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Twelve-month outcome in patients with stroke and atrial fibrillation not suitable to oral anticoagulant strategy: the WATCH-AF registry

Celine Guidoux,[1] Elena Meseguer,[1] Elodie Ong,[2] Philippa C Lavallée,[1] Cristina Hobeanu,[1] Linsay Monteiro-Tavares,[1] Hugo Charles,[1] Lucie Cabrejo,[1] Anna Martin-Bechet,[1] Ricardo Rigual,[1] Norbert Nighoghossian,[2] Pierre Amarenco [1]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/openhrt-2019-001187).

To cite: Guidoux C, Meseguer E, Ong E, *et al*. Twelve-month outcome in patients with stroke and atrial fibrillation not suitable to oral anticoagulant strategy: the WATCH-AF registry. *Open Heart* 2019;**6**:e001187. doi:10.1136/openhrt-2019-001187

Received 10 October 2019
Revised 7 November 2019
Accepted 18 November 2019

[1]Department of Neurology and Stroke center, Paris Univesity, Paris, France
[2]Department of Neurology and Stroke center, Centre Hospitalier Universitaire de Lyon, Lyon, France

Correspondence to
Dr Pierre Amarenco; pierre.amarenco@aphp.fr

ABSTRACT

Aims Long-term oral anticoagulant (LTOAC) reduces ischaemic stroke recurrences. Because of bleeding history, frailty, cognitive impairment, comorbidities or patient refusal, many cannot be discharged from stroke unit on LTOAC. Proportion and outcome of these patients is not well known.

Methods The Warfarin Aspirin Ten-a inhibitor Cerebral infarction and Haemorrhage and atrial fibrillation (AF) prospective registry enrolled consecutive patients with an acute stroke associated with AF. Scales to evaluate stroke severity, disability, functional independence, cognition, risk of fall, ischaemic and haemorrhagic risk stratification were systematically collected at admission, discharge, 3 and 12 months poststroke. The two main 12-month endpoints were death or dependency (modified Rankin Scale >3) and recurrent stroke.

Results Among 400 patients (370 brain infarctions, 30 brain haemorrhages), 274 were discharged on LTOAC, 31 died before discharge and 95 (24%) were not discharge on anticoagulant (frailty, bedridden or demented, EHRA/ESC contraindication to anticoagulant). Death or dependency and recurrent stroke occurred in 19.8% and 9.9%, respectively, in patient on anticoagulant, and 33.5% and 27.2% in those not on anticoagulant (both p<0.001). Patient not anticoagulated at discharge had a 1.6-fold increase in the risk of death or dependency at 12 months (HR 1.65; 95% CI 1.05 to 2.61; p=0.032) and a 2.5-fold increase in the risk of stroke (HR 2.46; 95% CI 1.36 to 4.44; p=0.003).

Conclusions One-fourth of patients with stroke associated with AF are not discharged on anticoagulation and have a dramatic increase in the risk of death or dependency at 12 months as well as recurrent stroke. Alternative treatments should be trialled in these patients.

INTRODUCTION

Patients admitted to hospital with stroke and atrial fibrillation (AF) (known before or discovered at admission) have a high risk of death, dependency and recurrent stroke.[1–4] The treatment of choice to prevent another ischaemic stroke is a long-term oral anticoagulant strategy.[5 6] However, many of these patients cannot be on oral anticoagulant because of contraindication to long-term oral anticoagulant, comorbidity, frailty, cognitive impairment, severe walking difficulties with frequent falls and patient refusal.[2] The proportion of these patients among patients presenting with a stroke and AF in stroke units is not precisely known.

The risk of death or dependency as well as the risk of recurrent stroke in this group is not well known either. Given that recent alternative treatment to long-term oral anticoagulant has been proposed, such as left atrial appendage closure,[7 8] we designed the Warfarin Aspirin Ten-a inhibitor Cerebral infarction and Haemorrhage and AF (WATCH-AF) prospective registry in which we collected consecutive patients admitted with an acute stroke within 72 hours of symptom onset in two busy stroke centres with thorough evaluation regarding risk stratification (CHA_2DS_2VASc, HAS-BLED, ATRIA scores), stroke severity, disability and functions (NIHSS, Rankin score, independent activity of daily living (IADL), Mini-Mental Status), risk of fall (STRATIFY score) as well as glomerular filtration rate, international normalised ratio (INR) and time in therapeutic range (TTR) while on vitamin K antagonist (VKA) before stroke. Based on these scores, we aimed to evaluate the proportion of patients not on a long-term oral anticoagulant after discharge from the stroke unit and during a 1-year follow-up. We also evaluated the 1-year risk of death or dependency, and of recurrent brain infarction/brain haemorrhage.

