Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study

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Summary

Background **Atrial fibrillation is an important cause of morbidity and mortality worldwide, but scant data are available for long-term outcomes in individuals outside North America or Europe, especially in primary care settings.**

Methods **We did a cohort study using a prospective registry of patients in 47 countries who presented to a hospital emergency department with atrial fibrillation or atrial flutter as a primary or secondary diagnosis. 15 400 individuals were enrolled to determine the occurrence of death and strokes (the primary outcomes) in this cohort over eight geographical regions (North America, western Europe, and Australia; South America; eastern Europe; the Middle East and Mediterranean crescent; sub-Saharan Africa; India; China; and southeast Asia) 1 year after attending the emergency department. Patients from North America, western Europe, and Australia were used as the reference population, and compared with patients from the other seven regions**

Findings **Between Dec 24, 2007, and Oct 21, 2011, we enrolled 15 400 individuals to the registry. Follow-up was complete for 15 361 (99·7%), of whom 1758 (11%) died within 1 year. Fewer deaths occurred among patients presenting to the emergency department with a primary diagnosis of atrial fibrillation compared with patients who had atrial fibrillation as a secondary diagnosis (377 [6%] of 6825 patients *vs* 1381 [16%] of 8536, p<0·0001). Twice as many patients had died by 1 year in South America (192 [17%] of 1132) and Africa (225 [20%] of 1137) compared with North America, western Europe, and Australia (366 [10%] of 3800, p<0·0001). Heart failure was the most common cause of death (519 [30%] of 1758); stroke caused 148 (8%) deaths. 604 (4%) of 15361 patients had had a stroke by 1 year; 170 (3%) of 6825 for whom atrial fibrillation was a primary diagnosis and 434 (5%) of 8536 for whom it was a secondary diagnosis (p<0·0001). The highest number of strokes occurred in patients in Africa (89 [8%] of 1137), China (143 [7%] of 2023), and southeast Asia (88 [7%] of 1331) and the lowest occurred in India (20 [<1%] of 2536). 94 (3%) of 3800 patients in North America, western Europe, and Australia had a stroke.**

Interpretation **Marked unexplained inter-regional variations in the occurrence of stroke and mortality suggest that factors other than clinical variables might be important. Prevention of death from heart failure should be a major priority in the treatment of atrial fibrillation.**

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Introduction

Atrial fibrillation is a leading cause of morbidity and mortality worldwide.[1–4] However, most understanding of atrial fibrillation is based on findings from clinical trials and observational studies done in North America and western Europe, which exclude patients with secondary atrial fibrillation.[3–7] Both of these factors might lead to an underestimation of the morbidity and mortality associated with atrial fibrillation. Over the past 20 years, findings from clinical trials have suggested that antithrombotic drugs substantially and significantly reduce stroke in patients with atrial fibrillation,[5,6,8,9] but comparatively less attention has been paid to other complications. Although evidence is emerging that guideline-based application[10–12] of antithrombotic therapy and blood pressure management is improving outcomes for patients in high-income countries,[13] no concurrent data are available about the outcomes of patients with atrial fibrillation in low-income or middle-income countries.

Several reports have described the characteristics of patients with atrial fibrillation in countries outside western Europe and North America.[14–16] These data have highlighted important differences in the clinical characteristics and treatment of patients with atrial fibrillation in these regions, compared with patients in Western Europe and North America. However; there are no data about whether outcomes for patients with atrial fibrillation vary between countries and if so, the reasons for such variations. To reduce mortality and morbidity from atrial fibrillation worldwide, the rate of a range of adverse outcomes in addition to strokes should be documented among a broad cohort of patients in different regions of the world and the reasons for any variations understood.

Methods

Study design and participants

The methods of this study have previously been described.[17] We did a cohort study using a prospective

Research in context

Evidence before this study

We searched MEDLINE on May 2, 2015, for English-language cohort studies published since 1998 of patients with atrial fibrillation recruited from a primary care setting (such as an emergency department or family practice), that included patients from all inhabited continents of the world. Studies had to include data on mortality and stroke outcomes. We used the search terms "cohort/longitudinal study", "registry", "atrial fibrillation", "global", "worldwide" and "inter/multi-national". Several cohort studies reported outcomes, but did not include patients from all inhabited continents, or they recruited patients predominantly from specialist practices. There are other ongoing cohort studies which have yet to report stroke and mortality data.

Added value of this study

The current study adds findings to those from previously published regional cohort studies, by allowing a direct comparison of management and outcomes between regions, using a common study method. In addition to providing numbers for stroke and death in all regions, the current study explores the reasons for variations between regions.

Implications of all the available evidence

The evidence suggests that there is a significant inter-regional variation in the occurrence of stroke, heart failure, and death among patients presenting to an emergency department with atrial fibrillation. The numbers of events in our study are similar to those observed in previously published regional cohorts. The data suggest that although stroke remains a major problem in Africa, southeast Asia, and China, globally, heart failure is by far the most common cause of death for patients with atrial fibrillation.

See Online for appendix

registry of patients at 164 sites in 47 countries, representing all inhabited continents (appendix). The registry enrolled patients who presented to an emergency department with atrial fibrillation or atrial flutter, identified by the treating physicians as the primary reason for their visit or as a secondary diagnosis. Although consecutive patients were not enrolled, centres were strongly encouraged to enrol patients as rapidly as possible and to avoid obvious biases in the way that patients were identified. When possible, we identified patients with atrial fibrillation from hospital databases of presenting emergency department diagnoses. All patients gave written consent for study participation.

