The changing epidemiology of non-valvular atrial fibrillation: the role of novel risk factors

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The growing ‘epidemic’ of atrial fibrillation (AF), with its associated morbidity and mortality, intersects with a number of risk factors including ageing and other conditions including thromboembolism, stroke, congestive heart failure, hypertension, and also perhaps metabolic syndrome and systemic inflammation. Currently in the USA, ~2.3 million people are diagnosed with AF and, on the basis of the US census, this number is expected to rise to 3.3 million by 2020 and to 5.6 million by 2050. This may even be a substantial underestimate: recent data from Rochester, MN, USA suggest that there has been an almost three-fold increase in the prevalence of AF over the last three decades, after adjustment for age. The explanations for this phenomenon are likely multifactorial, and the socio-economic implications considerable. Ongoing efforts towards understanding AF are driven, in part, by the concept that the primary causal factors of AF in most patients may be the consequence of a systemic condition of reduced vascular compliance, atherosclerosis, obesity, and inflammation. Such epidemiological investigations must be undertaken in association with studies aimed at defining the structural and electrical phenotypes and molecular genetics of AF, which may provide additional insights into their potential interactions with age and environmental factors.

Introduction

Atrial fibrillation (AF), an ‘old’ arrhythmia first described in 1909, has assumed increasing importance in the 21st century, in which the global demographic tide has resulted in a rapidly expanding elderly population.1,2,3 Currently, AF is the most common sustained cardiac arrhythmia affecting ~2.3 million individuals in the USA.4 In the last 15 years, hospital admissions resulting from AF have increased two- to three-fold based on data from the National Hospital Discharge Survey from 1985 to 1999.5 During this period, hospitalizations increased from 154 086 to 376 487 for a first-listed diagnosis of AF and from 787 750 to 2 283 673 for any diagnosis. This perceived increase was most apparent in successive age groups and was higher in men than in women. In the UK, AF accounted for 0.62% of the total National Health Service expenditures in 1995 and 0.97% in 2000.6

AF is an independent predictor of mortality and is associated with an increased incidence of embolic stroke, accounting for between 75 000 and 100 000 strokes per year in the USA.7 AF is primarily a disease of the elderly, and is in itself a powerful risk factor for stroke among patients with AF of advanced age. Indeed, AF is considered to be one of the three growing cardiovascular epidemics in the 21st century in conjunction with congestive heart failure (CHF), and type II diabetes mellitus, and/or metabolic syndrome.8 Moreover, AF and CHF frequently co-exist and each may exert an adverse prognostic impact upon the other.9 In this respect, the interaction between AF, CHF, diabetes, hypertension, stroke, and also perhaps inflammation,

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places AF at the centre of current research in some of the most clinically relevant areas of cardiovascular disease.10

Incidence and prevalence

Multiple studies of the incidence and prevalence of AF, including populations from the Framingham Study and Olmsted County, MN, USA; Scotland; Holland; and Western Australia, have demonstrated highly consistent findings (Figure 1). For reasons that are largely unexplained, the prevalence of AF was considerably greater in men than in women in the Framingham Study. AF is uncommon in individuals <60 years of age,11 but the prevalence increases markedly thereafter, with ~10% of the population having AF by 80 years of age. Approximately one-third of all patients with AF are aged >80. As octogenarians are the fastest growing segment of our society, it is estimated that the majority of the population with AF will be aged ≥80 by the year 2050.12

Future projections

In one cross-sectional study of ~1.9 million adults aged ≥20 from California, USA, the prevalence of AF ranged from 0.1% among adults <55 years of age to 9% in patients aged ≥80.12 On the basis of the US census projections for the next 50 years, it is estimated that ~3 million individuals will have AF by the year 2020, increasing to 5.6 million by the year 2050, with >50% of affected individuals being ≥80 years. Although the elderly are not only at the highest risk of stroke among the population with AF, but also at the highest risk of bleeding with anticoagulant treatment, these epidemiological features highlight the necessity of developing new strategies for the prevention of AF, including improved anticoagulation therapies. Moreover, increasing evidence suggests that the magnitude of these projections are probably significantly underestimated for several reasons:

