

# Stroke Associated with Atrial Fibrillation – Incidence and Early Outcomes in the North Dublin Population Stroke Study

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## Key Words

Atrial fibrillation · Stroke prevention · Anticoagulation

## Abstract

**Background:** Prospective population-based studies are important to accurately determine the incidence and characteristics of stroke associated with atrial fibrillation (AF), while avoiding selection bias which may complicate hospital-based studies. **Methods:** We investigated AF-associated stroke within the North Dublin Population Stroke Study, a prospective cohort study of stroke/transient ischaemic attack in 294,592 individuals, according to recommended criteria for rigorous stroke epidemiological studies. **Results:** Of 568 stroke patients ascertained in the first year, 31.2% (177/568) were associated with AF (90.4%, i.e. 160/177 ischaemic infarcts). The crude incidence rate of all AF-associated stroke was 60/100,000 person-years (95% CI = 52–70). Prior stroke was almost twice as common in AF compared to non-AF groups (21.9 vs. 12.8%,  $p = 0.01$ ). The frequency of AF progressively increased across ischaemic stroke patients stratified by increasing stroke severity (NIHSS 0–4, 29.7%; 5–9, 38.1%; 10–14, 43.8%;  $\geq 15$ , 53.3%,  $p < 0.0001$ ). The 90-day trajectory of recovery of AF-associated stroke was identical to

that of non-AF stroke, but Rankin scores in AF stroke remained higher at 7, 28 and 90 days ( $p < 0.001$  for all). **Discussion:** AF-associated stroke occurred in one third of all patients and was associated with a distinct profile of recurrent, severe and disabling stroke. Targeted strategies to increase anticoagulation rates may provide a substantial benefit to prevent severe disabling stroke at a population level.

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## Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting approximately 1% of adults [1]. The prevalence of AF in the population increases dramatically with age, occurring in 9% of those aged 80 years and older [1]. AF is an important contributor to mortality, cognitive decline, stroke and health care costs in diverse populations [2]. The Framingham study and others have demonstrated a fivefold increase in overall stroke risk associated with AF [3]. The proportion of stroke associated with AF increases progressively with age, ranging from 6.7% in individuals aged 50–59 years to 36.2% in those aged 80–89 years [4, 5].

While hospital registries and clinical trial cohorts have provided important advances in knowledge of AF-related stroke [5–8], large population-based studies are essential to fully capture the burden of stroke associated with AF in the general population. Well-conducted population studies allow unbiased inclusion of all patients with AF and stroke, including groups more likely to be treated in the community such as the very elderly, patients with mild stroke or those with severe stroke treated in a palliative care setting. Detailed studies in large population samples also allow estimation of the incidence of AF-associated stroke in the wider population, providing essential information for health policy and service development, and allowing valid international and temporal comparisons to be made. Population-based analysis also may provide valuable insights into the implementation of oral anticoagulation and other recommended prevention measures in patients with AF.

We performed a subgroup analysis of patients with AF and stroke in the North Dublin Population Stroke Study. We aimed to determine the population incidence rates, acute clinical characteristics, trajectory of initial functional recovery, and early outcome of stroke associated with AF, in comparison with stroke due to other aetiological mechanisms.

## Methods

### *Case Ascertainment*

The North Dublin Population Stroke Study is a population-based prospective cohort study of frequency and outcome of stroke and transient ischaemic attack (TIA) in North Dublin city (population 294,529). Detailed demographic data are available from the 2006 census [9], which was conducted close to the mid-point of the study ascertainment period. Ascertainment was conducted over 15 months to identify all cases of incident stroke or TIA within a 12-month period (from December 1, 2005, to November 30, 2006) using multiple overlapping hospital and community sources. Both 'hot' and 'cold' pursuit was undertaken, according to recommended rigorous criteria for 'ideal' stroke incidence studies [10]. Ascertainment sources in the community included North Dublin family general practitioners (94% participation), long-stay nursing facilities (95% participation), death certificate data and city coroner records. A 5-day minor stroke/TIA clinic was established to encourage referral of community-treated eligible patients.

Hospital ascertainment sources included outpatient clinics, referrals to all regional emergency departments, daily reviews of hospital admissions and consultation requests for neurology, elderly medicine, neurosurgery, vascular surgery and eye services, and biweekly review of requests for brain and vascular imaging studies. Ascertainment was conducted in 4 acute hospitals and 9 non-acute hospitals within North Dublin city. Patients with suspected stroke who died in hospital or without hospital referral

were ascertained by review of pathology department records, death certificates and coroner records.