Patients from North America, western Europe, and Australia were used as the reference population with which to compare patients from seven other geographical regions: South America, eastern Europe, the Middle East and Mediterranean crescent (including North Africa and Turkey), sub-Saharan Africa, India, China, and southeast Asia. With the use of World Bank definitions,[18] participating countries represented high-income (n=21), middle-income (n=22), and low-income (n=4) countries.

We assessed patients at 12 months (plus or minus 4 weeks) after enrolment, either in person or via telephone, with supplemental information obtained from medical records. We obtained data for the primary clinical outcomes of death and stroke, and the secondary outcomes of admission to hospital for heart failure, admission to hospital for myocardial infarction, major bleeding, and systemic embolism. The validated questionnaire for the verification of stroke-free status[19] was administered to all patients.

Statistical analysis

We summarised baseline characteristics and medical treatments at the emergency department visit of patients as mean (SD) or median (IQR) for continuous variables and frequency (percentage) for categorical variables, and compared them between the eight regions using an ANOVA or a Kruskal-Wallis test for continuous variables, and Pearson χ^2 or Fisher's exact test for categorical variables. The proportion of patients who had a clinical outcome within 1 year of the visit was presented for each of the eight regions. We used χ^2 test or Fisher's exact test to determine homogeneity in the proportion of 1-year events among the eight regions and whether the number of events differed between each region compared with those from North America, Western Europe, and Australia. We set the significance level at 0·005 to adjust for multiple comparisons.

To assess the contributions of patient characteristics, medication specifications, and region-level economic factors to regional variations in clinical outcomes, we developed a series of hierarchical logistic-regression models with random intercept at region level. Random effects were assumed to follow normal distribution on a log odds scale with an unstructured covariance matrix. We started with a two-level null model with patients at the first level and regions at second level, followed by three nested models with sequential adjustments for the following different sets of factors: (1) patient characteristics: age, sex, previous stroke or transient ischaemic attack, a history of heart failure, coronary artery disease, hypertension, diabetes mellitus, rheumatic heart disease, left-ventricular hypertrophy, left-ventricular systolic dysfunction, and the primary reason for emergency department visit; (2) treatments: medicines to achieve appropriate blood pressure control (≤140/90 mm Hg) in patients with hypertension, appropriate use of guideline-indicated therapy for heart failure (both β blockers and angiotensin receptor blockers or angiotensin-converting-enzyme inhibitors) and guideline-indicated use of oral anticoagulation therapy;[10]

	North America, western Europe, and Australia (n=3800)	South America (n=1134)	Eastern Europe (n=2542)	Middle East (n=887)	Africa (n=1137)	India (n=2536)	China (n=2023)	Southeast Asia (n=1341)	Overall (n=15 400)	p value*
Age (years)	69·7 (12·8); 71 (62–79)	68·3 (13·1)†; 70 (60–78)†	69·3 (11·0); 71 (62–78)†	58·6 (15·6)†; 60 (48–71)†	57·2 (18·8)†; 61 (46–71)†	57·9 (15·8)†; 60 (46–70)†	68·4 (13·2)†; 71 (60–78)†	69·5 (13·2); 72 (61–79)	65·9 (14·8); 68 (57–77)	<0·0001 (for both mean and median)
Sex										
Male	2273 (60%)	635 (56%)	1266 (50%)†	500 (56%)	533 (47%)†	1260 (50%)†	921 (46%)†	743 (55%)†	8131 (53%)	<0·0001
Existing conditions										
Hypertension	2468 (65%)	880 (78%)†	2052 (81%)†	498 (56%)†	612 (54%)†	1056 (42%)†	1126 (56%)†	859 (64%)	9551 (62%)	<0·0001
Previous stroke or TIA	517 (14%)	165 (15%)	319 (13%)	102 (11%)	160 (14%)	187 (7%)†	380 (19%)†	297 (22%)†	2127 (14%)	<0·0001
Diabetes mellitus	783 (21%)	205 (18%)	678 (27%)†	321 (36%)†	159 (14%)†	513 (20%)	313 (15%)†	391 (29%)†	3363 (22%)	<0·0001
History of heart failure	925 (24%)	400 (35%)†	1488 (59%)†	252 (28%)	725 (64%)†	449 (18%)†	756 (37%)†	353 (26%)	5348 (35%)	<0·0001
Rheumatic heart disease	70 (2%)	76 (7%)†	96 (4%)†	136 (15%)†	245 (22%)†	799 (32%)†	318 (16%)†	48 (4%)†	1788 (12%)	<0·0001
Coronary artery disease	1195 (31%)	276 (24%)†	1357 (53%)†	258 (29%)	76 (7%)†	653 (26%)†	848 (42%)†	353 (26%)†	5016 (33%)	<0·0001
Left ventricular hypertrophy	798 (21%)	379 (33%)†	1248 (49%)†	127 (14%)†	545 (48%)†	261 (10%)†	330 (16%)†	375 (28%)†	4063 (26%)	<0·0001
Left ventricular systolic dysfunction	594 (16%)	334 (29%)†	812 (32%)†	214 (24%)†	524 (46%)†	552 (22%)†	388 (19%)†	230 (17%)	3648 (24%)	<0·0001
Treatment variables										
Inadequate control of blood pressure	1659 (44%)	389 (34%)	893 (35%)†	314 (35%)†	356 (31%)†	556 (22%)†	683 (34%)†	507 (38%)†	5357 (35%)	<0·0001
Patients with heart failure who did not receive a β blocker	309 (8%)	222 (20%)	400 (16%)†	84 (9%)	551 (48%)†	482 (19%)†	476 (24%)†	212 (16%)†	2736 (18%)	<0·0001
Patients with heart failure who did not receive an ACE inhibitor or ARB	420 (11%)	168 (15%)	298 (12%)	87 (10%)	239 (21%)†	472 (19%)†	426 (21%)†	188 (14%)†	2298 (15%)	<0·0001
Guideline-indicated patients who did not receive oral anticoagulant therapy	1215 (32%)	621 (55%)	1084 (43%)†	284 (32%)	628 (55%)†	1110 (44%)†	1421 (70%)†	669 (50%)†	7032 (46%)	<0·0001
Economic variables										
Per capita GDP 2010 (US$)	44 501·6	10 503·5	10 039·4	8248·3	2210·4	1389·1	4515·2	28 666·1	11 213·1	
Proportion of GDP spent on health care 2010	13·8%	7·9%	7·1%	5·2%	6·1%	3·8%	5·0%	8·8%	10·6%	