Clinically undetected AF

Many episodes of AF remain undetected because of a lack of symptoms. For example, AF was diagnosed incidentally in 30% of patients for unrelated reasons on electrocardiogram examination in the Cardiovascular Health Study,13 and in 45% of patients in the Stroke Prevention in AF Trials.14 In a prospective study of 4618 individuals from Olmsted County, MN, USA, who developed a first episode of AF between 1980 and 2000, 18% of patients had typical symptoms, 29% had "clinically silent" AF, 38% had atypical symptoms, and the rest had unclassifiable symptoms (T. Tsang, personal communication). In another study of patients with paroxysmal AF, the ratio of asymptomatic to symptomatic episodes of AF was 12:1.15 In a more recent study, 38% of patients experiencing an AF episode of ≥48 h in duration, as documented by implanted permanent pacemakers with AF detection and electrogram storage capability, were asymptomatic.16

Changing incidence and prevalence

It has been generally accepted that the genesis of the AF epidemic has its roots in the increasing proportion of the elderly population. However, more recent data from the Framingham Study and another from Rochester, MN, USA, suggest that other factors, as yet poorly understood, are playing a major role in the marked increase and frequency of this disease.11,17 In the Framingham Study of individuals aged between 65 and 84 years of age, after adjusting for age, the prevalence of AF in men increased from 3.2% during 1968–70 to 9.1% during 1987–89. This was less marked in women in whom the prevalence increased from 2.8 to 4.7%. Similarly, a two- to three-fold increase in the age-adjusted prevalence of AF during 1960–69 compared with data from 1989 was demonstrated in the recent matched case-control study among residents of Rochester, MN, USA (Figure 2).17 This increase was noted in the control population as well as among patients who had experienced an ischaemic stroke, and did not differ between men and women.

These numbers suggest that we are in the throes of an extraordinary increase in the prevalence of this disease, over and above that which can be attributed to age alone. Although the analysis of multiple concurrent trends is a complex process, a clearer understanding of the causes of this rapid increase in the numbers of

Figure 1 Prevalence of AF in six natural history studies. CHS, Cardiovascular Health Study; W Australia, Western Australia. (Modified from Feinberg et al.4 with permission from American Medical Association.)

Figure 2 Prevalence of AF in 1871 patients in Rochester, MN, USA, with ischaemic stroke and their age- and gender-matched controls, stratified by age, gender, and calendar decade. (Reproduced from Tsang et al.17 with permission from American College of Cardiology Foundation.)
patients with AF is needed. The sheer magnitude of the population with this disease creates a major public health issue.

Factors contributing to the development of the AF epidemic

A relatively obvious explanation for the increase in numbers of patients with AF is that this is the result of ascertainment bias related to the increased use of the electrocardiogram in the community. However, this possibility was found to be an unlikely cause in the Rochester population,17 since over the 30-year period the utilization of the electrocardiogram increased by only 9–12%, in comparison to the two- to three-fold increase in the prevalence of AF. A further potential explanation is that the elderly of today are a ‘sicker population’, having a higher prevalence of comorbid conditions including hypertension, diabetes, CHF, coronary artery and valvular heart disease, and prior cardiac surgery. For centuries, highly selected individuals have lived to a very advanced age, providing an example of the Darwinian principle of ‘survival of the fittest’.17 During the 20th century, advances in preventive medicine and increasing socioeconomic prosperity have resulted in a marked increase in the proportion of the population attaining ‘old age’. This more recent trend, brought about by both primary and secondary prevention, plus advances in the treatment of acute and chronic cardiovascular disease, could result in a population of elderly survivors who may comprise a ‘sicker’ population in comparison with their counterparts who lived to a similar age 50 years ago.18–21

In this respect, in the Rochester study over a 30-year period, there were statistically significant but relatively modest increases in the prevalence of coronary artery disease, valvular heart disease, a history of prior myocardial infarction, and to a lesser extent CHF, diabetes, and a history of prior cardiac surgery. Nonetheless, when placed into perspective with the magnitude of the increase in prevalence of AF, the relatively modest increase in the prevalence of known comorbidities does not appear to offer more than a partial explanation.