All cases were assessed by a trained study physician, with in-person assessment performed by an experienced stroke physician where there was a query over the diagnosis of stroke, and in the case of suspected recurrent stroke or TIA.

Prestroke function was rated using the Modified Rankin Scale (MRS), and stroke severity (within 72 h) was measured using both the MRS and the National Institute of Health Stroke Scale (NIHSS), scored by trained study staff using a standard algorithm for MRS rating. Early follow-up was performed by telephone or in person at 7, 28 and 90 days following the index event. Ethics committee approval was obtained from all participating institutions, and consent was obtained from patients (or family if the patient was incapable of providing informed consent).

### *Definitions*

Consistent with American Heart Association guidelines, AF was defined as a history of physician-diagnosed AF preceding stroke onset, or a new diagnosis of chronic or paroxysmal AF at the time of or in the 3 months following the index event, confirmed by the absence of P waves (or the presence of flutter waves) with an irregular ventricular response on electrocardiography, cardiac monitoring and/or ambulatory rhythm monitoring. Patients identified with AF had medical record review to determine if the diagnosis was previously known. Antithrombotic treatment and the most recent international normalised ratio preceding stroke onset were recorded. The World Health Organization definition of stroke was used. As the study was observational, clinical management for patients was delivered according to the practice of the treating physician and was not provided by a defined protocol.

Inclusion criteria were: (1) new ischaemic or haemorrhagic stroke within the ascertainment period, (2) residence within census-defined North Dublin city. We excluded patients with TIA and patients resident outside North Dublin city, and patients coded as stroke or TIA (ICD-10 classification) identified on a search of the national hospital computerised database, for whom data protection regulations prevented review of medical records or patient contact (n = 15).

### *Statistical Analyses*

Parametric and non-parametric univariate comparisons of continuous variables were performed using Student's t test and Wilcoxon rank sum test as appropriate. Comparisons of categorical variables were performed using the  $\chi^2$  test. Survival analysis using Kaplan-Meier curves with the log rank test was performed to compare recurrence and survival in AF and non-AF stroke. Multivariable linear regression analyses were performed to identify independent variables predicting functional outcome. Statistical analyses were performed using Stata (version 9.0) and SAS.

## Results

### *Incidence of AF-Related Stroke*

Over the 1-year ascertainment period, 568 patients with new stroke events were included. Of these, 485 had first-ever and 83 had prior stroke. Overall, 90.8% (516/568)

were admitted to hospital and 9.2% (52/568) were treated in the community. In 93.5% (531/568) of the patients, brain CT or MRI was performed, and a further 1.9% (11/568) had information relating to pathological subtype available from coroner records or autopsy reports. 64.6% (367/568) of all patients had carotid imaging, either by duplex ultrasonography or magnetic resonance angiography. ECG was performed on 87.3% (496/568), and 24-hour cardiac rhythm monitoring was performed on 54.9% (312/568). Overall, 91.6% (520/568) had either ECG or cardiac monitoring. Most of the cases without cardiac monitoring were managed in the community or died before receiving medical attention (n = 35). AF was detected in 31.2% (177/568) of all new stroke events and 28.7% (139/485) of all first-ever strokes. A previous diagnosis of AF existed in 54.2% (96/177) at the time of the index stroke. New AF was detected in 45.8% (81/177), during initial hospitalisation in all except 1 patient (mean time to diagnosis 3.2 days). Paroxysmal AF was demonstrated in 32.2% (57/177) of patients with AF and stroke.

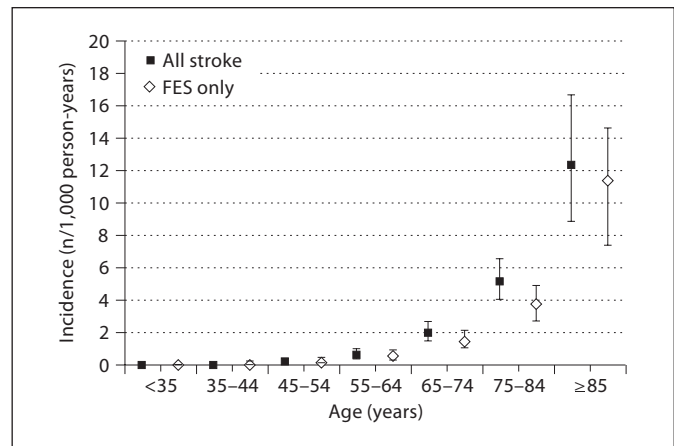
The crude incidence rate of all AF-associated stroke (first-ever and prior, ischaemic and haemorrhagic) was 60/100,000 person-years of observation (95% CI = 52–70). The crude incidence rate of all first-ever AF-associated stroke was 47/100,000 person-years (95% CI = 40–56) and of first-ever AF-associated ischaemic stroke was 42/100,000 person-years (95% CI = 35–51; fig. 1).

