The Prevalence, Impact and Economic Implications of Atrial Fibrillation in Stroke: What Progress Has Been Made?

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Key Words

Atrial fibrillation · Stroke · Prevalence · Risk · Economic evaluation

Abstract

Atrial fibrillation (AF) is a major risk factor for stroke, especially in the elderly. Increased life expectancies mean that AF-related stroke is a growing global public health concern. Improvements in the detection, treatment and prevention of the consequences of AF have occurred in recent years. However, the extent to which these improvements have impacted on the prevalence of AF, the risk of AF-related stroke and subsequent economic costs are unknown. This review provides a contemporary assessment of the epidemiological data on AF-related stroke aimed at assessing the effectiveness of primary prevention strategies and associated economic implications with reductions in stroke incidence. A systematic review of the literature was performed. Appropriately designed studies were identified and retrieved. Evidence on changes in the prevalence of AF, the risk of stroke associated with AF and the excess cost of AF-related stroke over the last 30 years was summarised. The results provide evidence that the age-adjusted prevalence of AF and the relative risk of stroke associated with AF has remained relative-

ly constant. Unless action is taken to improve detection of AF and reduce its consequences, a considerable increase in the social and economic burden associated with AF-related stroke is likely.

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Introduction

Atrial fibrillation (AF) is the most common of cardiac arrhythmias and is well recognised as a major risk factor for ischaemic stroke and transient ischaemic attacks. Approximately 15–20% of patients experiencing ischaemic stroke have AF [1–3]. Stroke severity and in-hospital mortality are also significantly greater in those with AF [1, 2, 4]. AF occurs most commonly in older populations. Therefore, the increased life expectancy in both developed and developing countries means that AF-related stroke has become a growing global public health concern. The associated costs of treating the consequences of AF potentially place a significant economic burden on health systems and society.

The increased recognition of AF as a major contributor to the burden of stroke has led to advances in the detection and treatment of AF and the development of strat-

egies to prevent AF-related stroke. The extent to which these advances in recent years have impacted on the prevalence of AF, the risk of stroke and the economic impact of AF-related stroke has not been explored.

Because of differences in the types, presentations and diagnoses of AF, epidemiological data reported in the literature vary according to the location of the study population and the method of diagnosis [5]. There are three main types of AF reported in the literature: paroxysmal or intermittent AF, which involves intermittent episodes that resolve spontaneously within a week; persistent AF, which can be reversed through surgical or pharmacological intervention, and permanent AF, in which the arrhythmia is constant but not reversible. Atrial flutter is considered to be a milder form of AF and is also associated with an increased risk of stroke [6].

Many AF sufferers experience no symptoms; between 24 and 50% of cases are reported as undiagnosed [7]. Asymptomatic AF is also more common in those with permanent AF than in those with intermittent AF [8, 9]. Consequently, AF is often not diagnosed until patients present to hospital with stroke, or it is incidentally diagnosed during routine electrocardiogram (ECG) examinations. This is concerning since asymptomatic AF affords the same stroke risk as symptomatic AF [10] and, if left undiagnosed, may provide additional risks associated with the lack of access to preventive treatments.

Diagnosis of intermittent AF may also be complicated by the fact that it may not be identified by a single ECG reading. Continuous ECG monitoring for periods of 24 h or more in stroke patients can approximately double the number of AF cases diagnosed when compared to a single short ECG reading [11, 12]. Nevertheless, gaining an understanding of the prevalence of AF and associated trends is important for estimating the proportion of the population that are at increased risk of stroke attributable to AF.

Quantifying the risk of stroke independently associated with AF can also be problematic. Increases in the number of AF patients with additional risk factors for stroke, such as cardiovascular disease or increased age, will increase the overall relative risk of AF-related stroke. However, improved treatment options for the management of AF and prevention of stroke have the potential to reduce the number of strokes associated with AF [13, 14]. Furthermore, improvements in knowledge about the AF-related stroke risk and treatment options may encourage both doctor prescription of anti-thrombotic medications and patient compliance. This is important, as stroke prophylaxis with anticoagulants has been reported as sub-

optimal [15]. Attenuation of the consequences of stroke, with improvements in care and treatment, may also impact on AF-related stroke and related costs. The extent to which these factors have impacted on AF-related stroke remains unclear.

