Characterization of Different Patient Populations with Atrial Fibrillation

Kloosterman, Mariëlle

DOI:
10.33612/diss.143841478

2 Characteristics and outcomes of atrial fibrillation in patients without traditional risk factors: a RE-LY AF registry analysis

Mariëlle Kloosterman, Jonas Oldgren, David Conen, Jorge A. Wong, Stuart J. Connolly, Alvaro Avezum, Salim Yusuf, Michael D. Ezekowitz, Lars Wallentin, Marie Ntep-Gweth, Philip Joseph, Tyler W. Barrett, Supachai Tanosmsup, William F. McIntyre, Shun Fu Lee, Ratika Parkash, Guy Amit, Alex Grinvalds, Isabelle C. Van Gelder, Jeff S. Healey.

Europace. 2020. doi:10.1093/europace/euz360.

ABSTRACT

Background: Data on patient characteristics, prevalence, and outcomes of AF patients without traditional risk factors, often labelled "lone AF", is sparse.

Methods: The RE-LY AF registry included 15,400 individuals who presented to emergency departments with AF in 47 countries. This analysis focused on patients without traditional risk factors, including: age ≥60 years, hypertension, coronary artery disease, heart failure, left ventricular hypertrophy, congenital heart disease, pulmonary disease, valve heart disease, hyperthyroidism, and prior cardiac surgery. Patients without traditional risk factors were compared to age- and region-matched controls with traditional risk factors (1:3 fashion).

Results: In 796 (5%) patients, no traditional risk factors were present. However, 98% (779/796) had less-established or borderline risk factors, including borderline hypertension (130-140/80-90 mmHg; 47%), chronic kidney disease (eGFR<60 ml/min; 57%), obesity (BMI>30; 19%), diabetes (5%), excessive alcohol intake (>14 units/week; 4%), and smoking (25%). Compared to patients with traditional risk factors (N=2388), patients without traditional risk factors were more often men (74% versus 59%, P<0.001), had paroxysmal AF (55% versus 37%, P<0.001) and less AF persistence after 1-year (21% versus 49%, P<0.001). Furthermore, 1-year stroke occurrence rate (0.6% versus 2.0%, P=0.013), and heart failure hospitalizations (0.9% versus 12.5%, P<0.001) were lower. However; risk of AF-related re-hospitalization was similar (18% versus 21%, P=0.09).

Conclusion: Almost all patients without traditionally-defined AF risk factors have less-established or borderline risk factors. These patients have a favourable 1-year prognosis, but risk of AF-related re-hospitalization remains high. Greater emphasis should be placed on recognition and management of less-established or borderline risk factors.

INTRODUCTION

Sixty-five years ago atrial fibrillation (AF) in the absence of heart disease was coined 'lone AF'.[1] However, that concept has come under scrutiny [2] as our knowledge of risk factors and their importance is evolving.[2-4] Over the last decade, a re-evaluation of traditional frameworks for understanding and managing of AF occurred, and focus has shifted towards optimal treatment of underlying conditions and risk factors. This includes less-established and borderline risk factors such as obesity, diabetes, sleep apnoea, borderline hypertension, chronic kidney disease, smoking, and excessive alcohol intake.[2,5] Furthermore, many thresholds for detecting and defining comorbid conditions have changed, making some conditions such as hypertension more prevalent.[2,4] Due to this improved ascertainment of underlying cardiovascular diseases and risk factors, the reported proportion of seemingly ''lone AF" decreased over the years from ~30% to ~3%.[2,6,7] Therefore it has been recommended that use of the term ''lone AF" should be avoided.[2] Nevertheless it still remains in use today.

Our current understanding of outcomes in AF patients previously thought to have ''lone AF" is largely confined to patients from North America and Europe.[3,6,8,9] This is a major limitation since we know that important regional variation exists among the global population of individuals with AF.[10-12] The current analysis aimed to examine patient characteristics, prevalence of less-established or borderline risk factors, and outcome in patients without traditional risk factors from different geographic regions using data from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) AF registry [10,11]

METHODS

RE-LY AF registry

The methods of the RE-LY AF registry have been described previously.[10,11] Patients from 164 sites in 47 countries, representing all inhabited continents, who presented to an emergency department or equivalent acute-care setting with AF or atrial flutter (AFL), were included in this prospective registry. The atrial rhythm disturbance could be either the primary reason for their visit or a secondary diagnosis. Although patients were not consecutive, study sites were encouraged to enrol patients as rapidly as possible to minimize bias. All patients gave written informed consent for study participation.

Study population

Between December 24, 2007 and October 21, 2011, 15,400 patients were enrolled, of whom 97.7% had AF and the rest had AFL. The present analysis excluded all patients with traditional AF risk factors including: advancing age (≥60 years), myocardial infarction, coronary artery disease, congenital heart disease, heart failure, left ventricular hypertrophy or systolic dysfunction, hypertension, rheumatic heart disease, significant valvular heart disease (defined as moderate to severe [grade 3] or severe [grade 4]), pulmonary disease including emphysema and chronic obstructive pulmonary disease, stroke or transient ischemic attack, hyperthyroidism, or recent cardiac surgery.

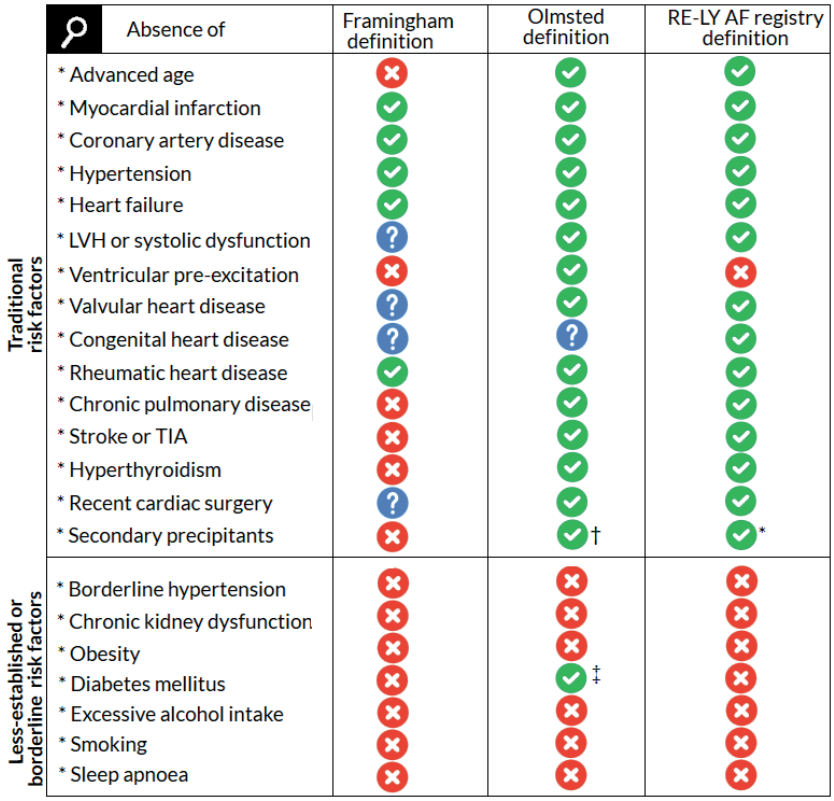

Figure 1. Traditional risk factors

The columns show the traditional risk factors used in the Framingham, Olmsted and RE-LY cohorts.[3,6,9]

* Secondary precipitants for AF were excluded, including acute coronary syndrome or arrest, pericarditis or pericardial effusion (in our cohort mainly caused by tuberculosis and HIV), myocarditis, pulmonary oedema, cerebrovascular vascular accident, aortic dissection, ICD shock or heart failure.