Data are mean (SD), median (IQR), or n (%). n=number of patients enrolled. TIA=transient ischaemic attack. ACE=angiotensin converting enzyme. ARB=angiotensin receptor blockers. GDP=gross domestic product. †p value is from the test of null hypothesis that there is no difference between regions, using ANOVA test for mean age, Kruskal Wallis test for median age, and χ^2 test for categorical variables. †Significantly different from North America, western Europe, and Australia, p<0·005.

Table 1: **Patient characteristics, treatments, and economic factors by region**

and (3) the ratio of region-level economic factors: gross domestic product (GDP) per person and the percentage of GDP spent on the health of people in participating countries in each region.[20] We calculated region-specific risk-adjusted event rates, intraclass correlation coefficients, and proportional changes in variance using established methods[21,22] (appendix). We did all statistical analyses with SAS 9.4 software.

Role of the funding source

The funder of the study participated in operational calls and gave technical advice about the design of the protocol, but had no role in data collection, data management, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study. A scientific steering committee led by SY, LW, ME, SJC, JO, and JSH was responsible for all important study decisions, including the decision to submit for publication. The steering committee was composed of scientific experts who were national leaders for this study.

Results

Between Dec 24, 2007, and Oct 21, 2011, we enrolled 15 400 individuals to the registry (table 1). Of these, 15 361 (99·7%) completed follow-up. The number of patients with follow-up was slightly lower in the Middle East (864 [97%] of 887), but was nearly 100% complete in all other regions. Follow-up was completed in April, 2012.

604 (4%) of 15 361 patients had a stroke by 1 year after their emergency-room visit with atrial fibrillation. Half the number of patients with a primary diagnosis of atrial

	North America, western Europe, or Australia (n=3800)	South America (n=1132)	Eastern Europe (n=2538)	Middle East (n=864)	Africa (n=1137)	India (n=2536)	China (n=2023)	South-east Asia (n=1331)	Overall (n=15 361)	p value*
Death	366 (10%)	192 (17%)†	220 (9%)	113 (13%)†	225 (20%)†	231 (9%)	285 (14%)†	126 (9%)	1758 (11%)	<0·0001
Stroke	94 (2%)	31 (3%)	111 (4%)†	28 (3%)	89 (8%)†	20 (1%)†	143 (7%)†	88 (7%)†	604 (4%)	<0·0001
Systemic embolism	15 (<1%)	3 (<1%)	29 (1%)†	4 (<1%)	10 (1%)	2 (<1%)	14 (1%)	7 (1%)	84 (1%)	<0·0001‡
Major bleeding	111 (3%)	26 (2%)	48 (2%)	12 (1%)	22 (2%)	8 (<1%)†	26 (1%)†	68 (5%)†	321 (2%)	<0·0001
Admission to hospital for heart failure	411 (11%)	78 (7%)†	337 (13%)†	97 (11%)	391 (34%)†	92 (4%)†	336 (17%)†	180 (14%)	1922 (13%)	<0·0001
Admission to hospital for myocardial infarction	75 (2%)	16 (1%)	73 (3%)	16 (2%)	20 (2%)	9 (<1%)†	21 (1%)	38 (3%)	268 (2%)	<0·0001

Data are n (%). n=number of patients with complete follow-up data. *p value is from the test of null hypothesis that there is no difference among regions, using χ^2 test or Monte Carlo estimates of Fisher's exact test. †Significantly different from North America, western Europe, or Australia, p<0·005. ‡Exact p value was estimated by Monte Carlo simulation with 100 000 samples.