A contemporary assessment of the epidemiological data is required to assess the effectiveness of primary prevention strategies and any associated economic implications with reductions in stroke incidence observed over the last 30 years. Summarising the current literature on the proportion of the total cost burden that can be attributed to AF-related stroke and any changes in the magnitude of these costs over time is an important part of monitoring the effectiveness of current preventive strategies. Therefore, the aims of this review were to (1) describe the prevalence of AF and how this may have changed over time, (2) provide contemporary estimates of the risk of stroke associated with AF and how this may have changed over time and (3) describe the excess costs of AF-related stroke compared with non-AF-related stroke and how this may have changed over time.

Methods

The methods used are based on those recommended in the international literature. In 2008, the National Heart, Lung, and Blood Institute convened an expert panel to identify gaps in the current research knowledge base for AF and make recommendations for future research strategies [16]. Two of their recommendations specific to this literature review were the following: (1) that systematic longitudinal large appropriately designed cohort studies be used to define trends and risk factors associated with AF, and (2) that longitudinal natural history studies be used to define the clinical course of AF.

Based on these recommendations, we included only large population-based cohort studies in this review. To allow comparability between studies over time, specific methodological criteria were established for each of the aims (see Search Strategy below). Studies meeting these criteria were included in the final analyses. The inclusion criteria for each of the aims are outlined in table 1.

Types of Participants

Adult populations (≥ 18 years of age) diagnosed with any type of AF or atrial flutter.

Diagnosis of AF

The diagnostic criteria differed according to each of the review questions. To examine the prevalence of AF, we included only studies in which all participants underwent routine ECG at baseline. This provided consistent diagnostic criteria and ensured capture of both symptomatic and asymptomatic AF cases. Cohort studies that were designed to exclude those with pre-existing medical conditions or relied solely on hospital, medical or health insurance company databases were excluded for the prevalence

Table 1. Selection criteria for studies included in the review

Prevalence studies	Stroke risk studies	Cost analysis studies
Population cohort studies or cross-sectional surveys	Cohort or case-control studies	Cohort or case-control studies
AF confirmed by ECG at baseline	AF confirmed by ECG or medical records	AF confirmed by ECG or medical records
Recruitment rate $\geq 60\%$	NA	NA
All forms of AF	All forms of AF	All forms of AF
Participants not excluded on the basis of medical history	Stroke diagnosed via ICD-10 or ICD-9 codes or brain imaging	Stroke diagnosed via ICD-10 or ICD-9 codes or brain imaging
	All strokes	All strokes
	Relative risks reported	Cost data presented separately for patients with and without AF
	Multivariable analyses used	

ICD-10 = *International Classification of Diseases*, 10th edition; ICD-9 = *International Classification of Diseases*, 9th edition; NA = not applicable.

analysis, because of the potential for selection or misclassification bias. Similarly, for the review of prevalence, we excluded studies where less than 60% [17] of the eligible population were recruited, in order to reduce the impact of selection bias in our comparisons. For the review of stroke risk and costs, we included studies where AF could be confirmed by ECG and/or identified from medical records. Those in which the presence of AF was obtained through patient self-report were excluded. All forms of AF were included, since many investigators did not differentiate between the type or cause of AF.

Outcome

The primary outcome of interest was all stroke types, including transient ischaemic attacks. AF is most commonly associated with the occurrence of ischaemic stroke, but not all investigators differentiated between stroke types. Because ischaemic stroke accounts for approximately 80% of all stroke [18], studies in which all strokes were included therefore predominantly comprise ischaemic strokes. We included both fatal and non-fatal strokes and only included studies in which stroke was confirmed on the basis of *International Classification of Diseases*, 9th or 10th edition coding and/or brain imaging. When establishing the risk of stroke associated with AF, we included only studies with relative risks produced using multivariable analysis, whereby well-known stroke risk factors such as age, gender and hypertension were adjusted for in the estimation.

Search Strategy

A separate search strategy was used for each of the review aims, as follows:

- (1) To establish the prevalence of AF, MEDLINE and EMBASE were searched using the following terms: (AF or atrial fibrillation).tw. and (prevalen\$ or epidemiolog\$).tw. and (cohort or 'case control' or 'cross sectional' or survey or 'population based').

- (2) To establish the risk of stroke associated with AF, MEDLINE and EMBASE were searched using the following terms: (AF or atrial fibrillation).tw. and (cohort or 'case control' or 'cross sectional' or survey or 'population based').tw. and (stroke or CVA or cerebrovascular\$).tw. and risk.tw.

- (3) To establish the excess cost of AF-related stroke, MEDLINE, EMBASE and Ecolit were searched using the following terms: (AF or atrial fibrillation).tw. and (cohort or 'case control' or 'cross sectional' or survey or 'population based').tw. and (cost\$ or economic\$).tw.