† Patients with AF related to surgery, trauma, or acute medical illness were excluded.

‡ Insulin dependent diabetes mellitus.

AF denotes atrial fibrillation; BMI, body mass index; eGFR, estimated glomerular filtration rate; TIA, transient ischemic attack.

These "traditional" risk factors are the ones used in the Olmsted Country and Framingham cohorts (Figure 1), [3,9] whose absence used to define "lone AF". The non-traditional risk factors, and the terminology '' less-established and borderline" are in line with the 2014 ''Lone AF does it exist" paper by Wyse et al. [2]

Patients with missing variables (N=10) or patients with secondary precipitants for AF including acute coronary syndrome, acute pericardial disease, heart failure, infection, or other acute cerebral-, pulmonary- or rheumatic disease, were excluded from the current analysis (Figure 2 and Supplementary Table 1).

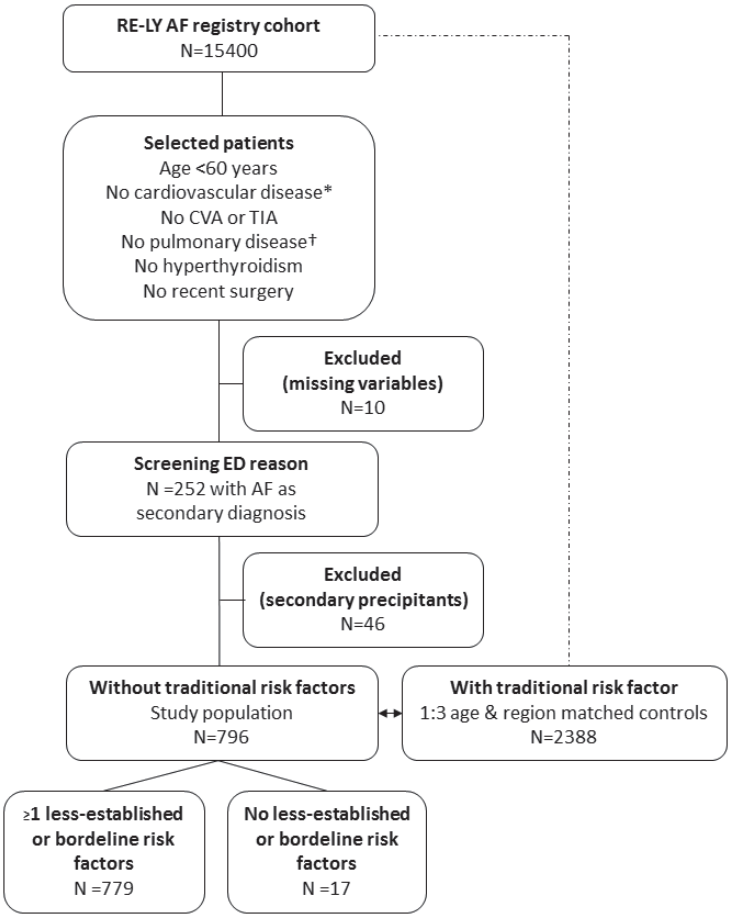

Figure 2. Flowchart

* No myocardial infarction, coronary artery disease, congenital heart disease, heart failure, left ventricular hypertrophy or systolic dysfunction, hypertension, rheumatic heart disease or significant valvular disease.
† Defined as emphysema or chronic obstructive pulmonary disease.
AF denotes atrial fibrillation; CVA, cerebrovascular accident; ED, emergency department; TIA, transient ischemic attack.

We studied the following less-established or borderline risk factors: borderline hypertension (RR 130-140/80-90 mmHg), chronic kidney disease (eGFR<60 ml/min), obesity (body mass index (BMI) >30), diabetes (oral glucose-lowering drugs and/or insulin), excessive alcohol intake (>14 units/week), smoking, and sleep apnoea (Figure 1).[2] Our aim was to examine patient characteristics, study prevalence of less-established or borderline risk factors, and assess outcome. We compared patients without traditional risk factors to age- and region-matched controls with traditional risk factors (1:3 fashion) from the RE-LY AF Registry.[10,11] Additionally, regional comparisons were performed to provide a global overview of region-specific differences.

Follow-up

Patients were assessed one year after attending the emergency department. The visit occurred either in-person or consisted of a telephone call. The validated questionnaire for the verification of stroke-free status was administered to all patients. Additional required information was collected from medical records and contact with treating physicians. Clinical data were collected on the endpoints death, stroke, major bleeding and systemic embolism, as well as admission to hospital for heart failure, myocardial infarction, AF or AFL. Data were collected on treatment of AF during follow-up including cardioversion, ablation, and rate and rhythm control therapy.

Statistical analysis

Baseline characteristics of patients without traditional risk factors and 1:3 matched subset of patients with traditional risk factors are shown for both groups overall and for the different regions. Patients from North America, Western Europe, and Australia were used as the reference population for comparison with patients from South America, Eastern Europe, the Middle East and Mediterranean crescent (including North Africa and Turkey), Sub-Saharan Africa, India, China, and Southeast Asia (participating countries by region were previously published).[10] Data are presented as mean (SD) and median (IQR) for continuous variables and frequency (percentage) for categorical variables. Differences between patients were evaluated by the Student *t* test and the Mann-Whitney U test, depending on normality of the data. Chi-square and Fisher's exact test were used for comparison of categorical variables. Comparisons between the regions, with North America, Western Europe and Australia as the reference group, were performed using an ANOVA or Kruskal-Wallis test for continuous variables and using Pearson's χ^2 test or Fisher's exact test for categorical variables. Outcomes were compared using logistic regression models with relative risk (RR) and 95% confidence interval (CI) reported. Models were subsequently adjusted for: sex, chronic kidney disease, diabetes mellitus, and anticoagulation/antiplatelet therapy, including warfarin, vitamin K antagonist or aspirin. The two-sided significance level was set at 0.005 to

adjust for multiple comparisons. All statistical analyses were performed using SAS 9.4 for UNIX (SAS Institute Inc., Cary, North Carolina).

RESULTS

Patient characteristics

Of the 15,400 patients enrolled in the RE-LY AF registry, 796 (5%) did not have traditionally-defined risk factors (Figure 2). Prevalence differed between the regions: ranging from 2% in Eastern Europe to 15% in the Middle East. Baseline characteristics are summarized in Table 1 for patients without and with traditional risk factors. Average age of patients without traditional risk factors was 45.7±10.1 years, and 74% were men. Compared to patients with traditional risk factors, patients without traditional risk factors were taller, weighed more, were more likely to be men, and had slightly better kidney function (Table 1).

