

Kloosterman et al . Atrial Fibrillation without Traditional Risk Factors: RE-LY AF registry analysis

## SUPPLEMENTARY MATERIALS

### Supplementary Table 1. Secondary precipitants for AF

Acute coronary syndrome / arrest	13
Pericarditis / Pericardial effusion (HIV and Tuberculosis*)	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, human immunodeficiency virus; ICD, implantable cardiac defibrillator. \*HIV and Tuberculosis associated pericarditis occurred in Africa.

**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
<b>ED management</b>			
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
<b>Medication after ED discharge (%)</b>			
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

\* 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†
<b>ED management</b>										
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
<b>Medication after ED discharge (%)</b>										
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‡

	<b>Patients without traditional risk factors</b>	<b>North America, Western Europe, and Australia</b>	<b>South America</b>	<b>Eastern Europe</b>	<b>Middle East</b>	<b>Africa</b>	<b>India</b>	<b>China</b>	<b>Southeast Asia</b>	<b>P-value†</b>
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‡

\* 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**

	<b>Without traditional risk factors</b>	<b>With traditional risk factors</b>	<b>P-value</b>
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

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‡

\* 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†
<b>MACCE (%)</b>	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‡
<b>Hospitalization (%)</b>	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.