Searches were limited to English-language citations, from January 1950 to September 2011. Grey literature, in the form of reports, was searched, and the reference lists of key articles from the searches were checked for additional relevant studies.

Data Collection and Management

Study identification and data extraction were performed by the first author (N.E.A.) based on the titles and abstracts of articles identified by the search strategy. For those abstracts that appeared to meet the review criteria, full-text articles were retrieved and assessed. Final selection of eligible studies and uncertainty over eligibility was resolved by consensus from the three review authors.

The methodological quality of the identified studies was assessed with reference to the Strengthening the Reporting of Observational Studies in Epidemiology statement [19]. Criteria derived from this statement that were used to assess the quality of studies were: detailed eligibility criteria; well-described sources and methods of selection of participants; well-described diagnostic criteria and method of diagnosis; reporting of potential sources of bias; reporting of the numbers of individuals at each stage of study, e.g. number eligible, number recruited, number analysed; description of the characteristics of the study population, and appropriate reporting of results. Additional criteria were applied to studies in which the risk of stroke associated with

Fig. 1. Summary of results from the three search strategies.

AF was reported. These were: clearly defined outcome definitions; an explanation of how loss to follow-up was addressed; reporting of the number of outcome events, and the extent to which relevant confounding factors were included in adjusted relative risk estimations.

Data Analysis

Because the prevalence of AF may vary between age groups, gender groups and ethnic groups [20, 21], results pertaining to the prevalence of AF were sub-categorised according to these factors. Where possible, prevalence rates were age adjusted and confidence intervals (CIs) were calculated to enable comparison between studies over time. Age categorisation varied greatly between studies. To promote comparability between studies, age-adjusted prevalence rates are reported for those aged ≥ 65 years.

The relative risk of stroke was compared between studies. Where possible, a meta-analysis of the combined results from comparable studies was performed to provide an overall assessment of the relative risk of stroke associated with AF. A test for heterogeneity was performed to assess whether there was variation in the true effects underlying the studies. A p value > 0.2 was used as a cut-off for homogeneity of the risk of stroke associated with AF. Where possible, the absolute risk of stroke associated with AF was also calculated.

Results

Figure 1 provides an overview of the results for each search strategy used and the final number of articles that were used to address each review aim.

Prevalence

In total, 421 articles were identified using the search strategy. Of these, 73 were identified as eligible following review of the title. This was reduced to 13 studies following review of the abstracts [22–34]. Following methodological assessment of the quality of the full articles, 3 studies were excluded since they did not meet the inclusion criteria [22, 24, 30], and a further 2 studies were excluded because of low response rates [29, 33]. This left 8 studies for inclusion in the review of changes to the prevalence of AF (fig. 1). These studies are summarised in table 2.

All included studies were part of large population-based cohort studies. Four were based in Europe, 3 in Asia and 1 in Australia. All forms of AF were included in the studies. Heeringa et al. [25] and Zhou and Hu [34]

Table 2. Characteristics of the AF prevalence studies included in the review

Study	Year	Location	Setting	Study design	Assessment method ¹	Diagnostic criteria	Person making assessment	Eligible patients included ² %	Percentage of total analysed	Total n
Lake et al. [23]	1966–1983	Australia	Busselton community	prospective cohort (whole community)	12-lead resting ECG	Minnesota code	not reported	64–94		1,770
Heeringa et al. [25]	1990–1993 (BL)	The Netherlands	Rotterdam	prospective cohort (whole community)	12-lead resting ECG plus GP and hospital records	ECG analysis system	confirmed by physicians and cardiologist	78	66	6,808
Chien et al. [26]	1992–2000	Taiwan	Chin-Shan township	prospective cohort (whole community)	ECG	well defined	cardiologist	83	99	3,560
Bilato et al. [27]	1995–1998 (BL) 6-year FU	Italy	2 towns in north-east Italy	prospective cohort (random sample)	ECG	not reported	cardiologist	90	99	1,576
De Ruijter et al. [28] ³	1997–1999 (BL) 6-year FU	The Netherlands		prospective cohort (whole community)	12-lead ECG	Minnesota code	not reported	87	95	566
Yap et al. [32]	2004–2005	Singapore	Singapore	whole area survey	12-lead resting ECG		cardiologist	85		1,839
Schmutz et al. [31]	2005–2007	Switzerland	Geneva	whole area survey – stratified and random	6-lead ECG	well defined	cardiologist	73		3,285
Zhou and Hu [34]	not reported	China	13 provinces	prospective cohort (cluster random sample)	(1) resting ECG; (2) medical records; (3) prior ECG	American College of Cardiology guidelines	physician and cardiologist	96		29,079

BL = Baseline; FU = follow-up.