Within the cohort, 8.5% (48/568) of the patients underwent neither ECG nor cardiac monitoring. A sensitivity analysis was performed to explore the effect on the calculated incidence rates allowing for the possibility of under-detection of AF in this subgroup, assuming that AF-associated stroke occurred in untested patients at the same rate as observed in tested patients. In this analysis, the calculated crude incidence rate of all AF-associated strokes increased to 69/100,000 person-years (95% CI = 60–79).

The proportion of stroke associated with AF increased progressively with increasing age. Among all stroke patients, AF-associated stroke accounted for 13.9% (23/166) of stroke in patients younger than 65 years, compared with 41.7% (110/264) of those aged 75 years or older, and 46.2% (42/91) of those aged 85 or older.

#### AF and Stroke Subtypes

As expected, there was a higher proportion of ischaemic infarcts in patients with AF (160/177) compared to those without AF (90.4 vs. 76.1%, p = 0.001). However, 9% (16/177) of all AF-associated strokes were haemorrhagic, 7.3% (13/177) with primary intracerebral haemorrhage and 1.7% (3/177) with subarachnoid haemorrhage. Of



**Fig. 1.** Crude incidence rate of all AF-associated stroke stratified by age, with comparison to rate for first-ever stroke. All stroke = First-ever and prior stroke (ischaemic and haemorrhagic); FES = first-ever stroke (ischaemic and haemorrhagic). Crude incidence rate calculated per 1,000 person-years.

these, 50% (8/16) were spontaneous, and 50% (8/16) occurred in patients on oral anticoagulation therapy. In 1 patient with AF-associated stroke, the pathological subtype was undetermined.

When classified by the Oxfordshire Community Stroke Project scheme [11], AF was associated with a higher frequency of total and partial anterior circulation infarct syndromes and a lower frequency of lacunar infarct syndromes (p < 0.001).

Using the classification of subtype by the TOAST system, 79% (127/160) were classified as cardio-embolic. The remainder of cases (n = 33) were classified as unknown or undetermined, for example where 2 or more aetiologies are demonstrated.

#### Risk Factors and Medications

When patients with haemorrhagic stroke were excluded, those with AF-associated ischaemic stroke were older (mean age 76.6 vs. 68.4 years, p < 0.001) and had higher rates of coronary artery disease (p = 0.002) but lower rates of current smoking compared to the non-AF cohort (p < 0.001). Prior stroke and TIA were also more common in the AF stroke cohort. Reflecting this observation, 21.9% (35/160) of patients with AF-associated ischaemic stroke had had a prior stroke before their index presentation, compared to 12.8% (38/298) of patients in the non-AF ischaemic stroke cohort (p = 0.01).

Among patients with AF-associated ischaemic stroke, 54.4% (87/160) had an existing diagnosis of AF prior to

