Global survey of the frequency of atrial fibrillation-associated stroke: ESUS Global Registry

Cover Title: Global frequency of AF-associated stroke

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Abstract

Background:

Atrial fibrillation (AF) is increasingly recognized as the single most important cause of disabling ischemic stroke in the elderly. We undertook an international survey to characterize the frequency of AF-associated stroke, methods of AF detection, and patient features.

Methods:

Consecutive patients hospitalized for ischemic stroke in 2013-2014 were surveyed from 19 stroke research centers in 19 different countries. Data were analyzed by global regions and World Bank income levels.

Results:

Of 2144 patients with ischemic stroke, 590 (28%, 95%CI: 25.6-29.5%) had AF-associated stroke, with highest frequencies in North America (35%) and Europe (33%) and lowest in Latin America (17%). Most had a history of AF prior to stroke (15%) or newly detected AF on ECG (10%); only 2% of ischemic stroke patients had unsuspected AF detected by post-stroke cardiac rhythm monitoring. The mean age and 30-day mortality rate of patients with AF-associated stroke (75 years, SD=11.5 years; 10%, 95%CI: 7.6-12.6%, respectively) were substantially higher than for patients without AF (64 years, SD=15.58years; 4%, 95% CI:3.3-5.4%, *p*<0.001 for both comparisons). There was a strong positive correlation between mean age and the frequency of AF (r=0.76; *p*=0.0002).

Conclusions:

This cross-sectional global sample of patients with recent ischemic stroke shows a substantial frequency of AF-associated stroke throughout the world in proportion to the mean age of the stroke population. Most AF is identified by history or ECGs; the yield of conventional short-duration cardiac rhythm monitoring is relatively low. Patients with AF-associated stroke were typically elderly (>75 years old) and more often women.

Introduction:

Atrial fibrillation (AF) is increasingly recognized as an important cause of ischemic stroke whose importance is magnified because of the remarkable efficacy of oral anticoagulants for stroke prevention.(1,2) Hospital-based registry data from the 1980s and 1990s, estimated that 16% of ischemic strokes were associated with AF.(3) However, studies published in the past decade consistently report higher frequencies,(4- 7) possibly due to increased surveillance and inclusion of older stroke cohorts.

The frequency and features of AF-associated stroke across global regions have not been previously studied, as data have primarily been collected from Europe and North America. Here, we report the prevalence of AF-associated stroke from 19 stroke centers in 19 countries and compare features with ischemic stroke not associated with recognized AF.

Methods:

The design and initial findings from the ESUS (Embolic Stroke of Undetermined Source) Global Registry have been previously published (8). Consecutive patients with recent ischemic stroke were obtained from 19 stroke centers in 19 different countries, targeting review of 100 patients with acute ischemic stroke at each site. Sites were instructed to retrospectively identify consecutive inpatients evaluated for recent stroke in 2013- 2014 from hospital discharge diagnosis codes or from databases associated with acute stroke units. The study complied with local institutional research board regulations; informed consent was not required at any site for this anonymized data collection. Data were entered into a central database at the Population Health Research Institute via on-line data entry or via an automated fax-based data entry system. Missing data were queried, and final data were exported to STATA 13.0 for statistical analysis.

AF-associated stroke was defined as an ischemic stroke associated with any history of AF, AF on any ECG done for the index stroke, or AF detected on cardiac rhythm monitoring (including inpatient telemetry or ambulatory monitoring with automated rhythm detection) done after stroke. Given the nature of the global registry data were not

collected about the duration of paroxysmal AF or about antithrombotic therapy before or after stroke.

Data were analyzed according to four global regions: Europe (9 sites), North America (2 sites), Latin America (3 sites), East Asia/Pacific (5 sites). Sites were also grouped into four World Bank income groups (low, lower-middle, upper-middle and high) (World Bank Group http://data.worldbank.org/about/country-classifications).

Categorical data were summarized as counts and percentages and comparisons were made using Chi-Square test. Continuous data were summarized using mean and standard deviation and comparisons were made using t-test or Wilcoxon rank test, as appropriate. Correlation coefficient was used to determine the association between mean age of stroke cohort and the frequency of AF among centers. All analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC). A 2-sided p-value of <0.05 was considered statistically significant.