The most common less-established or borderline risk factors were borderline hypertension (130-140/80-90 mmHg; 47%), chronic kidney disease (eGFR<60 ml/min; 57%), obesity (BMI >30 kg/m^2; 19%), and smoking (25%). (Table 1) In total 779 of 796 (98%) patients had one or more less-established or borderline risk factors. Less-established or borderline risk factors were present in a comparable or lower number in patients with traditional risk factors (Table 1).

Among patients without traditional risk factors, the prevalence of specific less-established or borderline risk factors differed between regions (Table 1). In North America and Western Europe obesity was common (30%), and in the Middle East, both obesity (25%) and diabetes mellitus (11%) were frequent. In Eastern Europe borderline hypertension (65%), excessive alcohol intake (8%), and smoking (38%) were often found. In South America (83%) and India (94%), high percentages of chronic kidney disease were observed, and in Africa 22% of patients used large amounts of alcohol.

Type and treatment of atrial fibrillation

Patients without traditional risk factors more often had paroxysmal AF (55% versus 37%, P<0.001), and were more likely to undergo cardioversion in the emergency department, either spontaneously or through electrical or chemical cardioversion (P<0.001) (Supplementary Table 2.1). Fewer patients without traditional risk factors left the emergency department in AF compared to patients with traditional risk factors (54% versus 77%, P<0.001). Patients without traditional risk factors received less medications, including anticoagulation, antiarrhythmic drugs, beta-blockade, and diuretics (all P<0.001) (Supplementary Table 2.1).

Table 1. Baseline characteristics in patients without and with traditional risk factors

	Overall	North America, Western Europe, and Australia	South America	Eastern Europe	Middle East	Africa	India	China	Southeast Asia	P-value†
AF without traditional risk factors - %	5.2%	7.5%	4.6%	1.5%	14.9%	3.2%	3.2%	4.5%	6.2%	
Number (matched 1:3)										
without traditional risk factors	796	286	52	37	132	36	80	90	83	
with traditional risk factors	2388	648	150	127	280	234	466	279	204	
Demographics										
Age - years (SD)										
without traditional risk factors	45.7±10.1	47.6±9.4	45.4±9.6	48.1±9.5	41.2±10.3*	43.3±11.8	45.5±9.6	45.3±10.8	47.2±9.5	<0.001
with traditional risk factors	46.4±11.9	54.3±7.3	49.2±8.7*	48.2±8.3*	46.5±9.3*	32.4±14.5	38.2±11.4	48.1±7.7	50.7±6.9	<0.001
Male (%)										
without traditional risk factors	588 (73.9)§	227 (79.4)	38 (73.1)	30 (81.1)	106 (80.3)	24 (66.7)	46 (57.5)*	59 (65.6)	58 (69.9)	0.001
with traditional risk factors	1410 (59.0)	484 (74.7)	97 (64.7)	94 (74.0)	177 (63.2)	96 (41.0)	203 (43.6)	136 (48.7)	123 (60.3)	< 0.001
Height - cm (SD)										
without traditional risk factors	172.4±10.2§	178.0±9.4	172.5±10.1*	177.5±9.1	171.2±7.9*	168.7±7.7*	162.9±8.7*	169.2±7.8*	166.8±9.0*	<0.001
with traditional risk factors	167.9±11.5	176.0±10.0	167.4±10.5*	175.7±8.9	166.1±9.2*	160.9±13.0*	161.7± 9.1*	165.6±8.7*	165.4±9.5*	<0.001
Weight - kg (SD)										
without traditional risk factors	79.6±18.7§	90.4±18.3	78.8±12.5*	84.6±14.8	80.1±17.8*	76.0±19.4*	64.6±12.9*	70.7±11.8*	65.8±12.3*	<0.001
with traditional risk factors	75.8±25.5	98.2±26.3	78.6±18.1*	91.1±20.3*	76.9±19.2*	59.2±20.0*	57.0±13.2*	65.2±14.4*	69.0±15.8*	<0.001
Body mass index - kg/m^2 (SD)										
without traditional risk factors	26.7±5.3	28.6±6.0	26.5±3.9*	26.7±3.2*	27.2±5.3	26.7±7.2	24.3±4.0*	24.6±3.5*	23.5±3.3*	<0.001
with traditional risk factors	26.6±7.4	31.7±8.4	28.0±5.7*	29.5±6.0*	27.9±6.4*	22.5±6.1*	21.7±4.4*	23.6±4.1*	25.4±5.2	<0.001

Table 1. Baseline characteristics in patients without and with traditional risk factors (continued)

	Overall	North America, Western Europe, and Australia	South America	Eastern Europe	Middle East	Africa	India	China	Southeast Asia	P-value†
eGFR - ml/min*1.73m^2 (SD)										
without traditional risk factors	87.9±27.0§	87.9±25.4	66.2±20.0*	83.1±20.8	87.0±22.7	86.4±29.2	62.1±24.9	88.9±25.7	100.8±32.8	<0.001
with traditional risk factors	80.0±55.5	80.7±54.2	66.7±22.2	83.7±24.3	750±32.3	86.8±54.0	61.5±21.3*	79.4±29.6	81.0±37.8	0.230
Blood pressure - mmHg (SD)										
▪ Systolic										
without traditional risk factors	125±20	130±21	120±18*	122±15	123±20*	115±16*	119±17*	122±21*	125±18	<0.001
with traditional risk factors	126±23	133±23	128±25	133±22	129±26	115±21*	119±19*	121±22*	129±21	<0.001
▪ Diastolic										
without traditional risk factors	79±14	84±15	77±13*	77±8*	77±14*	73±12*	77±11*	77±13*	76±12*	<0.001
with traditional risk factors	80±15	84±17	81±16	84±12	81±17	75±16*	77±11*	78±15*	78±16*	<0.001
Prior diagnosis of AF (%)										
without traditional risk factors	375 (47.1)§	159 (55.6)	25 (48.1)	28 (75.7)	35 (26.5)*	6 (16.7)*	25 (31.3)*	57 (63.3)	40 (48.2)	<0.001
with traditional risk factors	1428 (59.8)	435 (67.1)	101 (67.3)	90 (70.9)	152 (54.3)*	103 (44.0)*	195 (41.8*	220 (78.9)*	132 (64.7)	<0.001
AF type (%)										
▪ Paroxysmal										
without traditional risk factors	440 (55.3)§	175 (61.2)	18 (34.6)*	13 (35.1)*	70 (53.0)	18 (50.0)	43 (53.8)	44 (48.9)	59 (71.1)	<0.001
with traditional risk factors	887 (37.2)	331 (51.2)	26 (17.3)*	48 (37.8)	68 (24.3)*	26 (11.1)*	202 (43.3)	89 (31.9)*	97 (47.5)	<0.001
▪ Persistent										
without traditional risk factors	268 (33.7)§	99 (34.6)	26 (50.0)	20 (54.1)	42 (31.8)	8 (22.2)	28 (35.0)	33 (36.7)	12 (14.5)*	<0.001
with traditional risk factors	636 (26.6)	205 (31.7)	59 (39.3)	44 (34.6)	48 (17.1)*	42 (17.9)*	124 (26.6)	66 (23.7)	48 (23.5)	<0.001
▪ Permanent										
without traditional risk factors	88 (11.1)§	12 (4.2)	8 (15.4)	4 (10.8)	20 (15.2)*	10 (27.8)*	9 (11.3)	13 (14.4)*	12 (14.5)*	<0.001‡
with traditional risk factors	864 (36.2)	111 (17.2)	65 (43.3)*	35 (27.6)	164 (58.6)*	166 (70.9)*	140 (30.0)*	124 (44.4)*	59 (28.9)*	<0.001

