Global Survey of the Frequency of Atrial Fibrillation–Associated Stroke

Embolic Stroke of Undetermined Source Global Registry

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Background and Purpose—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 to 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% confidence interval, 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 before stroke (15%) or newly detected AF on electrocardiography (10%); only 2% of patients with ischemic stroke had unsuspected AF detected by poststroke 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% confidence interval, 7.6–12.6, respectively) were substantially higher than those of patients without AF (64 years; SD, 15.58 years; 4%; 95% confidence interval, 3.3–5.4; P<0.001 for both comparisons). There was a strong positive correlation between the 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 electrocardiography; 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 men. (Stroke. 2016;47:2197-2202. DOI: 10.1161/STROKEAHA.116.013378.)

Key Words: atrial fibrillation ■ cardiac rhythm monitoring ■ electrocardiography ■ embolism ■ stroke

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

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* A list of all ESUS Global Registry Investigators is given in the Appendix.

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in the past decade consistently report higher frequencies.4–7 possibly because of 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 a 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 to 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 electrocardiography 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 4 global regions: Europe (9 sites), North America (2 sites), Latin America (3 sites), and East Asia/Pacific (5 sites). Sites were also grouped into 4 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 χ2 test. Continuous data were summarized using mean and SD, and comparisons were made using t test or Wilcoxon signed-rank test, as appropriate. Correlation coefficient was used to determine the association between the 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% confidence interval [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 with upper-middle-income countries (15.6%; 95% CI, 12.8–18.4; Figure 1).

Table 1. Frequency of Atrial Fibrillation Among Patients With Ischemic Stroke

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

*See Appendix for specific hospitals, institutions, and investigators.

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 Patients With Ischemic Stroke
Of the 590 ischemic strokes associated with AF, 332 (56%; 95% CI, 52.1–60.3) had a history of AF before the index stroke, and an additional 207 (35%; 95% CI, 31.2–39.1) without a history of AF had AF diagnosed by electrocardiography 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 patients with ischemic stroke, 1108 (69%) patients (who did not have a diagnosis of AF before the index stroke or who were not diagnosed with AF on the basis of a 12-lead ECG) underwent ≥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 (<1.5 cm in largest diameter subcortical or pontine infarct) as their index stroke; this was significantly lower than the patients with non-AF–associated stroke where 20% presented with lacunar stroke as their index stroke. Nine percent of the patients with AF had ≥50% stenosis in the ipsilateral cervical carotid artery detected by ultrasound Doppler, magnetic resonance angiography, or computed tomographic angiography. In the patients with non-AF ischemic stroke, 15% had ≥50% ipsilateral carotid stenosis. Thirty-day mortality among patients with AF was significantly higher (10%; 95% CI, 7.6–12.6) compared with patients with non-AF ischemic stroke (4%; 95% CI, 3.3–5.4; \( P < 0.0001 \); Table 4).

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 old (44%) versus those <75 years old (18%; \( P = 0.0001 \)), with almost half of the ischemic strokes in women >75 years old associated with AF (46%). There was a strong positive correlation between the mean age of patients with stroke and the 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 because of the variation in mean ages of the stroke populations. There was a strong and significant correlation between the mean age of the stroke cohort and the frequency of AF among sites. Compared with other regions, Latin America had the lowest frequency of AF-related stroke; this likely reflects the lower average age of the stroke population in Latin America, which was on average a decade lower than stroke populations from other regions. The attributed risk of AF for ischemic stroke in a given population is expected to be influenced by the life expectancy of the population, and this might partly explain regional variations in frequency of AF between high-income and upper middle-income countries in our study. This regional variability could also be partly explained by the variability of access to diagnostic tests in each center; at least hypothetically, we can assume that access to prolonged monitoring for AF detection to be easier in high-income regions, compared with upper middle-income regions.

AF was identified in 28% (95% CI, 25.6–29.5) of consecutive patients with ischemic stroke, a higher fraction than in hospitalized patients with ischemic stroke in past decades (typically between 15% and 20%) probably because of increasing vigilance in detecting AF, the increasing prevalence of AF in the elderly, and inclusion of more elderly stroke cohorts.

Table 2. Frequency of Atrial Fibrillation Among Patients With Ischemic Stroke by Global Region

<table>
<thead>
<tr>
<th></th>
<th>Overall (19 sites)</th>
<th>Europe (9 Sites)</th>
<th>North America (2 Sites)</th>
<th>Latin America (3 Sites)</th>
<th>East Asia and Pacific (5 Sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Men, n (%)</td>
<td>Mean Age, y</td>
<td>n (%)</td>
<td>Men, n (%)</td>
</tr>
<tr>
<td>Ischemic stroke—all</td>
<td>2144 (100)</td>
<td>1175 (55)</td>
<td>67</td>
<td>292 (100)</td>
<td>149 (51)</td>
</tr>
<tr>
<td>Ischemic stroke with AF*</td>
<td>590 (28)</td>
<td>295 (50)</td>
<td>75</td>
<td>103 (35)</td>
<td>49 (48)</td>
</tr>
<tr>
<td>Ischemic stroke—no AF</td>
<td>1554 (72)</td>
<td>880 (57)</td>
<td>64</td>
<td>189 (65)</td>
<td>100 (53)</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation.
*History of AF before index stroke, AF on any electrocardiography, or AF documented on poststroke cardiac rhythm monitoring.
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 AF, which are often brief and of uncertain pathogenic relevance. The increase in the frequency of AF-associated stroke relative to other ischemic strokes has occurred despite more widespread use of oral anticoagulation in patients with AF. More than half of AF-related strokes occurred in patients with a known history of AF. Although no data on antithrombotic or anticoagulant therapy were 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 with 20% of patients without AF, and the differences in frequency were consistent across global regions and consistent with previous studies, suggesting that AF-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 cardioembolic or atheroembolic sources. However, previously published data on anticoagulation treatment in patients with AF who present with lacunar stroke show no benefit of anticoagulation compared with antiplatelet treatment in reducing the risk of recurrent stroke. With this knowledge, it would have been interesting to explore whether stroke subtype influenced physician decision on choosing an antithrombotic 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 with patients without AF across global regions. Our findings are consistent and in accordance with the larger randomized trials.