Table 2: **Crude data for patient outcomes**

	North America, western Europe, or Australia (n=3800)	South America (n=1132)	Eastern Europe (n=2538)	Middle East (n=864)	Africa (n=1137)	India (n=2536)	China (n=2023)	Southeast Asia (n=1331)	Overall (n=15 361)	p value*
Atrial fibrillation	70/1748 (4%)	56/573 (10%)†	57/1350 (4%)	17/385 (4%)	32/269 (12%)†	73/1328 (5%)	64/833 (8%)†	8/339 (2%)	377/6825 (6%)	<0·0001
Heart failure	41/182 (23%)	29/113 (26%)	44/304 (14%)	9/54 (17%)	100/443 (23%)	17/114 (15%)	76/371 (20%)	17/89 (19%)	333/1670 (20%)	0·0728
Stroke	0/24	13/38 (34%)†	5/37 (14%)	9/24 (38%)†	26/73 (36%)†	10/23 (43%)†	6/67 (9%)	0/8	69/294 (23%)	<0·0001‡
Respiratory failure	7/18 (39%)	0/7	2/7 (29%)	0/4	0/6	2/10 (20%)	8/24 (33%)	2/12 (17%)	21/88 (24%)	0·3032‡
Infection	11/91 (12%)	17/48 (35%)†	12/40 (30%)	12/33 (36%)†	8/30 (27%)	13/46 (28%)	13/58 (22%)	12/58 (21%)	98/404 (24%)	0·0367
Cancer	0/2	3/4 (75%)	0/0	1/1 (100%)	4/4 (100%)	0/3	2/4 (50%)	2/2 (100%)	12/20 (60%)	0·0360‡
Others	246/1766 (14%)	74/360 (21%)†	104/813 (13%)	68/374 (18%)	68/352 (19%)	121/1055 (11%)	120/685 (18%)	86/840 (10%)	887/6245 (14%)	<0·0001

Data are number of deaths/number of patients (%) for each combination of region and reason for ED visit. Patients with several reasons for visiting an emergency department were counted in more than one category. n=number of patients with complete follow-up data. *p value is from the test of null hypothesis that there is no difference among regions, using χ^2 test or Monte Carlo estimates of Fisher's exact test. †Significantly different from North America, western Europe, and Australia, p<0·005. ‡Exact p value was estimated by Monte Carlo simulation with 100 000 samples.

Table 3: **Crude mortality data based on the reason for initial emergency department visit**

fibrillation had a stroke compared with patients for whom atrial fibrillation was a secondary diagnosis (170 [3%] of 6825] *vs* 434 [5%] of 8536, p<0·0001). The crude 1-year occurrence of stroke also varied greatly between regions (table 2). The occurrence was lowest in India (20 [0.8%] of 2536), but was also low in North America, western Europe, or Australia (94 [3%] of 3800). At 1 year, stroke occurred in 111 (4%) of 253 patients in eastern Europe, 88 (7%) of 1331 in southeast Asia, 143 (7%) of 2023 in China, and 89 (8%) of 1137 in Africa. Although much less common, the occurrence of patients with systemic embolism in each region paralleled the occurrence of stroke (table 2).

Within 1 year, 1758 (11%) of 15361 patients in the cohort study had died (table 2). Fewer patients with a primary diagnosis of atrial fibrillation died than patients for whom atrial fibrillation was a secondary diagnosis (377 [6%] of 6825 *vs* 1381 [16%] of 8536, p<0·0001). The proportion of patients who presented to the emergency room with atrial fibrillation as a secondary diagnosis and mortality in these patients significantly varied between regions (table 3). The crude 1-year occurrence of death varied greatly between regions, from 220 (9%) of 2538 patients in eastern Europe, 366 (10%) of 3800 in North America, western Europe, and Australia, 285 (14%) of 2023 in China, 192 (17%) of 1132 in South America, and 225 (20%) of 1137 in Africa (table 2, figure 1).

Heart failure was the leading cause of death, accounting for a third of all deaths (figure 2) and was the leading cause of death in every region except South America and southeast Asia, where infectious causes were slightly more frequent than heart failure (43 [22%] of 192 patients *vs* 35 [18%] of 192, and 28 [22%] of 126 *vs* 22 [18%] of 126, respectively, figure 1). Infection was the second leading cause of death worldwide, and stroke the third leading cause (figure 2), responsible for 148 (8%) of 1758 deaths worldwide. Stroke caused death in 11 (10%) of 113 patients in the Middle East, 26 (12%) of 220 in eastern Europe, 35 (16%) of 225) in Africa, 18 (8%) of 231 in India, and 26 (9%) of 285 in China (figure 1).

Within 1 year of their initial visit to an emergency department, 1922 (13%) of 15 361 patients were admitted to hospital for heart failure worldwide, 321 (2%) had major bleeding, and 268 (2%) had a myocardial infarction.