¹ 12-lead ECG read by a cardiologist is the gold standard.

² Required to be ≥60%.

³ Participants were excluded if arrhythmia was not detected on subsequent examinations.

included extra cases of intermittent AF by including patients diagnosed with AF based on general practitioner (GP) and hospital discharge records in addition to baseline ECG readings. Consequently, there was a slightly greater prevalence rate of AF in that study than in those where only ECG was used to diagnose cases. Between 41 and 72% of AF cases detected in these studies were asymptomatic [28, 31, 32].

In all studies, there was a significant increase in the prevalence of AF with increasing age (table 3). This increase was consistent across gender and ethnic sub-groups. Males had a slightly greater prevalence of AF compared to females. However, in some regions the gender difference was less apparent, as indicated by overlapping CIs (table 4) [23, 25, 34]. Age-adjusted prevalence rates for AF were lower in Asian populations than in Caucasian populations.

There was no evidence for an increase in age-adjusted prevalence rates over time for the group as a whole or for the different sub-categories (table 4).

Risk of Stroke Associated with AF

A total of 544 articles were identified using the search strategy. Of these, 93 were identified as eligible following review of the title (fig. 1). Following review of the abstract, 8 studies were initially identified as eligible for inclusion, but 2 of these were subsequently excluded after assessment of the study methods. One of these was excluded because the relative risk of stroke-related AF was not reported [35] and the other because only univariable analyses were provided [36]. Of the 6 studies included in the final analysis, 5 were prospective cohort studies [26, 37–40] and 1 was a case-control study [21]. In 5 studies, ECG was used to diagnose AF, and so asymptomatic cases of

Table 3. Unadjusted prevalence rates and 95% CIs by age groups

Study	Prevalence rate				
	65–69 years	70–74 years	75–79 years	80–84 years	≥85 years
Lake et al. [23]	3.0 (1.9–4.7)	7.0 (4.8–10.4)	11.6 (8.5–15.6)		
Heeringa et al. [25] ¹	4.0 (3.0–5.2)	6.0 (4.8–7.6)	9.0 (7.3–11.1)	13.5 (10.9–16.7)	17.8 (14.5–21.7)
Chien et al. [26]	2.5 (1.5–4.1)			3.7 (1.8–6.5)	
Bilato et al. [27] ²	4.2		9.4		17
De Ruijter et al. [28]					10 (7.7–12.6)
Yap et al. [32]	0.9 (0.4–2.3)	1.4 (0.6–3.6)	1.2 (0.3–4.3)	5.8 (2.9–11.6)	
Schmutz et al. [31]	1.0	2.71	1.98	2.75	
Zhou and Hu [34] ¹	1.6 (1.2–2.1)	2.8 (2.0–3.8)	3.8 (2.5–5.5)	5.9 (3.2–9.9)	12.2 (5.7–21.8)

95% CIs are reported when available.

¹ Cases were identified by ECG and/or medical records.

² Weighted prevalence rates reported.

Table 4. Unadjusted and age-adjusted prevalence rates with 95% CIs by gender

Study	Year of study	Males ≥65 years		Females ≥65 years		Total ≥65 years	
		unadjusted	age adjusted	unadjusted	age adjusted	unadjusted	age adjusted
Lake et al. [23] ¹	1966–1983	7.4 (5.3–9.4)	7.4 (5.3–9.4)	5.1 (3.2–6.8)	5.1 (3.2–6.8)	6.3 (4.9–7.7)	6.3 (4.9–7.7)
Heeringa et al. [25] ²	1990–1993	9.5 (8.0–11.0)	9.0 (7.6–10.4)	7.5 (6.5–8.5)	7.5 (6.5–8.5)	8.1 (7.3–8.9)	8.2 (7.4–9.0)
Chien et al. [26] ³	1992–2000					2.8 (1.7–3.9)	2.9 (1.9–4.2)
Bilato et al. [27]	1995–1998		7.5 (5.4–9.6)		7.3 (5.7–9.0)		7.4 (6.2–8.8)
Yap et al. [32] ³	2004–2005	3.2 (1.5–4.9)	3.2 (1.5–4.9)	0.6 (–0.02 to 1.2)	0.9 (0.1–1.7)	1.7 (0.9–2.5)	1.7 (0.9–2.5)
Schmutz et al. [31] ⁴	2005–2007	3.4		1.4		2.5	
Zhou and Hu [34] ^{2,3}	not reported	2.9 (2.3–3.5)	2.8 (2.2–3.4)	2.1 (1.5–2.7)	2.1 (1.5–2.7)	2.5 (2.1–2.9)	2.5 (2.1–2.9)

¹ Participants were aged >60 years.