Table 1. Baseline characteristics in patients without and with traditional risk factors (continued)

	Overall	North America, Western Europe, and Australia	South America	Eastern Europe	Middle East	Africa	India	China	Southeast Asia	P-value†
Reason for initial ED visit (%)										
▪ Atrial Fibrillation										
without traditional risk factors	590 (74.1)§	207 (72.4)	45 (86.5)	32 (86.5)	108 (81.8)	20 (55.6)	52 (65.0)	75 (83.3)	51 (61.4)	<0.001
with traditional risk factors	1178 (49.3)	390 (60.2)	86 (57.3)	89 (70.1)	120 (42.9)*	63 (26.9)*	238 (51.1)*	109 (30.1)*	83 (40.7)*	<0.001
Less - established or borderline risk factors (%)										
Borderline hypertension (130 - 140/80 - 90 mmHg)										
without traditional risk factors	372 (46.8)	134 (46.9)	25 (48.1)	24 (64.9)	64 (48.5)	15 (41.7)	41 (51.9)	34 (37.8)	35 (42.2)	0.194
with traditional risk factors	1040 (43.7)	279 (43.1)	70 (47.0)	85 (66.9)*	94 (33.6)	77 (33.)	227 (49.1)	125 (45.0)	83 (40.7)	<0.001
Chronic kidney disease (eGFR<60)										
without traditional risk factors	456 (57.3)§	162 (56.6)	43 (82.7)*	29 (78.4)	48 (36.4)*	20 (55.6)	75 (93.8)*	48 (53.3)	31 (37.3)*	<0.001
with traditional risk factors	1563 (65.5)	355 (54.8)	115 (76.7)*	102 (80.3)*	121 (43.2)*	155 (66.2)*	449 (96.4)	192 (68.8)*	74 (36.3)*	<0.001
Obesity (body mass index>30)										
without traditional risk factors	153 (19.2)§	85 (29.7)	9 (17.3)	4 (10.8)	33 (25.0)	8 (22.2)	6 (7.5)*	5 (5.6)*	3 (3.6)*	<0.001
with traditional risk factors	566 (23.7)	309 (47.4)	47 (31.3)*	50 (39.4)	81 (28.9)*	19 (8.1)*	10 (2.1)*	19 (6.8)*	31 (15.2)*	<0.001
Diabetes mellitus										
without traditional risk factors	36 (4.5)§	8 (2.8)	0 (-)	0 (-)	14 (10.6)*	2 (5.6)	6 (7.5)	3 (3.3)	3 (3.6)	0.011‡
with traditional risk factors	378 (15.8)	132 (20.4)	24 (16.0)	21 (16.5)	75 (26.8)	13 (5.6)*	33 (7.1)*	28 (10.0)*	52 (25.5)	<0.001
Excessive alcohol intake (>14/ week)										
without traditional risk factors	31 (3.9)	18 (6.3)	0 (-)	3 (8.1)	0 (-)*	8 (22.2)*	0 (-)	2 (2.2)	0 (-)	<0.001‡
with traditional risk factors	62 (2.6)	43 (6.6)	2 (1.3)	5 (3.9)	1 (0.4)*	2 (0.9)*	1 (0.2)*	4 (1.4)*	4 (2.0)	<0.001‡
Smoking										
without traditional risk factors	197 (24.7)	65 (22.7)	14 (26.9)	14 (37.8)	42 (31.8)	8 (22.2)	6 (7.5)*	20 (22.2)	28 (33.7)	<0.001

Table 1. Baseline characteristics in patients without and with traditional risk factors (continued)

	Overall	North America, Western Europe, and Australia	South America	Eastern Europe	Middle East	Africa	India	China	Southeast Asia	P-value†
with traditional risk factors	519 (21.7)	184 (28.4)	29 (19.3)	41 (32.3)	77 (27.5)	19 (8.1)*	29 (6.2)*	81 (29.0)	59 (28.9)	<0.001
Sleep apnoea										
without traditional risk factors	15 (1.9)§	8 (2.8)	1 (1.9)	2 (5.4)	2 (1.5)	0 (-)	0 (-)	2 (2.2)	0 (-)	0.371‡
with traditional risk factors	146 (6.1)	93 (14.4)	7 (4.7)*	11 (8.7)	9 (3.2)*	0 (-)*	4 (0.9)*	20 (7.2)*	2 (1.0)*	<0..001

* Significantly different from North America/Western Europe, P<0.005. § Significantly different, P<0.01 between patients with and without traditional risk factors. † P-value is from the test of null hypothesis that there is no difference among regions, using ANOVA test for mean age, Kruskal Wallis test for median age and Chi-square test or Monte Carlo estimates of Fisher's exact test for categorical variables. ‡ Exact P-value was estimated by Monte Carlo simulation with 100,000 samples.
AF denotes atrial fibrillation; ED, emergency department; IQR, interquartile range; LVH, left ventricular hypertrophy; SD, standard deviation.

They experienced more AF recurrences (28% versus 21%, P<0.001), but AF persistence was less pronounced after 1-year (21% versus 49%, P<0.001) (Supplementary Table 3.1).

Outcomes

Complete one-year follow-up was available for 793 (99.6%) patients without traditional risk factors and 2374 (99.4%) patients with traditional risk factors (Table 2). Patients without traditional risk factors suffered less strokes (5 [0.6%] versus 48 [2%]; RR 0.31 [95% CI, 0.12-0.78, P=0.013]) and had a lower all-cause mortality within 1 year of initial emergency department visit (13 patients [1.6%] versus 165 [7%]; RR 0.24 [95% CI, 0.14-0.41, P<0.001]). Reasons for death in patients without traditional risk factors included: cancer (N=5), unknown (N=4), heart failure (N=3), and sudden cardiac death (N=1). Patients with traditional risk factors were more frequently hospitalized for heart failure (13% versus 0.9%, P<0.001). Hospitalizations for AF occurred often in both groups (18% in patients without versus 21% in patients with traditional risk factors, P=0.09). The highest rate of repeat hospital visits for AF was in North America and Western Europe (27%) (Supplementary Table 4). Adjustments for sex, chronic kidney disease, diabetes mellitus and anticoagulation use did not affect the observation of increased death, stroke, and heart failure hospitalization risk in patients with traditional risk factors (Table 2).