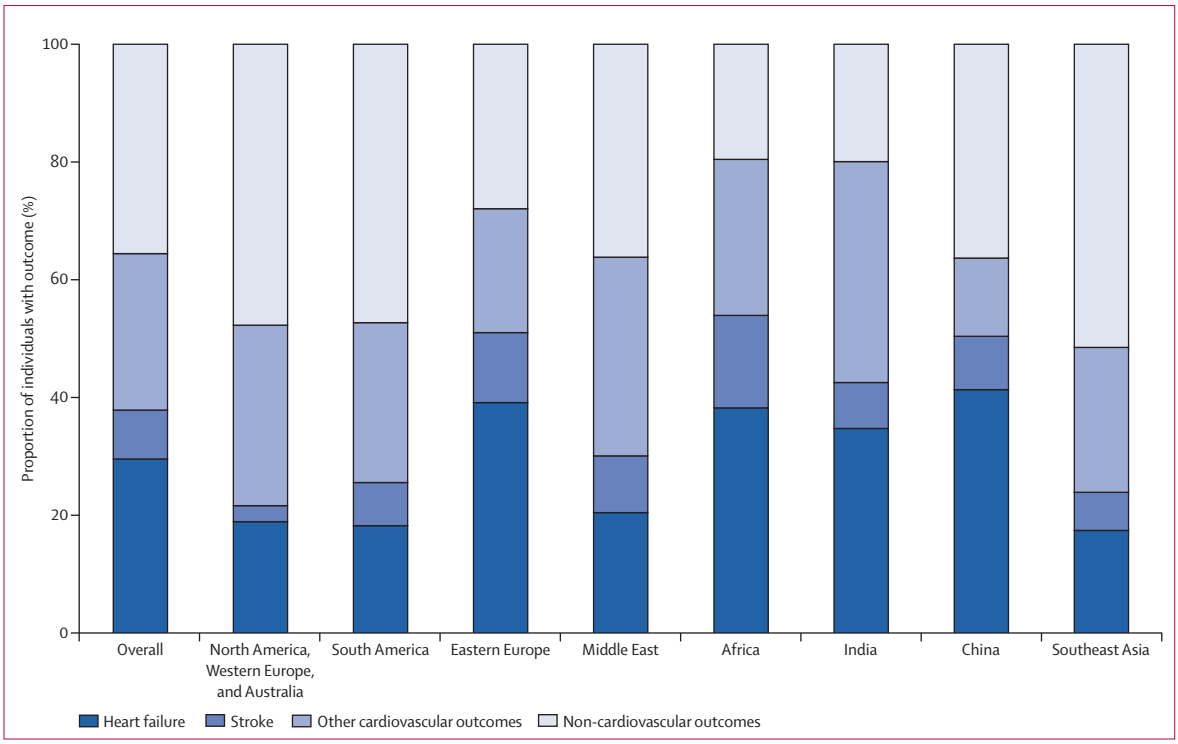

***Figure 1*: Crude proportions of deaths due to heart failure, stroke, other cardiovascular causes and non-cardiovascular causes**
Data divided by region.

The number of patients admitted to hospital for heart failure and the occurrence of major bleeding varied substantially between regions (table 2). The occurrence of myocardial infarction was low in all regions (table 2).

There were important differences in patient characteristics, treatments, and socioeconomic factors between regions in our cohort (table 1), which could have potentially influenced patient outcomes. Adjustment for these factors significantly reduced the variations in mortality and stroke between regions; however, most between-region variations persisted (table 4, figures 3, 4).

For the outcome of all-cause mortality, 3·2% of total variance was attributable to regional-level variance. Adjustment for patient characteristics, differences in treatment, and economic factors, respectively, slightly changed this value (figure 4, table 4). The addition of economic factors into the model, adjusting for differences in patient characteristics and treatments, reduced the between-region variation (ie, the reduction in variance from model 2 to model 3) by 30%. For the outcomes of stroke and admission to hospital for heart failure, around 13% of total variance was attributable to regional-level variance. Adjustment for the above factors again slightly changed this value (table 4).

The reductions in between-region variance accounted for by adjusting for patient, treatment, and economic factors are shown in table 4. 1788 (12%) of 15 400 patients had a history of rheumatic heart disease, the prevalence of which varied between regions (table 1).[17] Patients with rheumatic heart disease were younger than those without

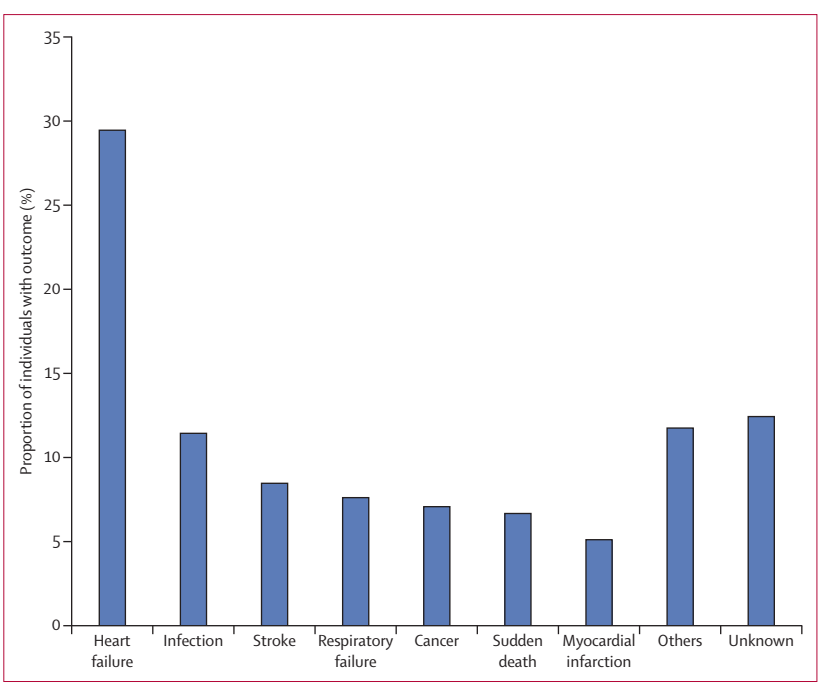

***Figure 2*: Causes of death in the overall cohort (crude data)**
Deaths from other causes (11·8%) include pulmonary embolism, peripheral embolism, aortic dissection/rupture, haemorrhage, trauma, and other.