Novel risk factors for AF

Inflammation

C-reactive protein, which is a sensitive marker of inflammation, is a powerful predictor of adverse cardiac events and has recently been linked to AF.22–24 A crucial, but as-yet-unanswered question, is whether indices of inflammation should be considered as direct ‘risk factors’ for AF by causing an atrial inflammatory state, or whether these are surrogates of other cardiovascular conditions that predispose to AF. In this respect, an elevated serum C-reactive protein level may be a ‘marker’ of atherosclerotic vascular disease and hypertension, which, in turn may cause AF via mechanisms related to reduced vascular compliance, left ventricular hypertrophy, diastolic dysfunction, and increased atrial stretch. Indeed, it has been demonstrated that left atrial volume is as powerful a predictor of the development of AF as it is an indicator of future cardiovascular events including myocardial infarction, stroke, and coronary revascularization.25

Obesity and metabolic syndrome

The surge in obesity, diabetes, and the metabolic syndrome, both in the developed and the developing world, is well documented and has reached alarming proportions.26,27 To what extent obesity is a risk factor for AF, independent of its association with other cardiovascular risk factors, remains a controversial issue in that the conclusions of different studies are discordant.28–31 Nonetheless, given the evidence that the metabolic syndrome is pro-inflammatory32,33 and that AF has been linked to an inflammatory ‘milieu’, the plausible relationship of these risk factors to the development of AF is a major focus of current investigation, including a prospective study in the Olmsted County, MN, USA, cohort. In a study from the Mayo Clinic, MN, USA, of a random sample of 1849 patients of age ≥65, 12% of patients developed new onset AF over a follow-up period of 4.0 ± 2.7 years. Predictors of AF in a multivariate analysis, after adjustment for age and sex, included body mass index with a relative risk of 1.39/10 kg/m².34 Moreover, obesity is an independent predictor of diastolic dysfunction which is, in itself, a major determinant of the development of AF.35

Sleep apnoea

The relationship between obstructive obesity and sleep apnoea is well documented,27,36–38 and the prevalence of sleep disordered breathing has been perhaps underappreciated. In one population-based study in nonobese patients, one in 5 adults were estimated to have at least mild obstructive sleep apnoea, and at least one in 15 patients had moderate obstructive sleep apnoea.37 A more recent study of patients with AF undergoing successful cardioversion at the Mayo Clinic, MN, USA, demonstrated a remarkably high recurrence of AF in untreated patients with obstructive sleep apnoea compared with patients treated with continuous positive airway pressure, and in control volunteers who had not participated in a sleep study.39 Another study from the Mayo Clinic, MN, USA, demonstrated that the frequency of obstructive sleep apnoea among patients undergoing cardioversion for AF was 49% compared with 39% (P = 0.0004) among patients drawn from a wider population of general cardiology without AF.40 This association remained highly significant after adjustment for relevant covariates.

To what extent AF is the consequence of hypoxaemia, hypercarbia, increased sympathetic and reduced vagal tone, and the increase in afterload and left ventricular wall stress noted in patients with obstructive sleep apnoea has not been clarified.27 All of these factors, particularly the increase in atrial stretch in conjunction with
sympathetic overactivity, could be contributory. In addition, in patients with sleep apnoea, hypoxia induces pulmonary artery vasoconstriction and increased right-sided pressures which act as a stimulus for atrial natriuretic peptide release, the levels of which are elevated in AF. Whether or not the frequent bradycardias noted during obstructive sleep apnoea, which may be a manifestation of the diving reflex, could also contribute to the development of AF is presently unknown. In addition, the relationships between obstructive sleep apnoea, obesity, the metabolic syndrome, hypertension, and AF require further exploration.

Is obstructive sleep apnoea a risk factor for AF or a risk marker of other comorbidities including inflammation, which may, in turn, predispose to AF? It should be emphasized that an association does not necessarily imply a cause-and-effect relationship, and there is a need for prospective studies of the associations between sleep-disordered breathing and AF in addition to other diseases, e.g. coronary artery disease, heart failure, and stroke.