Table 2. Outcomes of patients without traditional risk factors compared to age and region-matched patients with traditional risk factors

	Overall	Without traditional risk factors	With traditional risk factors	Unadjusted		Adjusted*	
				RR (95% CI)	*P-value*	*RR (95% CI)*	*P-value*
No. complete follow-up visit	3167	793	2374				
MACCE	235 (7.4)	18 (2.3)	217 (9.1)	0.25 (0.15-0.40)	<0.001	0.26 (0.16-0.43)	<0.001
▪ Death	178 (5.6)	13 (1.6)	165 (7.0)	0.24 (0.14-0.41)	<0.001	0.25 (0.14-0.44)	<0.001
▪ Stroke	53 (1.7)	5 (0.6)	48 (2.0)	0.31 (0.12-0.78)	0.013	0.35 (0.14-0.89)	0.027
▪ Systemic embolism	12 (0.4)	0 (0.0)	12 (0.5)	0.00 (-)	1.000	0.00 (-)	1.000
▪ Major bleeding	33 (1.0)	3 (0.4)	30 (1.3)	0.30 (0.09-0.98)	0.046	0.41 (0.12-1.39)	0.154
Hospitalization	814 (25.7)	146 (18.4)	668 (28.1)	0.66 (0.56-0.77)	<0.001	0.72 (0.61-0.85)	<0.001
▪ Hospitalization for heart failure	303 (9.6)	7 (0.9)	296 (12.5)	0.07 (0.03-0.15)	<0.001	0.08 (0.04-0.17)	<0.001
▪ Hospitalization for MI	23 (0.7)	2 (0.3)	21 (0.9)	0.29 (0.07-1.22)	0.090	0.36 (0.08-1.62)	0.184
▪ Hospitalization for AF	630 (19.9)	141(17.8)	489 (20.6)	0.87 (0.73-1.02)	0.093	0.94 (0.79-1.13)	0.529

All values are depicted as number (%) unless stated otherwise. Matching conducted 1:3 on age and region.

*Adjusted for sex, chronic kidney disease, diabetes mellitus, and anticoagulation use.

AF denotes atrial fibrillation; IQR, intra-quartile range; MACCE, major adverse cardiac and cerebrovascular event; MI, myocardial infarction; SD, standard deviation.

DISCUSSION

This observational study shows that almost all patients presenting to the emergency department without traditionally-defined AF risk factors have less-established or borderline risk factors upon closer examination. These patients without traditional risk factors have predominantly paroxysmal episodes, less AF persistence, and a low 1-year risk of death, stroke and heart failure hospitalizations (Figure 3). Nevertheless, their risk of AF-related re-hospitalization is high; with nearly one fifth returning to the emergency department within one year. Recognition and management of these non-traditional risk could help improve patient outcomes.[13]

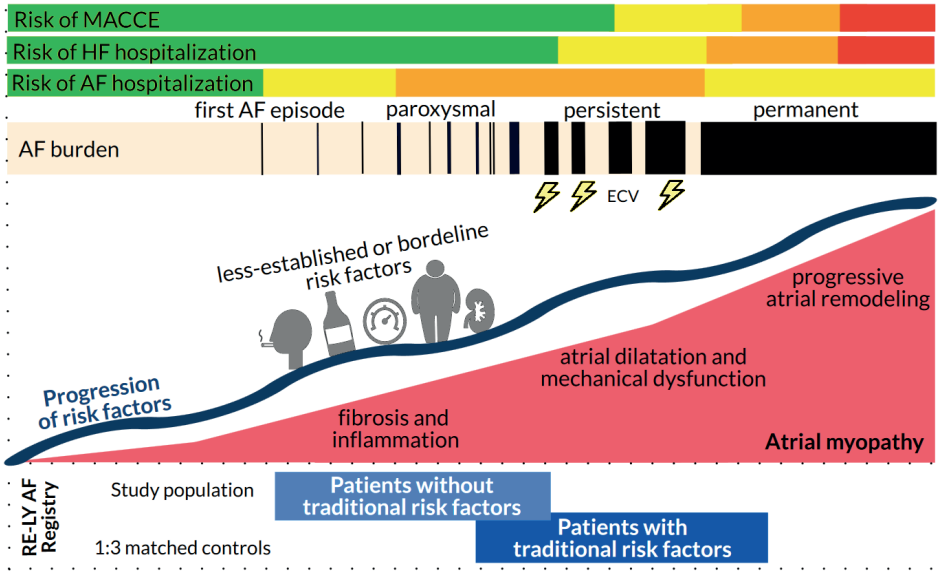

Figure 3. Take home figure

In the RE-LY AF registry, patients without traditional risk factors seemed to have less severe AF, with more paroxysmal AF (55% versus 37%, P<0.001) and less AF persistence (21% versus 49%, P<0.001) compared to matched controls with traditional risk factors. Additionally, their risk of heart failure hospitalizations (0.9% versus 12.5%) and major adverse cardiac or cerebrovascular events (MACCE) during 1-year follow up (2.3% versus 9.1%) was low. However, risk of AF-related re-hospitalization was high, almost 18%, similar to patients with traditional risk factors.

The term ''lone AF'' was first used in 1954 to describe patients in whom ''subsequent investigation shows that heart disease is absent''.[1] In the last few decades our understanding of AF pathophysiology and the multitude of systemic aetiologies and risk factors for AF has increased exponentially. We now know that AF without any risk factor is rare.[2] Weijs et al. have shown that in clinical practice almost half of the patients originally diagnosed with idiopathic AF developed cardiovascular diseases within 5 years.[14]

Other long-term follow-up studies corroborate these findings and show that almost all patients develop evident cardiovascular risk factors over time.[14,15] In the Olmsted study all patients who had a cerebrovascular event during long-term follow-up had developed at least one overt risk factor for thromboembolism.[3,9] The high presence of less-established or borderline risk factors in the RELY-AF registry (98% had one or more less- established or borderline risk factors) underscores the rarity of ''lone AF''.[2] In the current population, different profiles of less-established or borderline risk factors existed across the world, with obesity being common in North America and Western Europe; borderline hypertension in the Middle East and Eastern Europe; and chronic kidney disease in South America and India.

AF in the absence of traditional risk factors is often considered a benign disease.[2] We confirm that our large, global AF population without traditional risk factors has a low short-term risk of morbidity and mortality.[7,8,14] This can be explained not only by the lack of cardiovascular conditions in these patients, but also by their young age and low rate of AF persistence,[16,17] as both morbidity and mortality are increased in patients with AF progression.[18] Incident heart failure is common among patients with AF, and many traditional AF risk factors are also independent clinical predictors of heart failure. Additionally, prolongation of AF episodes >24 hours is associated with a higher rate of heart failure hospitalizations, and AF type and increased burden have been found to be associated with a higher risk of ischemic stroke.[19]

Although patients with AF without traditional risk factors had a lower risk of death and cardiovascular events, they had a substantial risk of repeat hospitalizations for AF. This highlights the importance of initial AF management during the emergency department visit, and the importance of appropriate follow-up for further optimization of AF management to prevent recurrent symptoms due to AF. Additionally, prevention of AF progression and management of new risk factors that may develop during follow-up of patients with AF could help to minimize the risk of adverse outcomes, including heart failure hospitalizations (Figure 3).[16,17]