Table 1 Baseline characteristics according to treatment groups

	All(n=400)	Dead before discharge (n=31)	LTOAC (n=274)	No LTOAC (n=95)
Age, mean (SD), years	78.7 (11.0)	83.8 (7.2)	78.1 (11.4)	78.7 (10.6)
Men	193 (48.3)	12 (38.7)	122 (44.5)	59 (62.1)
Medical history				
Hypertension	317 (79.3)	20 (64.5)	216 (78.8)	81 (85.3)
Diabetes	87 (21.8)	11 (35.5)	49 (17.9)	27 (28.4)
Dyslipidaemia	168 (42.0)	10 (32.3)	119 (43.4)	39 (41.1)
Former smokers	116 (30.1)	5 (17.2)	83 (31.4)	28 (30.4)
Current smokers	32 (8.3)	1 (3.4)	22 (8.3)	9 (9.8)
Regular alcohol consumption	42 (10.6)	1 (3.7)	29 (10.6)	12 (12.6)
Cerebrovascular disease	89 (22.3)	5 (16.1)	62 (22.7)	22 (23.2)
Coronary artery disease	68 (17.0)	5 (16.1)	42 (15.4)	21 (22.1)
Peripheral artery disease	30 (7.5)	0 (0)	20 (7.3)	10 (10.5)
Congestive heart failure	53 (13.3)	4 (12.9)	32 (11.7)	17 (17.9)
Significant valvular disease or prosthetic heart valves	38 (9.5)	2 (6.5)	31 (11.4)	5 (5.3)
Type of stroke				
TIA	35 (8.8)	0 (0)	28 (10.2)	7 (7.4)
Ischaemic stroke	335 (83.8)	26 (83.9)	240 (87.6)	69 (72.6)
Intracerebral haemorrhage	27 (6.8)	5 (16.1)	5 (1.8)	17 (17.9)
Subdural haematoma	2 (0.5)	0 (0)	1 (0.4)	1 (1.1)
Subarachnoid haemorrhage	1 (0.3)	0 (0)	0 (0)	1 (1.1)
Baseline NIHSS				
0	65 (16.4)	0 (0)	50 (18.5)	15 (15.8)
1–4	111 (28.0)	2 (6.7)	83 (30.6)	26 (27.4)
5–9	76 (19.2)	3 (10.0)	60 (22.1)	13 (13.7)
10–20	102 (25.8)	16 (53.3)	56 (20.7)	30 (31.6)
≥21	42 (10.6)	9 (30.0)	22 (8.1)	11 (11.6)
Examinations				
BMI, mean (SD), kg/m²	25.6 (5.0)	24.9 (4.3)	25.5 (5.0)	26.1 (5.3)
Systolic BP, mean (SD), mm Hg	148.7 (26.0)	145.3 (27.4)	146.0 (23.6)	157.8 (30.3)
Diastolic BP, mean (SD), mm Hg	78.4 (15.6)	76.5 (17.5)	77.6 (14.5)	81.4 (17.7)
Glucose, median (IQR), mg/dL	106.0 (93.0–133.0)	118.0 (107.0–142.0)	104.0 (93.0–129.0)	113.0 (96.0–142.0)
Haemoglobin A1C, median (IQR),%	5.9 (5.6–6.5)	6.1 (5.7–6.9)	5.9 (5.6–6.4)	6.0 (5.6–7.0)
Creatinine, median (IQR) umol/L	86.5 (71.0–110.5)	93.0 (70.0–118.0)	82.0 (70.0–102.0)	92.0 (74.0–119.0)
INR, mean (SD) (patients on VKA only) before baseline	2.3 (0.6)	2.3 (1.0)	2.3 (0.6)	2.3 (0.5)
<2	20 (34.5)	1 (33.3)	13 (36.1)	6 (31.6)
≥2 and ≤3	38 (65.5)	2 (66.7)	23 (63.9)	13 (68.4)
Time-in-therapeutic range (pts on VKA), median % (IQR) before baseline	62.5 (50.0–85.7)	53.6 (50.0–61.9)	62.5 (50.0–100.0)	66.7 (33.3–85.7)
<50%	15 (24.6)	0 (0)	9 (23.7)	6 (31.6)
50%–59%	13 (21.3)	3 (75.0)	8 (21.1)	2 (10.5)
60%–69%	7 (11.5)	1 (25.0)	4 (10.5)	2 (10.5)
≥70%	26 (42.6)	0 (0)	17 (44.7)	9 (47.4)