	Adjusted variables	Region-level effects		ICC* (%)	PCV† (%)
		Variance	p value ‡		
Death	Model 0: Null	0·109	<0·0001	3·2%	..
	Model 1: Patient characteristics	0·140	<0·0001	4·1%	–28·4%
	Model 2: Patient characteristics plus treatments	0·123	<0·0001	3·6%	–12·8%
	Model 3: Patient characteristics plus treatments plus economic factors	0·086	<0·0001	2·6%	21·1%
Stroke	Model 0: Null	0·498	<0·0001	13·1%	..
	Model 1: Patient characteristics	0·376	<0·0001	10·3%	24·5%
	Model 2: Patient characteristics plus treatments	0·356	<0·0001	9·8%	28·5%
	Model 3: Patient characteristics plus treatments plus economic factors	0·345	<0·0001	9·5%	30·7%
Admission to hospital for heart failure	Model 0: Null	0·498	<0·0001	13·2%	..
	Model 1: Patient characteristics	0·290	<0·0001	8·1%	41·8%
	Model 2: Patient characteristics plus treatments	0·291	<0·0001	8·1%	41·6%
	Model 3: Patient characteristics plus treatments plus economic factors	0·279	<0·0001	7·8%	44·0%

PCV=proportional change in variance. ICC=intraclass correlation coefficient. *ICC: PCV attributable to region-level variance. †Significance testing for variance of random effect by likelihood ratio test. ‡PCV: percentage of between-region variance reduction due to introduction of risk factors into the model.

Table 4: **Variance between regions and effect of adjustment on outcomes**

(mean 51·4 years [SD 15·7] *vs* 67·8 (13·6), p<0·0001). Additionally, fewer patients with rheumatic heart disease had a stroke compared with patients without rheumatic heart disease (crude data 50 [3%] of 1783 *vs* 554 [4%] of 13 578, p=0·0092). After adjustment for patient characteristics, treatments and economic factors, the prevalence of stroke was the same in patients with rheumatic heart disease as in those without (4·2% *vs* 3·9%, p=0·5124).

Discussion

This is the first large atrial fibrillation cohort study to prospectively include patients in all regions of the world with both primary and secondary atrial fibrillation. We included a large number of patients from low-income and middle-income countries. In an unselected emergency department setting, where atrial fibrillation represents 0·5%–1·0% of all visits and is often an acute presentation,[23,24] the findings from our study showed that after 1 year around 4% of these patients have had a stroke and around 11% die. Nearly a third of deaths were due to heart failure and 13% of patients required admission to hospital for heart failure within 1 year; highlighting the importance of heart-failure prevention and treatment for patients with atrial fibrillation. The occurrence of stroke and death in our study was higher than in previous randomised trials,[8,9,25,26] but similar to that in some regional cohort studies.[27–31] Our study extends the findings of earlier cohort studies, by using standardised methods to simultaneously estimate occurrences of events in all regions of the world, permitting direct comparisons between regions and allowing an exploration of the reasons for variation.

We documented substantial variation in the occurrence of death, stroke, and heart failure between global regions. These differences in the crude 1-year occurrence of stroke are consistent with information from some regional registries,[28–30] and also mirror variations by region in baseline stroke history.[17] The high occurrence of stroke in Africa and China and low number of occurrences in India also follow similar regional trends for all-cause mortality and admission to hospital for heart failure. However; our analyses can only ascribe a small proportion of this variability to regional differences in baseline clinical characteristics, treatments, and economic factors. This finding might reflect the limitations of our analytical technique to adjust for complex factors, or might imply that other undocumented factors, such as access to care and health-care organisation, played a part. However, our analyses clearly highlight the importance of economic factors in accounting for differences in all-cause mortality between regions.

Around 6% to 8% of patients in southeast Asia, China, and Africa had had a stroke by 1 year, which might partly be explained by the high proportion of patients in these regions with untreated hypertension.[17] In each of these regions, the prevalence of untreated hypertension was approximately 10%, which was more than double the prevalence in North America, western Europe, and Australia.[17] Additionally, the mean systolic blood pressure is 5·5 mm Hg higher in Africa and 3·3 mm Hg higher in China than in North America, Western Europe, and Australia.[17] However, given the linear association between raised blood pressure and risk of stroke, our approach to adjustment for blood pressure greater than 140/90 mm Hg might not have been sensitive enough to fully assess the effect of regional differences in blood pressure treatment on outcomes. Similarly, China and Africa were two of three regions with the lowest use of oral anticoagulation therapy (14% and 19%) and the lowest time-in-therapeutic range (36% and 33%). However, again, our assessment of inter-regional variability might have been insensitive, because it only considered anticoagulant use. The only other region with such low use of anticoagulation and poor time-in-therapeutic range was India (24% and 34%, respectively), which surprisingly had the lowest occurrence of stroke of all regions. However, because of a much greater prevalence of rheumatic heart disease, patients in India were 12 years younger than those in North America, western Europe, and Australia, and so were 40% less likely to have hypertension with an average systolic blood pressure that was lower by 3·3 mm Hg compared with North America, western Europe, and Australia. The Indian population with atrial fibrillation seems so different from other regions that multivariate modelling might not have been able to adjust for such large differences in stroke risk factors.