**Diastolic dysfunction and arterial stiffness**

Diastolic dysfunction, a common accompaniment of ageing, is associated with hypertension, obesity, diabetes, and coronary artery disease. It is becoming increasingly evident that heart failure in older patients is frequently noted in the absence of impaired systolic function, presumably as a result of diastolic dysfunction. In a study undertaken in Olmsted County, MN, USA of patients of age ≥65 in sinus rhythm at the time of an echocardiographic examination, it was noted that the subsequent development of AF in patients without diastolic dysfunction was only 1% compared with ~12% in patients with moderate degrees of diastolic dysfunction, and 20% of those with restrictive physiology, the most severe manifestation of diastolic dysfunction (Figure 3). In addition, the assessment of diastolic function provided incremental predictive information, over and above that obtained from the clinical risk factors. Moreover, increased left atrial volumes are associated with an incremental deterioration of diastolic function and provide additional predictive information in regard to the development of AF and stroke (Figure 4). Since it is well established that atrial stretch and dilatation increases the vulnerability of the atrium to the development of AF, a logical focus of further investigation currently ongoing involves an understanding of the relationships between arterial compliance, diastolic function, atrial volume, and inflammation. In this respect, left atrial volume may be a surrogate or marker of multiple other processes that lead to the development of AF, including arteriosclerosis and hypertension (Figure 4). In addition, left atrial volume is a predictor of other cardiovascular events including myocardial infarction, stroke, and coronary revascularization. Indeed, left atrial volume has been considered to be the haemoglobin A1c (a biomarker of long-term glucose control) of vascular disease.

In this respect recent data suggesting that angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers may reduce the rate of recurrence of AF after cardioversion, and might have a protective effect on the development of AF in patients with left ventricular dysfunction are intriguing. Another recent experimental study has demonstrated that candesartan reduces the accumulation of atrial collagen formation during episodes of AF, which may help to explain the beneficial effect of angiotensin II inhibition upon the recurrence of AF. The mechanisms are probably multiple and perhaps related to the pleiotropic effects of these drugs in addition to their effects upon the atrial substrate. Certainly haemodynamic changes that reduce atrial pressure and wall stress could be a factor, but other explanations postulate beneficial effects upon diastolic function, atrial fibrosis and remodelling, and

![Figure 3](https://academic.oup.com/eurheartjsupp/article-abstract/7/suppl_C/C5/456469/11012197.appl._CC/545469)  
**Figure 3** Age-adjusted cumulative survival without non-valvular atrial fibrillation (NVAF) by diastolic function profile in 960 Olmsted County patients of age ≥65 who were in sinus rhythm at the time of the echocardiographic examination. Subsequent development of AF was 9.8%. (Reproduced from Tsang et al. with permission from American College of Cardiology Foundation.)

![Figure 4](https://academic.oup.com/eurheartjsupp/article-abstract/7/suppl_C/C5/456469/11012197.appl._CC/545469)  
**Figure 4** Hypothetical construct of the pathophysiology of AF. In this schematic, atrial dilatation and atrial stretch act as a common denominator in increasing the vulnerability to AF. To what extent inflammation plays a role is under investigation, but in this substrate the etiologic role of diastolic dysfunction, hypertension, and mitral regurgitation is understandable. It is possible that conditions predisposing to increased arterial stiffness may also lead to left atrial dilatation by increasing the impedance to left ventricular ejection. (Reproduced from Gersh et al. with permission from HL DuPont.)
Epidemiology of stroke in patients with AF

AF accounts for ≈45% of all embolic strokes. The risk of stroke among placebo-treated patients in randomized trials of warfarin was 4.5% per year. In a collaborative analysis of five randomized trials, the AF Investigators identified five major risk factors for stroke; namely, prior stroke or transient ischaemic attack, a history of hypertension, advanced age, a history of CHF, and diabetes. It is noteworthy that all of these risk factors are age-related, which may explain why the risk of stroke in patients with AF increases with age so strikingly. The risk of stroke increases at least five-fold in patients with clinical risk factors, and this is in marked contrast to <1% per year risk of stroke in younger patients under the age of 60 without clinical risk factors. The powerful impact of age and other clinical risk factors on the risk of stroke in patients with AF raises the question: ‘Is risk due to the arrhythmia or the company it keeps?’