Continued

Table 1 Continued

	All(n=400)	Dead before discharge (n=31)	LTOAC (n=274)	No LTOAC (n=95)
Glomerular filtration rate, median (IQR), mL/min/1.73²	65.1 (49.3–81.0)	52.4 (37.0–75.4)	67.0 (52.6–83.5)	60.0 (43.4–76.8)
<30	26 (6.5)	4 (12.9)	14 (5.1)	8 (8.4)
30–59	143 (35.8)	13 (41.9)	91 (33.2)	39 (41.1)
≥60	231 (57.8)	14 (45.2)	169 (61.7)	48 (50.5)
NT-BPN, median (IQR), g/L	1512.0 (560.0–3644.0)	4152.0 (2225.5–7564.0)	1499.0 (520.0–3270.0)	1499.5 (497.5–3487.5)
Haemoglobin, mean (SD), g/L	13.4 (1.8)	13.1 (2.0)	13.5 (1.7)	13.3 (2.0)
Medication at discharge				
Antiplatelet	72 (18.1)	–	37 (13.6)	28 (29.5)
Anticoagulant (both long term and very short term)	294 (73.7)	–	244 (89.4)	45 (47.4)*
AVK	44 (15.0)	–	35 (14.3)	8 (17.8)*
NOAC	220 (74.8)	–	186 (76.2)	31 (68.9)*
Anticoagulant+antiplatelet	24 (6.0)	–	19 (7.8)	4 (8.9)*
BP lowering therapy	368 (92.0)	–	255 (93.1)	93 (97.9)
Lipid-lowering therapy	284 (71.0)	–	212 (77.4)	62 (65.3)
Glycaemia lowering therapy	87 (21.8)	–	52 (19.0)	26 (27.4)

* Short-term anticoagulant.
BMI, body mass index; BP, blood pressure; INR, international normalised ratio; LTOAC, long-term oral anticoagulant; NOAC, new oral anticoagulant; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

MATERIAL AND METHODS

Study subjects were consecutive stroke patients with AF admitted to the Bichat Stroke Centre and the Lyon Stroke Unit. Inclusion criteria were ischaemic or haemorrhagical stroke as well as transient ischaemic attack associated with AF hospitalised in both stroke unit within 72 hours of stroke onset. AF could be diagnosed before the stroke, at admission or up to 30 days after the stroke. Inclusions were prospective, consecutive and exhaustive during the accrual period, with verification that all patients with AF have been included. We had no exclusion criteria. Patients were then followed for 1 year. At the time of accrual, these two busy stroke centres had limited access to left atrial appendage closure facilities. Informed consent has been obtained from the subjects (or their legally authorised representative).

Clinical data 1 and 6 months before stroke were recorded, including: prestroke antiarrhythmic and antithrombotic treatments, prestroke AF stroke risk scales (CHA_2DS_2-VASC, ATRIA haemorrhage score, HAS-BLED) and pre-stroke functional scores (Rankin score evaluating disability, IADL- evaluating functional independence and STRATIFY Risk Assessment Tool, evaluating the risk of fall). In case the patient was not under anticoagulant, the treating physician was interviewed to understand the reasons. If the patient was under VKA, prestroke INR values over the 6 months before were collected.

During the hospitalisation, data collected were: clinical demographics at baseline, medical history, antiarrhythmic and antithrombotic treatment. NIHSS was recorded at baseline. MRI was analysed (or CT, in case MRI was not performed). Other diagnostic tests collected were 12-lead ECG, continuous intrahospital cardiac monitoring (telemetry), Holter-EKG, transthoracic and transoesophageal echography, intracranial and extracranial artery assessment. If ischaemic stroke was diagnosed, the underlying causes were graded according to the ASCOD classification.[9 10] In case of haemorrhagic stroke, the aetiology was also recorded, as well as the number and topography of microbleeds. Treatment, including thrombolysis and thrombectomy, other antithrombotic drugs, blood pressure lowering, lipid-lowering and glycaemia lowering drugs, was recorded. NIHSS, modified Rankin Scale (mRS) score, STRATIFY risk assessment tool and MMS were evaluated at discharge.