**Table 1.** Clinical characteristics of patients with ischaemic stroke, with and without AF

Characteristic	With AF (n = 160)	Without AF (n = 298)	p value
Mean age $\pm$ SD, years	76.6 $\pm$ 10.8	68.4 $\pm$ 14.3	<0.001
$\geq$ 65 years	139 (86.9)	189 (63.4)	<0.001
$\geq$ 75 years	99 (61.9)	119 (39.9)	<0.001
$\geq$ 85 years	41 (25.6)	33 (11.1)	<0.001
Female gender	85 (53.1)	138 (46.3)	NS
Risk factors			
Diabetes mellitus <sup>1</sup>	15 (9.4)	43 (15.0)	NS
Hypertension <sup>1</sup>	95 (60.1)	150 (52.6)	NS
Hyperlipidaemia <sup>1</sup>	73 (45.9)	105 (37.0)	NS
Current smoking	26 (16.3)	105 (35.2)	<0.001
Prior coronary artery disease <sup>1</sup>	52 (32.9)	56 (19.7)	0.002
Prior stroke <sup>1</sup>	35 (21.9)	38 (12.8)	0.01
Prior TIA <sup>1</sup>	31 (19.6)	34 (12.1)	<0.04
Prestroke medication			
Antiplatelet <sup>1</sup>	77 (50)	101 (36.3)	0.04
Antithrombotic	28 (18.2)	10 (3.7)	<0.001
Antihypertensive <sup>1</sup>	105 (68.2)	133 (47.8)	<0.001
Lipid-lowering therapy <sup>1</sup>	48 (31.4)	62 (22.3)	0.04
Stroke severity <72 h			
Median NIHSS (n = 397)	6 (IQR 3–13)	4 (IQR 2–8)	0.008
Mean MRS $\pm$ SD <sup>1</sup>	3.8 $\pm$ 1.4	3.0 $\pm$ 1.7	<0.001

Figures in parentheses are percentages unless specified otherwise. SD = Standard deviation; NS = non-significant; IQR = 25–75% interquartile range.

<sup>1</sup> 3–6% of data missing.

the qualifying stroke, but only 27.6% (24/87) were on warfarin therapy at stroke onset. A further 55.2% (48/87) were taking antiplatelet medication prior to ischaemic stroke onset, with 82.8% (72/87) taking either antiplatelet or warfarin therapy, or both (2 patients), and 17.2% (15/87) had no anti-thrombotic therapy. Among patients with known AF at stroke onset, 28.7% (25/87) had a previous stroke, only 32% (8/25) of whom were on warfarin. Compared to non-AF stroke, those with AF had higher rates of prestroke antiplatelet, antihypertensive and lipid-lowering therapy use ( $p < 0.05$  for all comparisons).

#### Stroke Severity and Disability

To eliminate the influence of prior stroke on stroke severity and disability, these analyses are reported in patients with first-ever ischaemic stroke only. No difference was observed in pre-stroke MRS among AF and non-AF patients with first-ever ischaemic stroke. However, those with AF had greater acute neurological impairment compared to those with non-AF stroke (median NIHSS 6 vs. 4,  $p = 0.008$ ; table 1). Within the ischaemic stroke cohort, AF was associated with a progressive increase in the proportion of patients with increasingly severe stroke

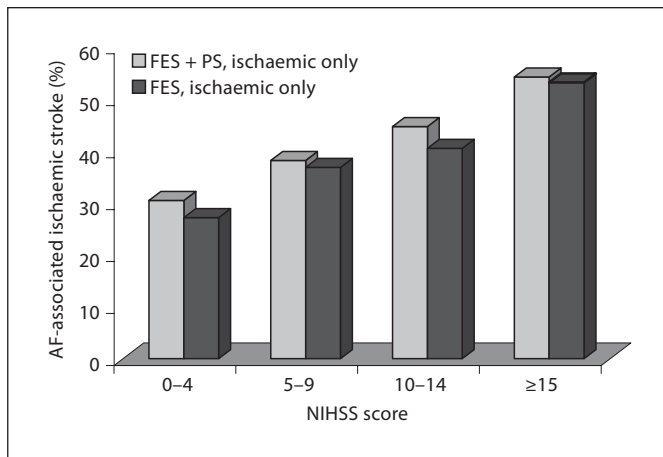
(NIHSS 0–4, 29.7%; 5–9, 38.1%; 10–14, 43.8%;  $\geq 15$ , 53.3%,  $p < 0.0001$  for trend). When repeated for first-ever stroke alone, a similar result was demonstrated ( $p = 0.001$ ; fig. 2). Similarly, greater acute (<72 h) functional disability was observed in the AF stroke cohort (median MRS 4 vs. 3,  $p < 0.001$ ; table 1).

The trajectory and extent of functional recovery were similar in the AF stroke cohort compared to the non-AF group (fig. 3). The mean functional improvement measured by the MRS between 72 h and 90 days after stroke was 0.5 in AF and non-AF first-ever ischaemic stroke groups. However, survivors with AF stroke had a greater disability at 7, 28 and 90 days following the event than those with non-AF stroke ( $p < 0.001$  for all comparisons; fig. 3). No difference in 90-day case fatality or recurrence rates was observed between AF and non-AF stroke groups (table 2).