Notwithstanding our adjusted analyses, blood pressure control[32] and the use of oral anticoagulation[33,34] are proven stroke-prevention therapies and should be promoted.

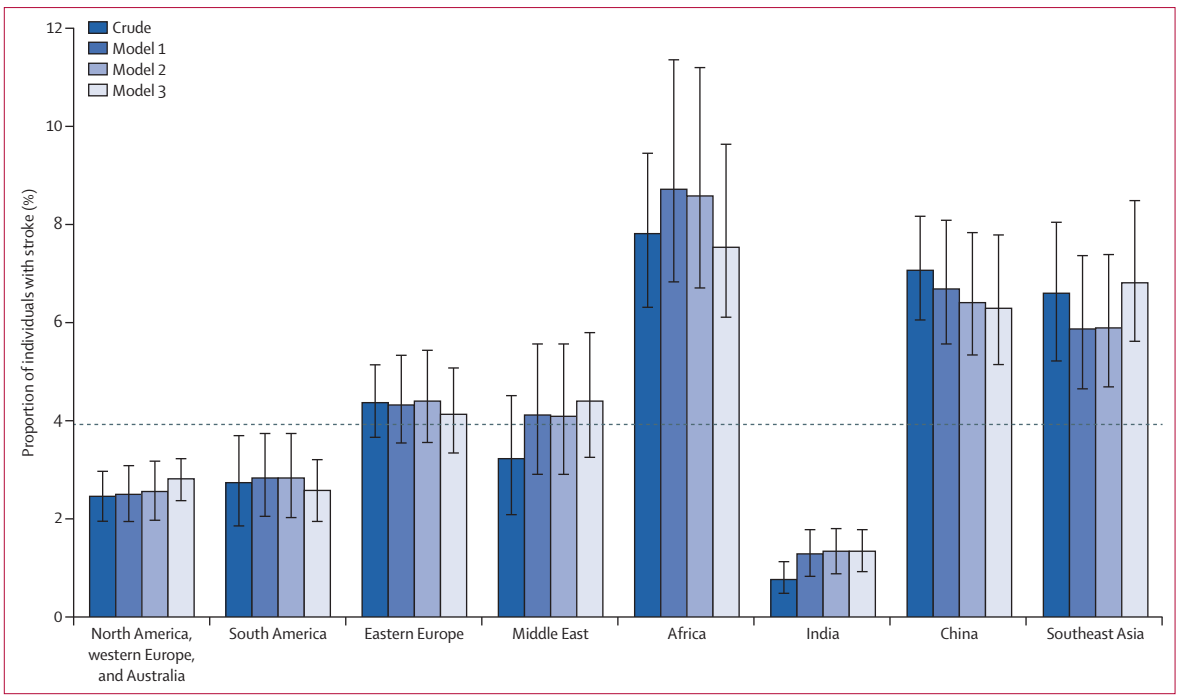

***Figure 3*: Crude and adjusted stroke at 1 year by region**
Data are means, error bars are 95% CIs constructed by the bootstrap method. Model 1: adjusted for patient characteristics. Model 2: additionally adjusted for treatments. Model 3: additional adjustment for region-level economic factors. Horizontal dashed line indicates overall crude event rate.