Based on this assessment and on ESC/EHRA guidelines,[11–13] for each patient, two vascular neurologists (EM, EO, CG, PA and Delphi method) discussed the preventive strategy at discharge. We then defined one group on a long-term oral anticoagulant strategy, one other not on a long-term oral anticoagulant strategy for various reasons (eg, patient refusal, contraindication to long-term oral anticoagulant, comorbidity, frailty, patient bedridden or with severe dementia, history of bleeding precluding a long-term oral anticoagulant strategy or adherence to treatment).

Follow-up was performed at 3 and 12 months by a vascular neurologist (EM, EO, CG, LC and PA) in a face-to-face visit or by phone call, in case the patient could

Table 2 Clinical scores at discharge according to treatment groups: long-term oral anticoagulant strategy (LTOAC) versus not on an LTOAC (no LTOAC)

	All (n=400)	LTOAC (n=274)	No LTOAC (n=95)
Discharge			
Length of stay, days	14.0 (12.7)	13.7 (13.3)	14.8 (10.6)
NIHSS			
0	109 (29.6)	87 (31.8)	22 (23.4)
1–4	141 (38.3)	113 (41.2)	28 (29.8)
5–9	53 (14.4)	35 (12.8)	18 (19.1)
10–20	51 (13.9)	33 (12.0)	18 (19.1)
≥21	14 (3.8)	6 (2.2)	8 (8.5)
RANKIN			
0–1—no disability	141 (35.5)	109 (40.2)	32 (33.7)
2–3—needing some help	132 (33.2)	106 (39.1)	26 (27.4)
4–5—dependent or bedridden	93 (23.4)	56 (20.7)	37 (38.9)
6—death	31 (7.8)	0 (0)	0 (0)
Stratify			
0—low risk of fall	242 (68.0)	182 (68.7)	60 (65.9)
1—moderate risk of fall	81 (22.8)	63 (23.8)	18 (19.8)
≥2—high risk of fall	33 (9.3)	20 (7.5)	13 (14.3)
MMSE			
≥30—cognition normal	23 (13.6)	19 (14.2)	4 (11.4)
25–30—mild cognitive impairment	69 (40.8)	53 (39.6)	16 (45.7)
≤24—moderate to severe cognitive impairment	77 (45.6)	62 (46.3)	15 (42.9)
ASCOD			
Atherothrombosis			
A0—no atherosclerosis	57 (14.2)	42 (15.3)	12 (12.6)
A3—atherosclerosis but not directly causal	177 (44.3)	121 (44.2)	42 (44.2)
A2—ipsilateral atherosclerosis <50%	87 (21.8)	68 (24.8)	13 (13.7)
A1—ipsilateral atherosclerosis >50%	44 (11.0)	35 (12.8)	7 (7.4)
A9—insufficient workup to grade A	35 (8.7)	8 (2.9)	21 (22.1)
Small vessel disease			
S0—no small vessel disease	286 (71.5)	217 (79.2)	48 (50.5)
S30—severe leukoaraiosis, old lacune, microbleed	53 (13.3)	35 (12.8)	16 (16.9)
S2—small deep infarct without old lacunes	8 (2.0)	6 (2.2)	2 (2.1)
S1—small deep infarct with old lacunes	1 (0.2)	1 (0.3)	0 (0)
S9—insufficient workup to grade S	52 (13.0)	15 (5.5)	29 (30.5)
Cardiac disease			
C1—definite cardiac source of embolism	367 (91.7)	265 (96.7)	76 (80.0)
C3—causally unrelated cardiac abnormality	3 (0.8)	2 (0.7)	1 (1.1)
C9—insufficient workup to grade C	30 (7.5)	7 (2.6)	18 (18.9)

NIHSS, National Institute of Health Stroke Scale.

not come to the visit. Current place of residency, rehabilitation facilities, visit to healthcare physician and loss of productivity, if applicable, were recorded. Medication was collected as well as vital signs. Barthel Index, NIHSS, mRS, STRATIFY risk assessment tool and MMSE were performed at 3 and 12-month visits.