Clinical implications

In all patients presenting with AF without an obvious cardiac cause, a thorough initial search for less-established or borderline risk factors, which vary between geographic regions, is recommended.[4,5,20] In some cases, no risk factors will be present as AF can occur as a primary electrical disease, however in many cases borderline or non-traditional risk factors may be found. These patients seem to have less severe AF and a lower risk of adverse events. However, also these non-traditional risk factors require treatment or

careful follow-up since they may contribute to progression of AF and the occurrence of cardiovascular morbidity and mortality.[13]

Early identification of less-established or borderline risk factors with timely, holistic treatment; targeted, tailored, and adjusted over time according to the individual needs of these patients, may facilitate the maintenance of sinus rhythm and improve cardiovascular outcomes.[13] Given the complexity of AF management and the heterogeneity of patients' risk factor profiles, integrated AF care by a multidisciplinary team in specialized AF clinics is recommended.[4,5,20]

Strengths and limitations

Selection of sites within regions was not random and might have introduced recruitment bias in comparing the regions, making this a convenience sample. Furthermore, our population without traditional risk factors is determined not only by definition, but also by the organization of the healthcare systems, given differences in the extent of the search for underlying factors, and the robustness of diagnostic tools used in the different world regions. It is conceivable that risk factors or other secondary precipitants have been missed. Detailed echocardiographic and ECG data were not collected in this study. Follow up was only one year, which limits the comparison of outcomes with low incidence; including stroke and death. Strengths include the relatively large, matched group of patients and the broad global representation of countries, many of which have never been included in previous registries or clinical trials of patients without traditional risk factors of AF.

CONCLUSION

Almost all patients without traditionally-defined AF risk factors have less-established or borderline risk factors. These patients have a lower burden of AF and a more favourable 1-year prognosis, but their risk of AF-related re-hospitalization remains high. Greater emphasis should be placed on the recognition and management of these AF risk factors, as this could improve patient outcomes.

REFERENCES

1. Evans W, Swann P. Lone auriculair fibrillation. *British heart journal*. 1954; 16: 189-194.
2. Wyse DG, Van Gelder IC, Ellinor PT, et al. Lone atrial fibrillation: does it exist? *J Am Coll Cardiol*. 2014; 63: 1715-1723.
3. Jahangir A, Lee V, Friedman PA, et al. Long-term progression and outcomes with aging in patients with lone atrial fibrillation: a 30-year follow-up study. *Circulation*. 2007; 115: 3050-3056.
4. Lau DH, Nattel S, Kalman JM, Sanders P. Modifiable Risk Factors and Atrial Fibrillation. *Circulation*. 2017; 136: 583-596.
5. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016; 37: 2893-2962.
6. Brand FN, Abbott RD, Kannel WB, Wolf PA. Characteristics and prognosis of lone atrial fibrillation. 30-year follow-up in the Framingham Study. *JAMA*. 1985; 254: 3449-3453.
7. Weijs B, Pisters R, Nieuwlaat R, et al. Idiopathic atrial fibrillation revisited in a large longitudinal clinical cohort. *Europace*. 2012; 14: 184-190.
8. Jouven X, Desnos M, Guerot C, Ducimetiere P. Idiopathic atrial fibrillation as a risk factor for mortality. The Paris Prospective Study I. *Eur Heart J*. 1999; 20: 896-899.
9. Kopecky SL, Gersh BJ, McGoon MD, et al. The natural history of lone atrial fibrillation. A population-based study over three decades. *N Engl J Med*. 1987; 317: 669-674.
10. Oldgren J, Healey JS, Ezekowitz M, et al. Variations in cause and management of atrial fibrillation in a prospective registry of 15,400 emergency department patients in 46 countries: the RE-LY Atrial Fibrillation Registry. *Circulation*. 2014; 129: 1568-1576.
11. Healey JS, Oldgren J, Ezekowitz M, et al. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. *Lancet*. 2016; 388: 1161-1169.
12. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. *Nat Rev Cardiol*. 2016; 13: 501.
13. Rienstra M, Hobbelt AH, Alings M, et al. Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial. *Eur Heart J*. 2018; .
14. Weijs B, de Vos CB, Tieleman RG, et al. The occurrence of cardiovascular disease during 5-year follow-up in patients with idiopathic atrial fibrillation. *Europace*. 2013; 15: 18-23.
15. Katritsis DG, Toumpoulis IK, Giazitzoglou E, et al. Latent arterial hypertension in apparently lone atrial fibrillation. *J Interv Card Electrophysiol*. 2005; 13: 203-207.
16. Rienstra M, Van Gelder IC, Hagens VE, Veeger NJ, Van Veldhuisen DJ, Crijns HJ. Mending the rhythm does not improve prognosis in patients with persistent atrial fibrillation: a subanalysis of the RACE study. *Eur Heart J*. 2006; 27: 357-364.
17. Chamberlain AM, Alonso A, Gersh BJ, et al. Multimorbidity and the risk of hospitalization and death in atrial fibrillation: A population-based study. *Am Heart J*. 2017; 185: 74-84.
18. De With RR, Marcos EG, Van Gelder IC, Rienstra M. Atrial fibrillation progression and outcome in patients with young-onset atrial fibrillation. *Europace*. 2018; 20: 1750-1757.
19. Ganesan AN, Chew DP, Hartshorne T, et al. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *Eur Heart J*. 2016; 37: 1591-1602.
20. Mahajan R, Pathak RK, Thiyagarajah A, et al. Risk Factor Management and Atrial Fibrillation Clinics: Saving the Best for Last? *Heart Lung Circ*. 2017; 9: 990-997.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Secondary precipitants for AF

Secondary precipitants	Number
Acute coronary syndrome / arrest	13
Pericarditis / pericardial effusion*	6
Acute pulmonary oedema	2
Cerebrovascular accident	4
Aortic rupture	1
Heart failure	14
Hypertension	1
ICD shock	1
Myocarditis	1
Rheumatic heart disease	3

*HIV and tuberculosis associated pericarditis occurred in Africa.
HIV denotes human immunodeficiency virus; ICD, implantable cardiac defibrillator.

Supplementary Table 2.1. Emergency department management in patients without and with traditional risk factors

	Without traditional risk factors	With traditional risk factors	P-value
ED management			
Cardioversion in ED			
▪ Electrical	101 (12.7)	144 (6.0)	<0.001*
▪ Chemical	179 (22.5)	267 (11.2)	
▪ Spontaneous	122 (15.3)	186 (7.8)	
▪ None	394 (49.5)	1791 (75.0)	
Patient in AF at ED discharge	432 (54.3)	1842 (77.1)	<0.001
Medication after ED discharge			
Acetylsalicylic acid	353 (44.3)	968 (40.5)	0.059
Clopidogrel	33 (4.1)	188 (7.9)	<0.001
Warfarin	131 (16.5)	911 (38.1)	<0.001
Other vitamin K-antagonist†	84 (10.6)	432 (18.1)	<0.001
Diuretics	87 (10.9)	1321 (55.3)	<0.001
ACE-inhibitor	58 (7.3)	789 (33.0)	<0.001
ARB	26 (3.3)	275 (11.5)	<0.001
Beta-blocker	372 (46.7)	1347 (56.4)	<0.001
Verapamil/diltiazem	99 (12.4)	367 (15.4)	0.043
Digoxin	101 (12.7)	955 (40.0)	<0.001
Amiodarone	97 (12.2)	383 (16.0)	0.009
Flecainide	33 (4.1)	43 (1.8)	<0.001
Propafenone	53 (6.7)	64 (2.7)	<0.001
Sotalol	36 (4.5)	81 (3.4)	0.142
Statin	79 (9.9)	574 (24.0)	<0.001

All values are depicted as number (%).
* An overall P-value for all groups (Type 3 test).
†Acenocoumarol or Phenprocoumon.
ACE-inhibitor denotes angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; ED, emergency department.