² Cases were identified by ECG and/or medical records.

³ These studies were performed in Asian populations.

⁴ Participants were aged 70–85 years, and only a 6-lead ECG was used.

AF were included [26, 37–40]. In 1 study, GP records were used to identify AF cases [21]. Two studies were designed to exclude those patients with valvular or rheumatic AF [21, 37].

When comparing the results of the 6 included studies, no apparent differences in the adjusted relative risk of stroke between the studies were observed (table 5).

The adjusted relative risk of stroke associated with AF was generally consistent across studies and sub-groups. There was no apparent increase or decrease in adjusted

relative risks over time between ethnic groups or for different age groups. The effect of gender on AF-related stroke risk was inconsistent. In one study, women had a greater adjusted relative risk of stroke than men [38], whereas in the other studies there were no differences between men and women [21, 39].

Sufficient data were provided for inclusion in the meta-analysis in 5 of the 6 studies to assess stroke risk associated with AF. In 3 studies, an overall relative risk was provided, and so these were combined to calculate an

Table 5. Summary of studies reporting the association between AF and stroke

Study	Year	Location	Study design	Eligibility criteria	Method of AF diagnosis	Diagnostic criteria for stroke	Diagnostic method for stroke	Percent- age of eligible screened	Total number eligible (with AF)	FU time ¹ years	Total fol- lowed up	Adjusted relative risk for stroke ²	Unadjusted absolute risk %	Percentage on anticoagu- lants
Wolf et al. [37]	1948– 1982	United States Framingham	prospective cohort	free of CVD at baseline, aged 30–62 years rheumatic AF excluded	ECG	all strokes including TIA	hospital admission confirmed by study neurologist and CT	66%	311	34	97%	age group 50–59 years: 4.1 (1.5–10.8) 60–69 years: 2.6 (1.4–4.9) 70–79 years: 4.0 (2.6–6.2) 80–89 years: 4.8 (2.5–9.2)		'seldom used'
Stewart et al. [39]	1972– 1976 (baseline)	Scotland Renfrew and Paisley	prospective cohort	residents 45–64 years	6-lead ECG	all strokes	ICD-10 discharge data	80%	100	20		men: 2.5 (1.3–4.8) women: 3.2 (1.0–5.0)	men: 17.0 women: 29.8	not reported
Friberg et al. [38]	1976– 1994	Denmark Copenhagen	prospective cohort with random sampling	residents 40–79 years previous stroke excluded	12-lead ECG	symptoms >24 h	hospital records using ICD-10 codes		276	mean 4.7		men: 1.7 (1.0–2.9) women: 7.8 (4.9–12.5)	men: 7.8 women: 20	men: 3.7 men: 4.9
Rietbrock et al. [21]	1987 onwards	UK	case-control study	≥40 years valvular AF excluded	GP medical records	all strokes	GP records	NA	51,807 cases 253,759 controls	2.5 (0.9–4.9)	NA	1.95 (1.87–2.02)	10.7	15–22
Simons et al. [40]	1988– 2004	Australia Dubbo	prospective cohort	all residents 60+ years	ECG	ischaemic stroke	ICD-10 hospital codes	73%	16			3.06 (1.52–6.19)		not reported
Chien et al. [26]	1992– 2000	Taiwan Chin-Shan	prospective cohort	>35 years at baseline	ECG	excluded TIA	confirmed with imaging		38	13.8 (13.5– 14.6)	100%	3.58 (1.92–6.66)	31.6	not reported
Meta-analysis												men and women: RR 2.0 (1.9–2.0) women: RR 6.2 (4.2–9.3) men: RR 2.0 (1.3–3.0) (p = 0.07)	tests for heterogeneity indicated that homogeneity was met in the studies on men (p = 0.37) but not for women (p = 0.06) or for men and women combined (p = 0.07)	

CVD = Cardiovascular disease; TIA = transient ischaemic attack; ICD-10 = *International Classification of Diseases*, 10th edition; NA = not applicable; RR = relative risk.¹ Follow-up (FU) times are shown as medians (interquartile range), except where indicated otherwise.² 95% CIs in parentheses.