A history of hypertension appears in virtually every study to be a major independent risk factor for stroke. The strong association between AF, hypertension, and stroke could be explained on the basis of reduced aortic compliance, left ventricular hypertrophy, diastolic dysfunction, and increased left atrial dimension, giving rise to stasis and thrombus formation. On the other hand, this could be another example of AF as a ‘marker’ of vascular disease that causes AF, but perhaps the putative causes of stroke arise from the atherosclerotic aorta and cerebral vessels. These concepts potentially have major therapeutic implications including the use of left atrial appendage occlusion devices, and specific forms of antithrombotic therapy. Nonetheless, it should also be emphasized that this is currently a conceptual framework, which requires confirmation.

Genetic epidemiology

The genetic epidemiology of AF is of great interest, and although the familial occurrence of AF has been known for many years, it was generally considered a rare event. Several studies, however, have identified families with AF, and linkage studies have identified different chromosomal loci that are quite disparate in location. Almost all patients in these families, however, are relatively young and very few fall into the age group that comprises the majority of patients with AF over 65 years of age. This poses a question of whether the putative genes causing AF in younger patients are also involved in a disease that is so prevalent in the elderly. Is AF in the elderly a manifestation of an interaction between the genetic substrate present in younger patients and modifier genes and environmental factors, including among the latter atherosclerosis, hypertension, diastolic dysfunction, and atrial fibrosis? Does AF among older and younger patients share a genetic locus, or are these entirely different diseases both in terms of their natural history and genetic substrates? All of these are interesting questions, for which answers are being sought, and will hopefully help unravel the relationship between traditional and novel risk factors of the increased prevalence of AF in today’s society (Figure 5).

Conclusion

AF, a ‘simple’ arrhythmia characterized by ‘irregular heart beats’ is now accepted as a common and rapidly growing clinical problem and disease entity. An emerging and sophisticated, invasive, and pharmacological therapeutic armamentarium has increasingly required the expertise of an electrophysiologist. Nonetheless, our understanding of the mechanisms leading to AF and the ultimate role of prevention, which may involve drugs such as ACE inhibitors and aldosterone antagonists, among others, emphasizes the multidisciplinary approach that is required.

A crucial question is: to what extent are systemic cardiovascular conditions a risk factor vs. a risk marker? This is also applicable to the role of AF and the left atrium as a direct cause of thromboembolic stroke, as opposed to a surrogate of other cardiovascular diseases and processes, which in themselves may lead to stroke and thromboembolism via pro-inflammatory and pro-thrombotic mechanisms. Familial linkage studies are slowly starting to unravel the genetics of AF as an ‘electrical disease’ particularly in younger individuals.

Whether these mutations play a role in the majority of older patients with disease of the atrial substrate and in the presence of modifiers such as sleep apnoea and hypertension remains to be proved.

Figure 5 Hypothetical schematic illustrating future approaches to the genomics of AF. The issue is whether the genetic basis for the ‘electrical’ disease identified in younger patients plays a role in the common presentation of AF in the elderly. It could be that AF in the elderly could result from an interaction between the genetic substrate in younger patients and a diseased, aged, atrial substrate, or that AF in these two populations is an entirely different disease from the pathophysiological and genetic basis.
In summary, as we are confronted with a daunting prospect of a rapidly growing epidemic of AF, hopefully an increased understanding of the pathophysiology and genetics of this complex condition will be translated into the clinical arena. The scale of the epidemic is such that there is a dire need for breakthroughs in the prevention and treatment of this disease or group of diseases.

Acknowledgements

Thrombosis Quorum is supported by an educational grant from AstraZeneca. This Supplement has been developed as part of the Thrombosis Quorum initiative, under the direction of the Thrombosis Quorum Steering Group [G. Agnelli (Chairman), P. Bath, J. Emmerich, B. Gersh, M. Ögren, S. Schulman, and J. Weitz].

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