### Table 3. Identification of Atrial Fibrillation Among Patients With Ischemic Stroke by Global Regions

<table>
<thead>
<tr>
<th>Region</th>
<th>All Regions (19 Sites)</th>
<th>Europe (9 Sites)</th>
<th>North America (2 Sites)</th>
<th>Latin America (3 Sites)</th>
<th>East Asia and Pacific (5 Sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)*</td>
<td>n (%)*</td>
<td>n (%)*</td>
<td>n (%)*</td>
<td>n (%)*</td>
</tr>
<tr>
<td>All ischemic strokes</td>
<td>2144 (100)</td>
<td>911 (100)</td>
<td>292 (100)</td>
<td>384 (100)</td>
<td>557 (100)</td>
</tr>
<tr>
<td>Total AF†</td>
<td>590 (28)</td>
<td>298 (33)</td>
<td>103 (35)</td>
<td>67 (17)</td>
<td>122 (22)</td>
</tr>
<tr>
<td>History of AF before index stroke</td>
<td>332 (15)</td>
<td>163 (18)</td>
<td>70 (24)</td>
<td>27 (7)</td>
<td>72 (13)</td>
</tr>
<tr>
<td>AF on any ECG but no history of AF before index stroke</td>
<td>207 (10)</td>
<td>105 (12)</td>
<td>28 (10)</td>
<td>33 (9)</td>
<td>41 (7)</td>
</tr>
<tr>
<td>AF on cardiac rhythm monitoring, but no AF on any ECG and no history of AF (ie, detected only by monitoring)</td>
<td>51‡ (2)</td>
<td>30 (3)</td>
<td>5 (2)</td>
<td>7 (2)</td>
<td>9 (2)</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; and ECG, electrocardiography.

*Percent of all ischemic strokes.
†Includes a history of AF before index stroke, AF on any ECG, or AF on poststroke cardiac rhythm monitoring.
‡Of 1605 ischemic stroke patients without AF by history or ECG.
Our findings show a significant correlation between the mean age of patients with stroke and the frequency of AF, which is statistically significant and in keeping with several recent observational data.\(^9,15,16\)

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. There were no sites included from low- and middle-income countries, including sub-Saharan countries where the global burden of stroke is known to be the greatest.\(^17\) 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 patients with stroke who were not hospitalized for stroke. Because of the primary reason of the registry, several interesting stroke-related data, such as therapy, outcome, and cardiovascular risk factors, 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 patients with ischemic stroke around the world and is the most frequent cause of ischemic stroke in elderly women. These strokes are potentially preventable.

**Appendix: Embolic Stroke of Undetermined Source Global Registry Investigators**

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This study was supported by Bayer Healthcare, Hamilton Health Sciences Strategic Initiatives Program, and the Canadian Stroke Prevention Intervention Network.

Disclosures
Dr Bosch received research support from Bayer Healthcare. Dr Mundis is an employee of Bayer Pharma AG. Dr Hankey, in the past 3 years, has received honoraria from Bayer Healthcare for lecturing about stroke prevention in atrial fibrillation at sponsored scientific symposia, Medscape, and Web MD for participating in a discussion about stroke prevention in atrial fibrillation for theheart.org. Dr Sargento-Freitas has received travel support and speaking fees from Boehringer-Ingelheim, Bayer, and BMS-Pfizer. Dr Brouns has received consultancy or speaker honoraria from Pfizer, Medtronic, Shire Human Genetics Therapies, Sanofi-Aventis, Boehringer-Ingelheim, Daiichi Sankyo, Portola, and Medtronic. Dr Muir received an honorarium for speaking at a symposium organized by Bayer at the European Stroke Organization Conference in 2015. Dr Connolly received consulting and speaking fees from Portola, and Medtronic. Dr Muir received research funding from Bayer, WL Gore, and Bristol Myers Squibb and consulting fees from Boehringer-Ingelheim, Daiichi Sankyo, Amgen, and Bayer. Dr Kasner received research funding from Bayer, WL Gore, and Bristol Myers Squibb and consulting fees from Boehringer Ingelheim, Bayer, and BMS-Pfizer. Dr Sargento-Freitas has received travel support and speaking fees from Portola, and Medtronic. Dr Bosch received research support from Bayer Healthcare. Dr Hankey, in the past 3 years, has received honoraria from Bayer Healthcare for lecturing about stroke prevention in atrial fibrillation at sponsored scientific symposia, Medscape, and Web MD for participating in a discussion about stroke prevention in atrial fibrillation for theheart.org. Dr Sargento-Freitas has received travel support and speaking fees from Boehringer-Ingelheim, Bayer, and BMS-Pfizer. Dr Brouns has received consultancy or speaker honoraria from Pfizer, Medtronic, Shire Human Genetics Therapies, Sanofi-Aventis, Boehringer-Ingelheim, Daiichi Sankyo, Portola, and Medtronic. Dr Muir received an honorarium for speaking at a symposium organized by Bayer at the European Stroke Organization Conference in 2015. Dr Connolly received consulting fees from Bayer. Dr Hart received research support and stipends for advisory committee participation for Bayer Healthcare.

References
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