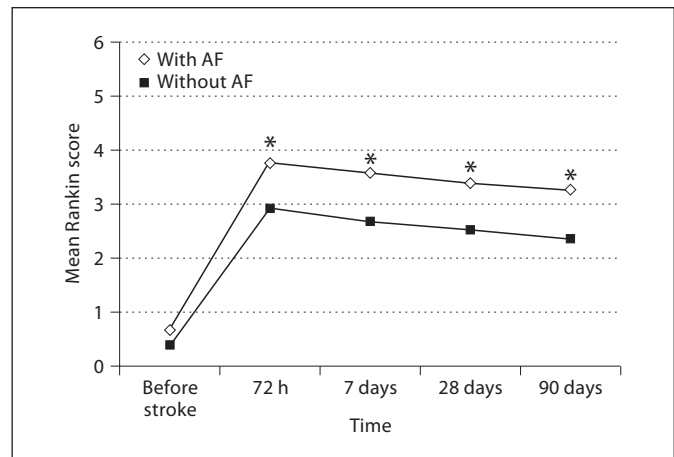
#### Multivariable Analysis of Predictors of 90-Day Disability

After stratification by prestroke Rankin score to control for the potential confounding effect of prestroke disability, we performed multivariable analysis to examine





**Fig. 2.** Proportion of ischaemic stroke associated with AF, stratified by stroke severity (NIHSS), showing within-group comparison to first-ever stroke. FES + PS = First-ever stroke and prior stroke,  $n = 397$  ( $p < 0.0001$  for trend); FES = first-ever stroke only,  $n = 333$  ( $p < 0.001$  for trend).



**Fig. 3.** Trajectories of functional recovery of AF-associated and non-AF stroke based on serial MRS score measurements. First-ever ischaemic stroke, excluding patients where AF status is unknown – i.e. no cardiac monitoring performed. \*  $p < 0.001$ .

potential predictors of 90-day functional outcome in ischaemic stroke patients. Among individuals with a pre-stroke MRS of zero, AF was strongly associated with poor 90-day functional outcome, defined as an MRS  $>3$  ( $p = 0.001$ ). The odds ratio for poor functional outcome associated with AF was 2.1 (95% CI = 1.3–3.7). However, when AF was included in a multivariable linear regression model with age, gender, NIHSS, diabetes mellitus, hypertension, coronary artery disease, warfarin and lipid-lowering treatment, only age ( $p < 0.001$ ,  $\beta = 0.05$ ) and NIHSS ( $p < 0.001$ ,  $\beta = 0.18$ ) predicted functional outcome at 90 days, suggesting that the relationship between AF and disability was mediated via early stroke severity.

When the analyses were repeated among the 520 patients in whom ECG or cardiac monitoring were performed, our findings remained unchanged.

## Discussion

In a large prospective study, we found a high incidence of AF-associated stroke at a population level. We combined rigorous overlapping case ascertainment methods with careful clinical characterisation of individual patients, to provide a detailed overview of AF-associated stroke in a large segment (almost 7%) of the Irish population. To avoid bias in such studies, it is important to include community-treated patients and the very elderly, who are at high risk of AF-related stroke and are often

**Table 2.** Case fatality and early stroke recurrence rates of ischaemic stroke with and without AF

	AF ( $n = 160$ )	No AF ( $n = 298$ )	p value
Case fatality			
7 days	12 (7.5)	19 (6.4)	0.7
28 days	24 (15.0)	36 (12.1)	0.4
90 days	37 (23.1)	49 (16.4)	0.09
Recurrent stroke			
7 days	3 (2.0)	7 (2.4)	0.7
28 days	7 (4.4)	12 (4.0)	0.6
90 days	8 (5.0)	21 (7.1)	0.09

Figures in parentheses are percentages.

excluded from hospital and clinical trial registries [12]. Almost one tenth of patients in our study were treated in the community and 16% were aged 85 or older, suggesting high ascertainment in these groups. Our data allow accurate estimation of the current burden of AF-associated stroke in the Irish population. When adjusted for population differences, our findings may also allow estimation of the incidence in other populations, providing a baseline for geographic comparisons and trends over time.