Results:

Frequency of AF-associated stroke by site, global region, and age

Of 2144 patients with recent ischemic stroke (mean age 67 years, SD = 15.39 years) collected from 19 stroke research centers in 19 countries, the frequency of AF-associated stroke was 28% (95% CI: 25.6-29.5%), ranging from 11% in Manila, Philippines to 45% in Galway, Ireland (Table 1). The prevalence of AF-associated stroke was highest at sites in Europe (33%) and North America (35%) and lowest at Latin American sites (17%), (Table 2). When comparing the 14 sites from high income countries (n=1516) and 5 sites from upper-middle income countries (n=628), the prevalence of AF-associated stroke was higher at sites in high-income countries (32.5%, 95% CI: 30.1% - 34.8%) compared to upper middle income countries (15.6%, 95% CI: 12.8% - 18.4%) (Figure 1)

Patients with AF-associated stroke were, on average, substantially older (mean age 75 years, SD = 11.45 years), than patients with ischemic stroke unassociated with AF (mean age 64 years, SD = 15.51 years) (p<0.001), and this decade difference was consistent

across global regions (Table 2). There was a strong and significant correlation between the mean age of the stroke cohort and the frequency of AF among sites (Figure 2).

Identification of AF among ischemic stroke patients

Of the 590 ischemic strokes associated with AF, 332 (56%, 95%CI: 52.1%-60.3%) had a history of AF prior to the index stroke, and an additional 207 (35%, 95%CI: 31.2-39.1%) without a history of AF had AF diagnosed by ECG done for evaluation of the index stroke, and 51(8%, 95% CI: 6.4% - 10.9%) had AF diagnosed by prolonged cardiac rhythm monitoring(Table 3). In our study cohort of 2144 ischemic stroke patients, 1108 (69%) patients, (who did not have a diagnosis of AF prior to the index stroke or who were not diagnosed with AF on the basis of a 12 lead ECG), underwent $\geq$ 24 hour cardiac rhythm monitoring and the yield of cardiac rhythm monitoring to detect AF was 4.6%.

Clinical features of ischemic stroke patients with and without associated AF

In patients with AF-associated stroke only 6% presented with a lacunar stroke (<1.5cm in largest diameter subcortical or pontine infarct) as their index stroke, this was significantly lower than the non-AF associated stroke patients where 20% presented with lacunar stroke as their index stroke. 9% of the AF patients had $\geq$ 50% stenosis in the ipisilateral cervical carotid artery detected by ultra sound Doppler, magnetic resonance angiography or computed tomographic angiography. In the non-AF ischemic stroke patients 15% had $\geq$ 50% ipsilateral carotid stenosis. 30 day mortality among AF patients was significantly higher (10%, 95% CI: 7.6-12.6) compared to non-AF ischemic stroke patients (4%, 95% CI: 3.3-5.4%) (p<0.0001).

Relationship between the frequency of AF-associated stroke and the mean age of the ischemic stroke cohort

Overall, AF was more common in those >75 years (44%) versus those < 75 years (18%) (*p*=0.0001), with almost half of the ischemic strokes in women >75 years associated with

AF (46%). There was a strong positive correlation between mean age of stroke patients and frequency of AF among sites. (r=0.76; $p = 0.0002$)

Discussion:

This global registry project demonstrates that AF-associated ischemic stroke is common: 28% of ischemic strokes at the 19 international sites and one-third of strokes at sites in Europe and North America. Our findings show that patients with AF were almost a decade older than patients without AF across global regions. Differences in prevalence between sites and regions are largely due to the variation in mean ages of the stroke populations. The attributed risk of AF for ischemic stroke in a given population is expected to be influenced by the life expectancy of the population, (9), and this might partly explain regional variations in frequency of AF between high- income and upper middle- income countries in our study.

AF was identified in 28% (95% CI: 25.6-29.5%) of consecutive ischemic stroke patients, a higher fraction than in hospitalized ischemic stroke patients in past decades (typically between 15-20%)(3) probably due to both increasing vigilance in detecting AF, the increasing prevalence of AF in the elderly(9), and inclusion of more elderly stroke cohorts. Recent studies published since the Registry demonstrate that prolonged (>1 month) cardiac rhythm monitoring identifies additional patients with cryptogenic stroke who have episodes of paroxysmal atrial fibrillation,(10,11) which are often very brief and of uncertain etiologic relevance.(12) The increase in the frequency of AF-associated stroke relative to other ischemic strokes has occurred despite more widespread use of oral anticoagulation in AF patients.(9) More than half of AF-related strokes occurred in patients with a known history of AF. Although no data on antithrombotic or anticoagulant therapy was available, this finding stresses the importance of optimizing stroke prevention in patients with known AF.

In our stroke cohort 6% of the patients with AF had lacunar stroke as their index stroke compared to 20% of patients without AF, and the differences in frequency were consistent across global regions and consistent with previous studies, suggesting that AF-

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related strokes are more frequently larger. It must be acknowledged that accurate subtyping of stroke may not be possible in all cases even with advanced neuroimaging and vascular imaging techniques and that some "lacunar" strokes could have cardio embolic or atheroembolic sources. However previously published data on anticoagulation treatment in patients with AF who present with lacunar stroke shows no benefit of anticoagulation compared to antiplatelet treatment in reducing the risk of recurrent stroke. (13,14) With this knowledge, it would have been interesting to explore whether stroke subtype influenced physician decision on choosing an anti-thrombotic for secondary stroke prevention. Unfortunately we did not collect data on the discharge antithrombotic in our study cohort.