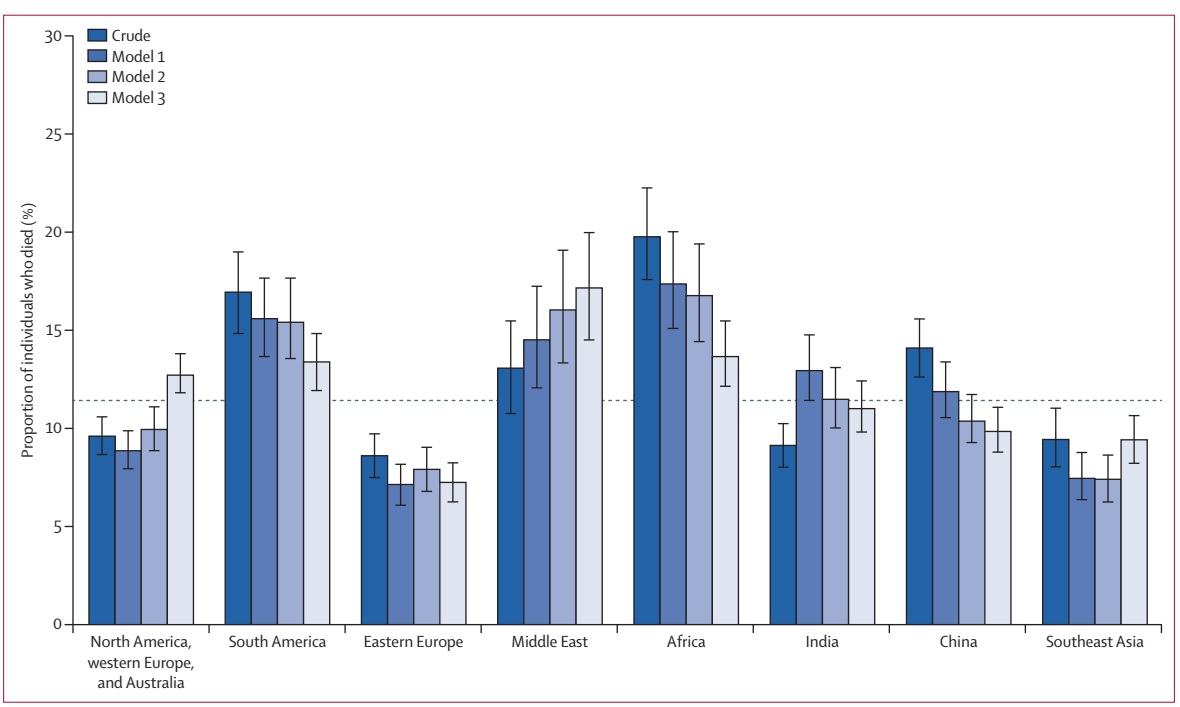

***Figure 4*: Crude and adjusted mortality at 1 year by region**
Data are means, error bars are 95% CIs constructed by the bootstrap method. Model 1: adjusted for patient characteristics. Model 2: additionally adjusted for treatments. Model 3: additional adjustment for region-level economic factors. Horizontal dashed line indicates overall crude event rate.

Because hypertension is present in more than two-thirds of patients with atrial fibrillation worldwide,[17] it is disappointing that the rate of control of hypertension is less than 20% globally and even lower in low-income and middle-income countries.[35] Blood pressure control is particularly important, since antihypertensive treatment

prevents both stroke and heart failure.[32] Results from the RE-LY AF cohort study have shown the importance of heart failure in the population with atrial fibrillation. Compared with the risk of developing stroke, patients with atrial fibrillation were three times more likely to develop heart failure and 3·5 times more likely to die from it. Heart failure was the leading cause of death and 12·5% of patients with atrial fibrillation were admitted to hospital for heart failure within 1 year. As for patients with hypertension, the use of evidence-based, prognosis-improving therapies for heart failure, such as β blockers, angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers varied significantly between regions. Thus, strategies to improve the hypertension control,[36,37] oral anticoagulation,[13,38] and heart failure therapy[39] have potential to improve outcomes of patients with atrial fibrillation.

Our study presents new, important observations for two additional groups of patients with atrial fibrillation: those presenting with atrial fibrillation as a secondary diagnosis and those with rheumatic heart disease. Patients with atrial fibrillation who presented to the emergency room for reasons other than atrial fibrillation were 3 times more likely than patients with primary atrial fibrillation to die, have a stroke or be admitted to hospital for heart failure. Clinical trials typically exclude patients with significant comorbidities who are at greater risk of adverse outcomes. Patients from poor regions, particularly Africa and South America, were more likely to present to the emergency department for conditions other than atrial fibrillation, perhaps because patients in these regions wait for severe complications, such as stroke or heart failure, before seeking medical attention. This explanation is consistent with the high crude mortality occurrence in these regions in our study.

Patients with rheumatic heart disease had a lower risk of stroke compared with patients without rheumatic heart disease, but they were much younger and so, after adjustment for risk-factors and age, their stroke risks were similar. This finding is counter to conventional wisdom that stroke risk should be very high in patients with rheumatic heart disease.[40] The Framingham study[41] showed that atrial fibrillation increased stroke risk by five times in patients without rheumatic heart disease, but by 17 times in patients with rheumatic heart disease. However, only a few people had atrial fibrillation and rheumatic heart disease in the Framingham study. With the widespread use of echocardiography, rheumatic heart disease might be diagnosed at an early stage before heart failure develops and stroke risk is increased.[42] Additionally, patients with rheumatic heart disease in this cohort study mainly lived in low-income and middle-income countries, and were younger and had a very low prevalence of other stroke risk factors compared to earlier rheumatic heart disease cohorts.[41,43] Finally, unlike our study, most previous data for the risk of stroke in patients with rheumatic heart disease come from small studies which included few patients from middle-income and low-income countries and were done many years ago, in an era when blood pressure was managed less aggressively and oral anticoagulation used less frequently.

Our study had the following limitations: we enrolled patients who presented to an emergency department, thus the number of clinical events might not be representative of patients with other presentations. Patients were recruited in as unbiased a fashion as possible; however, in most cases they were not consecutively enrolled, and thus our cohort is a convenience sample, not a representative, population-based sample. Additionally, our selection of sites within regions was not random, and might have introduced bias into the comparison of outcomes between regions. Finally, follow-up in this registry was completed just as new oral anticoagulant medications were being introduced, thus these data will now be complemented by data from global registries that include patients receiving new oral anticoagulants.[44] However, the general conclusions from our study of high occurrences of heart failure and poor outcomes in patients with secondary atrial fibrillation are likely to be unchanged.

In conclusion, within 1 year of presentation to an emergency department with atrial fibrillation, more than 10% of patients died, 4% had a stroke, and 12% were admitted to hospital for heart failure. There are opportunities to improve outcomes in most countries by fuller use of proven therapies, such as oral anticoagulation, and pharmacotherapies for hypertension and heart failure. Prevention of heart failure death should be a major priority in the treatment of patients with atrial fibrillation.

Contributors

JSH, JO, SY, LW, ME, and SJC designed this study, with advice from PR. JN and JW did the statistical analyses and all authors helped to interpret the data. JSH wrote the final draft, and all authors reviewed and revised the manuscript.

Declaration of interests

JSH has a personnel award from the Heart and Stroke Foundation, Ontario Provincial Office (MC7450). All other authors declare no competing interests.

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