The prevalence of AF-associated stroke in our cohort is substantially higher than that reported in previous studies, with AF observed in one third of all new stroke events in North Dublin compared to 15–24% in earlier

reports [4, 13, 14]. In part this may relate to differences in methods, particularly relating to the definition and detection of AF between studies. In contrast to several earlier studies which classified AF-associated stroke as that occurring only with previously known AF, we used a broad definition, including stroke occurring with a prior AF diagnosis, new AF detected at stroke onset and paroxysmal AF detected within the following 3 months. We included new AF at stroke onset based on convincing data from the Framingham study, indicating that newly detected AF persists in most cases, suggesting a role as a causative factor rather than a consequence of stroke [15]. Similarly, evidence suggests that paroxysmal AF may confer a high stroke risk equal in importance to that observed with chronic AF [16, 17]. One third of AF-associated stroke patients in our cohort had paroxysmal AF indicating an important contribution to stroke risk which may have been underascertained in previous studies [18].

Over 95% of patients included in our study had brain imaging or autopsy, allowing accurate determination of pathological subtype in most patients. We found that one tenth of patients with AF had haemorrhagic stroke, only half of which occurred in association with warfarin therapy. A similar finding has been observed by other investigators [19]. The explanation for haemorrhagic stroke in AF patients not taking warfarin is unclear. It may indicate a higher prevalence of risk factors for haemorrhagic stroke in older patients with AF, such as hypertension, antiplatelet medication use or cerebral amyloid angiopathy. This observation emphasises the need for improved methods to risk stratify patients for warfarin therapy in AF, particularly among older individuals.

Previous studies have reported worse disability in AF-associated stroke compared to non-AF stroke [20, 21]. However, it has been unclear whether this is a consequence of greater age and co-morbid illness or more severe stroke among patients with AF. Consistent with some earlier studies, we found that AF was associated with older age, worse prestroke functional status, and greater acute stroke severity than non-AF stroke, leading to greater disability within the first 3 days after onset [14, 20]. By serial Rankin score measurements, we found that AF stroke improved at a similar rate to non-AF patients but remained with worse disability at 3 months. After eliminating the influence of prestroke disability, we found that both age and NIHSS independently predicted functional outcome. The greater  $\beta$ -coefficient associated with NIHSS in our multivariable model indicates that stroke severity was the major contributor to poor functional outcome.

Although AF was not associated with a higher frequency of early recurrent stroke, late stroke recurrence was strongly associated with AF in our cohort. A prior history of stroke or TIA was almost twice as common in the AF stroke group. Recurrent stroke is associated with greater disability, mortality and health care costs compared to first-ever stroke. Particularly concerning is our observation that only 32% of patients with known AF and prior stroke were taking warfarin at the time of their recurrent ischaemic stroke. Multiple factors contribute to the non-prescribing of warfarin in patients with AF, including patient preference, patient age and co-morbid illnesses, and physician-related factors such as specialty training [22]. Our data highlight the importance of improving strategies to optimise warfarin-prescribing rates, particularly in individuals with prior stroke or TIA at highest risk of recurrence [23].

Our study is not without some limitations. Although a high proportion (over 90%) of subjects underwent ECG or cardiac rhythm monitoring, we cannot exclude the possibility that some patients with AF were not detected, leading to underestimation of rates of AF-associated stroke. We explored the potential impact of underascertainment in our sensitivity analysis. Given the high prevalence of other risk factors for stroke in individuals with AF such as hypertension, it is also possible that some stroke events were not directly attributable to AF in the group with AF-associated stroke.

When viewed in context with previous studies, our data support the concept of AF-associated stroke as a distinct pathophysiological and clinical entity, with a characteristic profile of severe, recurrent and disabling stroke. Our data also suggest that AF-associated stroke may be more common than previously considered, occurring in approximately one third of all ischaemic stroke in our population when broadly defined as prior, new and paroxysmal AF. A substantial opportunity may exist for improved stroke prevention at a population level, as opportunistic screening of older individuals for AF is feasible, relatively inexpensive and effective [24]. Consistent evidence indicates that warfarin therapy is highly beneficial for stroke prevention in AF, in both randomised trial and clinical practice settings [25]. A recent French population-based study found a decrease in the incidence of AF-associated stroke, likely explained by improvements in the use of antithrombotic therapy [26, 27]. However, international data indicate low implementation rates of warfarin therapy for AF in clinical practice, even among those at highest risk for stroke [28]. Within health systems, improved structures such as multidisciplinary AF

clinics and targeted opportunistic screening may improve AF detection, individualised risk stratification and warfarin treatment rates [24]. While requiring further evaluation, these approaches may yield significant reductions in the burden of stroke due to AF in populations.

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