In our study cohort, the 30 day mortality was significantly higher for patients with AF when compared to patients without AF across global regions. Our findings are consistent and in accordance with the larger randomized trials.

Our findings show a significant correlation between the mean age of stroke patients and frequency of AF which is statistically significant and in keeping with several recent observational data. (9,16,17)

Limitations of this study include participation by a limited number of selected, high-volume stroke centers and therefore the results may not be generalizable to all patients with ischemic stroke. A single site in each country may not accurately reflect the frequency of AF for the country. This hospital/stroke unit-based registry did not capture stroke patients who were not hospitalized for stroke. Due to the primary reason of the registry, several interesting stroke-related data such as therapy, outcome, cardiovascular risk factors, etc. were only collected in the subgroup of ESUS patients and thus not available for patients with AF-related stroke.

However, the study sites represented many global regions allowing unique comparison of AF-associated stroke around the world and the frequency of AF in our study (28%) is broadly in line with figures reported in recent studies, supporting the external validity of our findings.

In summary, this study provides a unique perspective on the global burden of AF-associated stroke. AF-associated stroke comprises an important (28%, 95% CI: 25.6-29.5%) subset of ischemic stroke patients around the world, and is the most frequent cause of ischemic stroke in elderly women. These strokes are potentially preventable.

1st Author: Disclosures: None**.**

"Due to the large number of co-authors, additional disclosures will follow if the manuscript is accepted"

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Table 1. Frequency of atrial fibrillation among ischemic stroke patients

Site*	All Ischemic Stokes		Atrial Fibrillation associated stroke N(%)
	N	Mean age (SD) in years	
Manila, Philippines	175	62 (0.50)	20 (11%)
Mexico City, Mexico	225	56 (0.50)	30 (13%)
Beijing, China	69	59 (0.46)	11 (16%)
Amsterdam, Netherlands	99	68 (0.50)	17 (17%)
Moscow, Russia	106	66 (0.50)	18 (17%)
Rome, Italy	91	67 (0.50)	19 (21%)
Tokyo, Japan	75	68 (0.49)	16 (21%)
Buenos Aires, Argentina	73	68 (0.50)	16 (22%)
Sao Paulo, Brazil	86	60 (0.49)	21 (24%)
Perth, Australia	114	67 (0.48)	32 (28%)
Philadelphia, United States	120	67 (0.50)	38 (32%)
Paris, France	69	69 (0.49)	23 (33%)
Heidelberg, Germany	91	73 (0.50)	30 (33%)
Seoul, South Korea	124	69 (0.49)	43 (35%)
Hamilton, Canada	172	73 (0.50)	65 (38%)
Brussels, Belgium	119	74 (0.50)	46 (39%)
Glasgow, United Kingdom	73	67 (0.50)	29 (40%)
Coimbra, Portugal	123	74 (0.49)	53 (43%)
Galway, Ireland	140	71 (0.50)	63 (45%)
Total	**2144**	**67 (0.50)**	**590 (28%)**

*See appendix for specific hospitals, institutions and investigators

Table 2. Frequency of atrial fibrillation among ischemic stroke patients by global region

	Overall			Europe (9 sites)			North America (2 sites)		
	N (%)	Men n (%)	Mean age (yrs.)	N (%)	Men n (%)	Mean age (yrs.)	N (%)	Men n (%)	Mean age (yrs.)
Ischemic stroke – all	2144 (100%)	1175 (55%)	67	911 (100%)	508 (56%)	70	292 (100%)	149 (51%)	70
Ischemic stroke with AF*	590 (28%)	295 (50%)	75	298 (33%)	151 (51%)	77	103 (35%)	49 (48%)	77
Ischemic stroke - no AF	1554 (72%)	880 (57%)	64	613 (67%)	357 (58%)	67	189 (65%)	100 (53%)	67

	Latin America (3 sites)			East Asia and Pacific (5 sites)		
	N (%)	Men n (%)	Mean age (yrs.)	N (%)	Men n (%)	Mean age (yrs.)
Ischemic stroke	384 (100%)	180 (47%)	59	557 (100%)	338 (61%)	65
Ischemic stroke with AF*	67 (17%)	30 (45%)	67	122 (22%)	65 (53%)	74
Ischemic stroke - no AF	317 (83%)	150 (47%)	58	435 (78%)	273 (63%)	62

AF = atrial fibrillation
*History of AF prior to index stroke, AF on any ECG, or AF documented on post-stroke cardiac rhythm monitoring.

