAL) has shown that AF-related healthcare costs averaged US$4,700 per patient per year during the first few years following diagnosis, but annual costs varied greatly according to the AF clinical course.[32] Patients accepting permanent AF from the outset had the lowest resource utilization and costs. Among

patients with recurrent AF, the frequency of recurrences was strongly associated with higher resource utilization, with each recurrence increasing annual costs by a mean of US$1,600. In a privately insured population, the direct annual direct cost of AF was US$15,553 per patient, in excess of US$12,349 compared with enrollees without AF—i.e. AF patients were approximately five times more costly.[33]

As a result of increasing age and improved survival rates in those with coronary artery disease, heart failure, and hypertension, an increase in the prevalence of atrial fibrillation is likely to be exponential and sustained in the foreseeable future.

Post-hoc analysis of the rate versus rhythm control trials suggests that benefits of sinus rhythm may have been offset by the adverse effects of antiarrhythmic therapy.[34] The arrival of safer AADs may allow patients to reap the benefits of sinus ryhthm without the drawbacks of current AADs. In addition, there is emerging evidence that in a select group of patients, catheter ablation of AF may help restore and maintain sinus rhythm with the cost of ablative strategy meeting the cost of medical therapy at around five years.[35,36] An estimate based on the Markov model suggests that ablation therapies can be cost-effective in middle-aged patients at moderate risk of stroke as opposed to pharmacological rhythm control (see *Table 2*).[35] Nevertheless, since long-term outcome of catheter ablation and its effects on mortality and morbidity are not yet known, prospective randomized trials are necessary to compare the benefits and cost-effectiveness of this treatment strategy.

Conclusion

As a result of increasing age and improved survival rates in those with coronary artery disease, heart failure, and hypertension, an increase in the prevalence of AF is likely to be exponential and sustained in the foreseeable future. This imposes the substantial future burden of the associated morbidity and mortality from stroke and heart failure on society. Economic reports prompt consideration of more efficient ways of delivering care for patients with AF to lead to a reduction in costly hospitalizations. New AADs with improved safety and tolerability may allow patients to reap the benefits of sinus ryhthm without the toxicities of current agents. Preventive strategies to eliminate or minimize the risk factors that lead to the development of AF may be the most cost-effective way to reduce AF burden. ■

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