overall risk of stroke with AF [21, 26, 40]. In 2 of the studies, the adjusted relative risk of stroke was reported according to gender, and the results of these studies were combined to calculate the risk of stroke for men and women [38, 39]. The overall excess risk of stroke associated with AF was 2.0 (95% CI 1.9–2.0). In men alone, the excess risk of stroke associated with AF was 2.0 (95% CI 1.3–3.0), while it was 6.2 (95% CI 4.2–9.3) for women (table 5). In one study, the relative risk of stroke was reported by age group. This ranged from 2.6 in the 60- to 69-year-old age group to 4.5 in the 80- to 89-year-old age group [37].

The absolute risk of stroke associated with AF also varied between studies. This ranged from 7.8 to 31.6 [21, 26] and was generally higher for women [38, 39]. In the 3 studies in which the use of anticoagulant medication was reported, usage was low, ranging from ‘seldom’ to 27% [21, 37, 38].

Excess Costs of AF-Related Stroke

We identified only 3 observational studies where authors specifically reported the excess cost of AF-related stroke compared with non-AF-related stroke [41–43]; 2 were retrospective cohort studies using registry data [42, 43], while the other was a prospective cohort study [41]. The retrospective cohort studies included over 1,000 stroke patients with AF, and only direct inpatient costs were included [42]. The prospective cohort study included 116 stroke patients with AF from four hospitals. This study was used to compare both the direct and indirect costs associated with AF-related stroke and non-AF-related stroke. A detailed description of each study is provided in table 6.

In all studies, the direct costs of stroke were greater in patients with AF than in those without AF. However, this was reported as statistically significant in only 2 of the studies [41, 42]. AF-related stroke cost an average of between 7 and 20% more than non-AF-related stroke [41–43]. The excess cost was primarily attributable to longer lengths of hospital stay, but also to a greater frequency of recurrent stroke events over a 3-year period [42]. Acute hospital costs remained greater for AF-related stroke when adjustment was made for potentially confounding variables such as gender, age and co-morbidities [41]. The excess costs associated with AF-related stroke were lower when fatal events were included in the analyses because of the higher mortality rate associated with AF-related stroke [42]. This may, in part, account for the lower excess costs reported by Meretoja et al. [43]. Multiple linear regression was used by authors in the Swedish study to demonstrate

a significant association between AF and greater 3-year stroke costs [42]. There were too few studies to enable assessment of changes in AF-related stroke costs over time.

Discussion

We have found that the age-adjusted prevalence of AF appears to have remained relatively constant over the last 30 years. Large cohort studies have only been performed in Asian populations in the last 10 years, thereby making it difficult to identify time trends in this population. In contrast, a more accurate view of changes in prevalence was afforded for Caucasian populations, using data over a 30-year period.

We further confirm that the prevalence of AF increases dramatically with age and tripled between the ages of 65–70 to 85 years and over. This increase was consistent across ethnic and gender groups. The increased prevalence of AF with age is concerning given that it is estimated that the proportion of the population aged ≥ 80 years will increase globally from 1.3% in 2005 to 4.5% by 2050 [44]. In Europe, this proportion is projected to increase from 3.5 to 9.6%, and in North America from 3.5 to 7.8% [44]. Even though the prevalence of AF in Asian populations is lower than in other populations, the projected population increase in this group is greatest. The proportion of the population over 80 years of age is projected to increase from 1 to 4.5% across Asia from 2005 to 2050 [44], with China estimating an increase from 1 to 6.5–10.9% [45]. The extent to which the lower prevalence of AF in these countries is attributable to current lower life expectancies is unknown. These increases in life expectancy and lower fertility rates in most developed and developing countries are highly likely to lead to an increase in the prevalence of AF over this same time period [44]. Even in Asian countries, AF is likely to become a major contributor to the health and economic burden of chronic disease.