Supplementary Table 2.2. Emergency department management of patients without traditional risk factors in different regions

	Patients without traditional risk factors	North America, Western Europe, and Australia	South America	Eastern Europe	Middle East	Africa	India	China	Southeast Asia	P-value†
ED management										
Cardioversion in ED										
▪ Electrical	101 (12.7)	66 (23.1)	10 (19.2)	9 (24.3)	7 (5.3)*	4 (11.1)	3 (3.8)*	1 (1.1)*	1 (1.2)*	<0.001‡
▪ Chemical	179 (22.5)	37 (12.9)	24 (46.2)*	4 (10.8)	47 (35.6)*	3 (8.3)	15 (18.8)	34 (37.8)*	15 (18.1)	<0.001
▪ Spontaneous	122 (15.3)	53 (18.5)	5 (9.6)	7 (18.9)	18 (13.6)	9 (25.0)	2 (2.5)*	11 (12.2)	17 (20.5)	0.007
▪ None	394 (49.5)	130 (45.5)	13 (25.0)	17 (45.9)	60 (45.5)	20 (55.6)	60 (75.0)*	44 (48.9)	50 (60.2)	<0.001
Patient in AF at ED discharge	432 (54.3)	139 (48.6)	28 (53.8)	20 (54.1)	68 (51.5)	22 (61.1)	61 (76.3)*	42 (46.7)	52 (62.7)	<0.001
Medication after ED discharge										
Acetylsalicylic acid	353 (44.3)	126 (44.1)	29 (55.8)	9 (24.3)	81 (61.4)*	10 (27.8)	27 (33.8)	37 (41.1)	34 (41.0)	<0.001
Clopidogrel	33 (4.1)	6 (2.1)	1 (1.9)	0 (-)	5 (3.8)	0 (-)	13 (16.3)*	3 (3.3)	5 (6.0)	<0.001‡
Warfarin	131 (16.5)	56 (19.6)	6 (11.5)	12 (32.4)	25 (18.9)	3 (8.3)	7 (8.8)	8 (8.9)	14 (16.9)	0.007
Other vitamin K-antagonist °	84 (10.6)	42 (14.7)	2 (3.8)	13 (35.1)*	4 (3.0)*	4 (11.1)	14 (17.5)	1 (1.1)*	4 (4.8)	<0.001‡
Diuretics	87 (10.9)	17 (5.9)	7 (13.5)	3 (8.1)	9 (6.8)	6 (16.7)	32 (40.0)*	7 (7.8)	6 (7.2)	<0.001‡
ACE-inhibitor	58 (7.3)	22 (7.7)	4 (7.7)	4 (10.8)	10 (7.6)	2 (5.6)	10 (12.5)	3 (3.3)	3 (3.6)	0.329‡
ARB	26 (3.3)	3 (1.0)	2 (3.8)	1 (2.7)	6 (4.5)	0 (-)	3 (3.8)	5 (5.6)	6 (7.2)	0.045‡
Beta-blocker	372 (46.7)	139 (48.6)	16 (30.8)	24 (64.9)	87 (65.9)*	13 (36.1)	32 (40.0)	36 (40.0)	25 (30.1)*	<0.001
Verapamil/diltiazem	99 (12.4)	55 (19.2)	3 (5.8)	0 (-)*	6 (4.5)*	2 (5.6)	21 (26.3)	3 (3.3)*	9 (10.8)	<0.001‡
Digoxin	101 (12.7)	19 (6.6)	5 (9.6)	4 (10.8)	13 (9.8)	9 (25.0)*	30 (37.5)*	9 (10.0)	12 (14.5)	<0.001‡
Amiodarone	97 (12.2)	11 (3.8)	18 (34.6)*	7 (18.9)*	9 (6.8)	6 (16.7)	19 (23.8)*	10 (11.1)	17 (20.5)*	<0.001‡
Flecainide	33 (4.1)	27 (9.4)	0 (-)	0 (-)	0 (-)*	3 (8.3)	0 (-)*	0 (-)*	3 (3.6)	<0.001‡

Supplementary Table 2.2. Emergency department management of patients without traditional risk factors in different regions (continued)

	Patients without traditional risk factors	North America, Western Europe, and Australia	South America	Eastern Europe	Middle East	Africa	India	China	Southeast Asia	P-value†
Propafenone	53 (6.7)	12 (4.2)	6 (11.5)	7 (18.9)*	15 (11.4)	0 (-)	0 (-)	2 (2.2)	11 (13.3)*	<0.001‡
Sotalol	36 (4.5)	24 (8.4)	1 (1.9)	4 (10.8)	2 (1.5)	4 (11.1)	0 (-)	0 (-)*	1 (1.2)	<0.001‡
Statin	79 (9.9)	26 (9.1)	5 (9.6)	10 (27.0)*	14 (10.6)	0 (-)	11 (13.8)	6 (6.7)	7 (8.4)	0.016‡

All values are depicted as number (%).

* Significantly different from North America/Western Europe, P<0.005.

° Acenocoumarol or Phenprocoumon.

† P-value is from the test of null hypothesis that there is no difference among regions, using ANOVA test for mean age, Kruskal Wallis test for median age and Chi-square test or Monte Carlo estimates of Fisher's exact test for categorical variables.

‡ Exact P-value was estimated by Monte Carlo simulation with 100,000 samples.

ACE-inhibitor denotes angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; ED, emergency department.

Supplementary Table 3.1. AF presence, treatment and medication during 1-year follow-up in patients without and with traditional risk factors

	Without traditional risk factors	With traditional risk factors	P-value
AF recurrence	224 (28.1)	499 (20.9)	<0.001
AF persistence	170 (21.4)	1157 (48.5)	<0.001
Anti-arrhythmic drugs	213 (26.8)	507 (21.2)	0.002
Rate control drugs	374 (47.0)	1742 (72.9)	<0.001
Acetylsalicylic acid	308 (38.7)	873 (36.6)	0.338
Anticoagulation use: Warfarin	111 (13.9)	856 (35.8)	<0.001
Anticoagulation use: Other	52 (6.5)	313 (13.1)	<0.001
Evaluated by a specialist	515 (64.7)	1712 (71.7)	<0.001
▪ Cardiologist	409 (51.4)	1473 (61.7)	<0.001
▪ Electrophysiologist	92 (11.6)	172 (7.2)	<0.001
▪ Internist	28 (3.5)	123 (5.2)	0.167
Procedures since enrolment			
▪ Cardioversion	107 (13.4)	257 (10.8)	0.040
▪ AF ablation	51 (6.4)	101 (4.2)	0.013
▪ AV node ablation	6 (0.8)	14 (0.6)	0.604
▪ PM or ICD	10 (1.3)	53 (2.2)	0.091

All values are depicted as number (%).
AF denotes atrial fibrillation; AV, atrioventricular; ICD, implantable cardiac defibrillator; PM, pacemaker.