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Table 3. Identification of atrial fibrillation among ischemic stroke patients by global regions

	All Regions (19 sites)		Europe (9 sites)		North America (2 sites)		Latin America (3 sites)		East Asia and Pacific (5 sites)	
	N	%*	N	%*	N	%*	N	%*	N	%*
All ischemic strokes	2144	100%	911	100%	292	100%	384	100%	557	100%
Total AF[+]	590	28%	298	33%	103	35%	67	17%	122	22%
History of AF prior to index stroke	332	15%	163	18%	70	24%	27	7%	72	13%
AF on any ECG but no history of AF prior to index stroke	207	10%	105	12%	28	10%	33	9%	41	7%
AF on cardiac rhythm monitoring, but no AF on any ECG and no history of AF (i.e. detected only by monitoring)	51^	2%	30	3%	5	2%	7	2%	9	2%

AF = atrial fibrillation
* Percent of all ischemic strokes.
+ includes a history of AF prior to index stroke, AF on any ECG, or AF on post-stroke cardiac rhythm monitoring.
^ Of 1605 ischemic stroke patients without AF by history or ECG

Table 4. Clinical features of ischemic stroke patients according to atrial fibrillation by global regions

	Overall			Europe and Central Asia (9 sites)		North America (2 sites)		Latin America (3 sites)		East Asia and Pacific (5 sites)	
	AF (n=590)	No AF (n=1554)	pvalue Chi-Sq	AF	No AF	AF	No AF	AF	No AF	AF	No AF
Participants with age >=75 years - n(%)	337 (57%)	425 (27%)	<.0001	186 (62%)	211 (34%)	65 (63%)	58 (31%)	26 (39%)	64 (20%)	60 (49%)	92 (21%)
Women >=75 years - n(%)	191 (32%)	222 (14%)	<.0001	109 (37%)	109 (18%)	40 (39%)	34 (18%)	15 (22%)	35 (11%)	27 (22%)	44 (10%)
Cardiac rhythm monitoring >=24 hours after stroke - n(%)	370 (63%)	1049 (68%)	0.0362	195 (65%)	415 (68%)	53 (51%)	166 (88%)	36 (54%)	147 (46%)	86 (70%)	321 (74%)
Lacunar infarct visualized on CT/MRI* - n(%)	33 (6%)	306 (20%)	<.0001	11 (4%)	109 (18%)	7 (7%)	26 (14%)	4 (6%)	38 (12%)	11 (9%)	133 (31%)
Ipsilateral cervical carotid stenosis > 50% or occlusion - n(%)	55 (9%)	238 (15%)	0.0003	29 (10%)	95 (15%)	17 (17%)	35 (19%)	5 (7%)	49 (15%)	4 (3%)	59 (14%)
Death within 30 days - n(%)	58 (10%)	66 (4%)	<.0001	36 (12%)	35 (6%)	18 (17%)	20 (11%)	1 (1%)	3 (1%)	3 (2%)	8 (2%)

AF = atrial fibrillation
* Small (≤1.5cm in largest diameter) subcortical or pontine infarct.

Figure 1: Frequency of AF and mean age according to country income strata

High-income countries - 14 sites

AF 32%
Mean age 77y

Non AF 68%
Mean age 67y
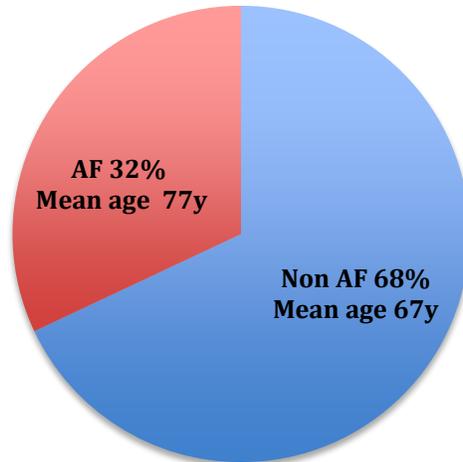
Upper-middle income countries - 5 sites

AF 16%
Mean age
69y

Non AF 84%
Mean age 58y
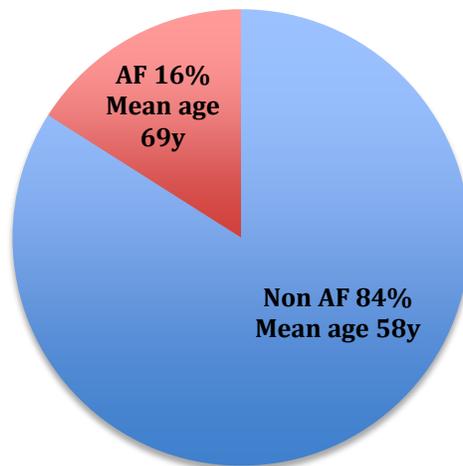
Figure 2. Relationship between the frequency of AF-associate stroke and the mean age of the ischemic stroke cohort.