It has been hypothesised that increases in the survival of those with cardiovascular disease and stroke could result in an increase in the age-adjusted prevalence of AF [46]. An alternative hypothesis is that advances in medical treatments, such as ablations and primary rate or rhythm reversal interventions, and improved prevention strategies should, in theory, reduce the prevalence of AF. These two opposing factors may contribute to the lack of change in the prevalence of AF, despite advances in these areas. Studies of secular trends in the age-adjusted prevalence of AF, based on ECG diagnosis, provide variable results. In one study, AF prevalence in men rose over an

Table 6. Characteristics of the studies of the cost of AF-related stroke

Study	Year	Location	Setting	Study design	AF diag-nosis	Stroke diag-nosis	Total cohort with AF	Total follow-up	Time period (cost calculation)	Cost inclusions	Factors attributed to costs	Costs excluding fatalities	Fatalities
Ghatnekar and Glader [42]	2001	Sweden	registry data	retrospective cohort	ECG	ICD-10 codes I61, I63 and I64	6,611	1,619 NA	first 3 years	direct inpatient costs	direct: inpatient acute care, re-admissions	AF: EUR 10,192 non-AF: EUR 9,374	fatalities were excluded
Bruggenjurgen et al. [41]	2000–2001	Germany	4 hospitals	prospective cohort	ECG	neurological assessment and imaging	558	116 383 (69%) of all participants 71 (61%) of AF population	first 12 months	direct and indirect costs	direct: acute hospital care, rehabilitation, medication, outpatient care, home nursing and nursing home care; health-care professional visits, re-admissions indirect: e.g. work absenteeism	multivariable analysis results: direct – AF EUR 11,799, non-AF EUR 8,817; indirect – AF EUR 3,125, non-AF EUR 4,513	fatalities were excluded
Meretoja et al. [43]	2007	Finland	all Finish hospitals	retrospective cohort (registry data)	medical records	ICD-10 codes I60, I61 and I63	6,898	1,306 NA	first 12 months	direct costs	direct: hospital care, medications, nursing home, hospital-based outpatient care, re-hospitalisation	AF: USD 31,723 (EUR 22,206) ¹ all stroke patients (including AF patients): USD 29,576 (EUR 20,703) ¹	1,783 (26%)

ICD-10 = *International Classification of Diseases*, 10th edition; NA = not applicable.¹ Results converted to Euros; exchange rate: EUR 1 = USD 1.3 (January 2007).

18-year period [47]. However, declining response rates over time may have resulted in biased estimates in that study [47]. Similar increases over time were found in studies in which AF was diagnosed by a GP or in hospital. This increase over time may be an artefact resulting from the increased availability of ECG and increased awareness and diagnosis of AF [15, 48]. In contrast, Wolf et al. [49] found that there was no significant change in the prevalence of ECG-defined AF over time. Thus, there is some inconsistency between studies on whether or not there has been a change in the prevalence of AF over time.

Our finding of a lack of change in age-adjusted prevalence rates over time may also be due, in part, to the fact that the studies we captured included both symptomatic and asymptomatic cases of AF. The large number of asymptomatic cases incidentally diagnosed makes it difficult to independently assess the impact of effective treatment or management of AF and the prevention of the consequences of AF at a population level.

AF-related strokes are often more severe [50]. Early detection can allow preventive treatments to be implemented that reduce the risk of stroke as well as attenuate stroke severity. Prioritisation of care, such as stroke unit admission, for stroke patients with AF may also improve outcomes in this group. Further research is needed to investigate the impact of stroke prevention and management on reducing stroke severity and improving outcomes in AF-related stroke.

We found that there was a 2- to 3.5-fold increase in the risk of stroke among those with AF when compared to those without AF. This compares with a 4- to 5-fold increased risk that is often reported in the literature [51, 52]. This 4- to 5-fold increase is primarily based on the adjusted relative risks reported by Wolf et al. [37]. The authors of that study did not report an overall relative risk for their cohort, but instead reported results by age group. The relative risk ranged from 2.6 in the 60- to 69-year-old group to 4.5 in the 80- to 89-year-old group. When viewed within the context of the whole cohort, this is not dissimilar to our own results. The calculated relative risks reported in the literature will also be dependent upon the statistical analyses used and the type and number of other stroke risk factors accounted for in the multivariable analyses. Our inclusion of studies in which multivariable analyses had been undertaken may account for the lower relative risks reported in our review. In addition, many of the prospective studies in this review contained only small numbers of AF patients [26, 39, 40]. These studies had the advantage of reliable case definition through ECG diagnosis and included both symptomatic and

asymptomatic AF. The lower relative risk reported in the only case-control study in this review may have resulted from misdiagnosis of AF, as the patients were identified from medical records [21]. The large number of AF patients in that study would have skewed our meta-analysis results towards a slightly lower relative risk value.