Supplementary Table 3.2. AF presence, treatment and medication during 1-year follow-up of patients without traditional risk factors in different regions

	Patients without traditional risk factors	North America, Western Europe, and Australia	South America	Eastern Europe	Middle East	Africa	India	China	Southeast Asia	P-value†
AF recurrence	224 (29.0)	122 (43.4)	9 (18.4)*	16 (43.2)	12 (9.3)*	10 (29.4)	8 (10.8)*	28 (32.2)	19 (23.5)*	<0.001
AF persistence	170 (22.0)	41 (14.6)	9 (18.4)	9 (24.3)	23 (17.8)	10 (29.4)	31 (41.9)*	28 (32.2)*	19 (23.5)	<0.001
Anti-arrhythmic drugs	213 (27.5)	102 (36.0)	19 (38.8)	19 (51.4)	6 (4.7)*	6 (17.6)	17 (23.0)	16 (18.4)*	28 (34.6)	<0.001
Rate control drugs	374 (48.4)	146 (51.8)	13 (26.5)*	17 (45.9)	73 (56.6)	14 (41.2)	43 (58.1)	31 (35.6)	37 (45.7)	0.001
Acetylsalicylic acid	308 (39.8)	125 (44.3)	14 (28.6)	10 (27.0)	70 (54.3)	10 (29.4)	20 (27.0)	29 (33.3)	30 (37.0)	<0.001
Anticoagulation use: Warfarin	111 (14.4)	47 (16.7)	2 (4.1)	5 (13.5)	18 (14.0)	4 (11.8)	8 (10.8)	6 (6.9)	21 (25.9)	0.008‡
Anticoagulation use: Other	52 (6.7)	29 (10.3)	2 (4.1)	7 (18.9)	3 (2.3)	0 (-)	7 (9.5)	1 (1.1)	3 (3.7)	<0.001‡
Evaluated by a specialist	515 (64.7)	218 (76.2)	37 (71.2)	26 (70.3)	74 (56.1)*	27 (75.0)	29 (36.3)*	42 (46.7)*	62 (74.7)	<0.001
▪ Cardiologist	409 (79.4)	166 (76.1)	23 (62.2)	20 (76.9)	66 (89.2)	23 (85.2)	29 (100.0)*	34 (81.0)	48 (77.4)	0.004
▪ Electrophysiologist	92 (17.9)	62 (28.4)	11 (29.7)	1 (3.8)	0 (-)*	0 (-)*	0 (-)*	4 (9.5)	14 (22.6)	<0.001‡
▪ Internist	28 (5.4)	5 (2.3)	2 (5.4)	5 (19.2)*	8 (10.8)	4 (14.8)	0 (-)	4 (9.5)	0 (-)	<0.001‡
Procedures since enrolment										
▪ Cardioversion	107 (13.4)	61 (21.3)	6 (11.5)	11 (29.7)	11 (8.3)*	4 (11.1)	0 (-)*	6 (6.7)*	8 (9.6)	<0.001‡
▪ AF ablation	51 (6.4)	36 (12.6)	4 (7.7)	4 (10.8)	1 (0.8)*	0 (-)	1 (1.3)*	1 (1.1)*	4 (4.8)	<0.001‡
▪ AV node ablation	6 (0.8)	5 (1.7)	1 (1.9)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0.465‡
▪ PM or ICD	10 (1.3)	4 (1.4)	2 (3.8)	0 (-)	2 (1.5)	0 (-)	0 (-)	2 (2.2)	0 (-)	0.552‡

All values are depicted as number (%).

* Significantly different from North America/Western Europe, p<0.005.

† P-value is from the test of null hypothesis that there is no difference among regions, using ANOVA test for mean age, Kruskal Wallis test for median age and Chi-square test. or Monte Carlo estimates of Fisher's exact test for categorical variables.

‡ Exact P-value was estimated by Monte Carlo simulation with 100,000 samples.

AF denotes atrial fibrillation; ASA, acetylsalicylic acid; AV, atrioventricular; ICD, implantable cardiac defibrillator; PM, pacemaker.

Supplementary Table 4. Outcomes of patients without traditional risk factors by region

	Patients without traditional risk factors	North America, Western Europe, and Australia	South America	Eastern Europe	Middle East	Africa	India	China	Southeast Asia	P-value†
MACCE (%)	18 (2.3)	3 (1.0)	3 (5.8)	0 (-)	2 (1.5)	1 (2.8)	2 (2.5)	3 (3.3)	4 (4.8)	0.160‡
▪ Death	13 (1.6)	2 (0.7)	3 (5.8)	0 (-)	2 (1.5)	1 (2.8)	2 (2.5)	2 (2.2)	1 (1.2)	0.189‡
▪ Stroke	5 (0.6)	1 (0.3)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	1 (1.1)	3 (3.6)	0.133‡
▪ Systemic embolism	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	-
▪ Major bleeding	3 (0.4)	1 (0.3)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	0 (-)	2 (2.4)	0.365‡
Hospitalization (%)	146 (18.3)	80 (28.0)	6 (11.5)	9 (24.3)	11 (8.3)*	6 (16.7)	0 (-)*	17 (18.9)	17 (20.5)	<0.001
▪ For heart failure	7 (0.9)	1 (0.3)	0 (-)	0 (-)	1 (0.8)	3 (8.3)*	0 (-)	1 (1.1)	1 (1.2)	0.026‡
▪ For MI	2 (0.3)	1 (0.3)	0 (-)	0 (-)	0 (-)	1 (2.8)	0 (-)	0 (-)	0 (-)	0.338‡
▪ For AF	141 (17.7)	78 (27.3)	6 (11.5)	9 (24.3)	10 (7.6)*	4 (11.1)	0 (-)*	17 (18.9)	17 (20.5)	<0.001
No. of hosp. in last year, mean (SD)	1.2±1.3	2.0±1.4	1.0±0.0*	1.6±1.3	1.6±0.7	2.8±1.0	-	1.9±1.3	1.3±0.8	<0.001

* Significantly different from North America/Western Europe, p<0.005.

† P-value is from the test of null hypothesis that there is no difference among regions, using ANOVA test for mean age, Kruskal Wallis test for median age and Chi-square test or Monte Carlo estimates of Fisher's exact test for categorical variables.

‡ Exact P-value was estimated by Monte Carlo simulation with 100,000 samples.

AF denotes atrial fibrillation; MI, myocardial infarction; MACCE, major adverse cardiovascular or cerebral event including death, stroke, systemic embolism or major bleeding; SD, standard deviation.