The extent to which anticoagulant medication was used was not reported in many of the studies in this review [26, 39, 40]. Vitamin K antagonists or anticoagulant treatments such as warfarin can reduce the relative risk of stroke by as much as 64% [13, 14], with aspirin or antiplatelet therapy having a lesser benefit of around 19% [14]. Increased awareness of the mechanisms of AF-related stroke and advances in drug therapies should mean that later studies would include larger numbers of AF patients on these medications. The prescription of anticoagulant therapy such as warfarin in patients with AF increased in England between 1994 and 2003 from 25 to 53% in men and from 21 to 41% in women, with over 80% of patients receiving some form of stroke prevention [15]. A recent study in Taiwan reported lower uses of stroke prevention medication of about 53%, with only 11% of those admitted with stroke using warfarin prior to admission [53].

Interestingly, we found that the study that had the lowest relative risk of stroke associated with AF also had the greatest reported usage of antiplatelet and/or anticoagulant therapy [21]. The fact that participants in this study had been identified from medical records and, therefore, clinically diagnosed by a GP may also have increased the likelihood of participants being on such therapies. Conversely, the slightly higher relative risk reported by Chien et al. [26] may reflect the lower use of preventive treatment in developing countries [53]. Nevertheless, even when patients are provided with antiplatelet therapy, only about half are treated with the appropriate levels to optimally reduce the risk of stroke [54, 55].

We found that strokes related to AF generally accumulate 7–20% more in direct costs than other strokes, with the majority being due to direct hospital and medical costs. This information is important for obtaining a more accurate estimate of the cost of stroke attributable to AF. For example, the total lifetime costs of AF-related strokes occurring in a single year were estimated in an Australian report to be AUD 215.7 million in 2008–2009 [56]. However, these data are based on the estimated cost per stroke multiplied by the percentage of stroke patients with AF estimated for the whole population. Hence, this is likely to underestimate the true cost of AF-related stroke by 7–20%. This should also be taken into account when the cost-effectiveness of interventions aimed at detecting AF

and preventing AF-related stroke are assessed. To date, cost-effectiveness analyses relating to anti-thrombotic medications, and screening and detection programmes have not accounted for this excess cost associated with AF-related stroke [7, 57–59]. Notably, there have been very few studies conducted to estimate the economic impact of AF-related stroke compared with non-AF-related stroke. The quantification of costs related to AF and stroke is also limited by methodological differences between studies in regards to resource use estimation and the valuation of costs associated with different health care systems. Since relatively little has been published in this area, we were unable to assess any potential changes in the magnitude of cost differentials over time. Further research in this area is needed, as well as assessments of the differentials in stroke severity and whether this is changing with improved preventive treatment and management of stroke.

Finally, there are some limitations that need to be acknowledged. Our strict selection criteria enhanced the accuracy of our comparison of prevalence changes over time but meant that only a small number of studies were included in the review. This would have reduced the sensitivity of our comparisons and meant that only a broad overview of trends in prevalence and stroke risk could be obtained. In general, the small number of articles included in our review is a reflection of the lack of high-quality data available on this topic. Also, to maximise our capture rate for the prevalence studies, we included 2 studies in which participants were screened at baseline using ECG but also identified cases of AF based on medical records. In these studies, slightly inflated prevalence rates were reported. However, this increase was not significant.

A further limitation of our review is that selection of eligible papers was not blinded, and the initial identification of articles for inclusion was performed by one researcher, creating potential selection bias. We attempted to minimise this by using consensus from the three authors for the final selection of papers that were included in the review.

Conclusion

This literature review provides a contemporary summary of the progress that has been made with regards to AF in stroke over the last 4 decades. It has further enabled us to identify future public health priorities in this area. First, the age-adjusted prevalence of AF appears not to be changing and may be subject to the competing impacts of

advances in the prevention of AF and improved long-term management of AF, so that those with AF are living for longer. There has also been little change in the overall relative risk of stroke associated with AF. However, in studies with higher levels of anti-thrombotic use, a slightly lower relative risk of stroke associated with AF was reported. Ageing global populations are likely to result in large increases in the total population prevalence of AF over the next 4 decades. This will place significant health and cost burdens on health systems in both developed and developing nations and will be compounded by the additional excess costs associated with AF-related stroke.

Finally, the large percentage of undiagnosed asymptomatic cases in the community and poor compliance with effective usage and monitoring of medications such as warfarin make stroke prevention particularly challenging. Increased public health efforts are required to identify symptomatic and asymptomatic AF through population screening programmes and to implement strategies to improve prescription of and compliance with taking anticoagulant medications. Improved diagnosis and treatment of AF and its consequences are important for stroke prevention, and renewed efforts in this area are needed if we are to address this growing problem.

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Disclosure Statement

The authors have no conflicts of interest associated with this research.

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