Main outcomes were death or dependency, and cerebrovascular recurrence (ischaemic or haemorrhagic); other outcomes were cardiac events, revascularisation procedure, major bleeding, aspiration pneumonia, deep venous thrombosis or pulmonary embolism, left atrial appendage closure and death. These outcomes were

Table 3 Reasons for not being on a long-term oral anticoagulant strategy after discharge (n=95)

Patient refusal	2/95 (2.1)		
Bleeding risk	82/95 (86.3)		
Previous haemorrhage		54/82 (65.8)	
Intracranial			42/54 (77.8)
GI bleed			5/54 (9.3)
ENT			1/54 (1.9)
Respiratory tract			2/54 (3.7)
Superficial/haematoma			3/54 (5.6)
Genitourinary tract			4/54 (7.4)
Chronic anaemia			2/54 (3.7)
Trauma			4/54 (7.4)
Other			2/54 (3.7)
Never bleed but perceived as at increased risk of bleeding		28/82 (34.1)	
Unobservant or perceived as unobservant	1/95 (1.1)		
Uncertainty about patient's ability to understand treatment*	6/95 (6.3)		
Others	17/95 (17.8)		
Chronic alcoholism or drug addiction			0/17 (0.0)
Severe hepatic disease			0/17 (0.0)
Specific contraindication to VKA			0/17 (0.0)
Specific contraindication to NOAC			1/17 (5.8)
Bedridden and cognitive deterioration			16/17 (94.1)

*Cognitive deterioration, low level of education, not French speaking.
ENT, ear, nose, throat; NOAC, new oral anticoagulant; VKA, vitamin K antagonist.

collected during initial hospitalisation, at 3 months and 12 months

Statistical analysis

Quantitative variables were expressed as means (±SD) in case of normal distribution or median (IQR) otherwise. Qualitative variables were expressed as counts (percentage).

Events rates were estimated at 12 months of follow-up from Kaplan-Meier estimates. Cumulative event curves were constructed using the Kaplan-Meier method. The 12-month event rates were compared according to treatment at discharge using the Cox proportional hazard model. For a given endpoint, deaths that were not included in the endpoint were treated as censoring events. Patients with no information at 12 months were treated as censored cases on the basis of the last follow-up available. Patients dead before discharge were not included in this analysis.

Univariate comparison between the primary outcome and brain infarction or brain haemorrhage and patient characteristics (ie, baseline demographics, risk factors, biological factors, main investigation findings and treatments) was done using the Student's t-test for continuous and the X^2 test for qualitative variables. For variables with skewed distributions, Student's t-test was performed using log-transformed values.

All factors associated with the primary endpoint and brain infarction or brain haemorrhage in univariate analysis (at nominal p<0.10) were implemented in a stepwise multiple Cox-regression analysis with an entry and removal values set to 0.10. MMS score, ratio E/Eal, left atrium surface and aortic atheroma ≥4 mm were not considered candidate variables due to the high rate of missing data (>25%). Owing to missing data on glucose, haemoglobin A1C, ejection fraction and pulmonary arterial pressure, multiple imputation of missing values by means of chained equations was done (10 imputed data sets were generated with the use of all patient characteristics described below).

For each imputed data, the complete model (ie, containing all significant factors with a p<0.10) was implemented. Then the 10 estimates coefficients of each variable were combined and the least significant factor was removed from the model. The process was continued until the final model was obtained. The proportional-hazards assumption was verified with the use of Schoenfeld residuals.

All statistical tests were done at the two-tailed α level of 0.05. All statistical analyses were generated using SAS V.9.3 for windows.

RESULTS

Characteristics of patients

A total of 400 patients were enrolled in the WATCH-AF registry. Per protocol, 300 (75%) patients were included at the Bichat Stroke Centre (Paris) between 25 March 2014 and 10 April 2016 and 100 (25%) at the Lyon Stroke Unit between 27 December 2015 and 14 May 2016, and followed 1 year. Baseline characteristics of patients are presented in tables 1 and 2. A total of 370 patients (92.5%) had an ischaemic stroke as qualifying event and 30 patients (7.5%) had haemorrhagic stroke. Overall, the mean age of patients was 79 years (SD, 11). Male represented near half of the population. A large proportion of patients had hypertension (79.3%).

Among patients on VKA before baseline, only 43% of patients had a TTR ≥70%.

Among 400 patients enrolled, 31 patients died before discharge (7.8%), 274 patients belonged to the group on a 'long-term oral anticoagulant therapy' strategy (68.5%), and 95 patients belonged to the group 'not on a long-term oral anticoagulant therapy' strategy (23.8%) for various reasons, mainly contraindications to long-term oral anticoagulant therapy, listed in table 3.

Outcomes

At 12 months, death or dependency occurred in 19.8% of patients on a long-term oral anticoagulant strategy and in

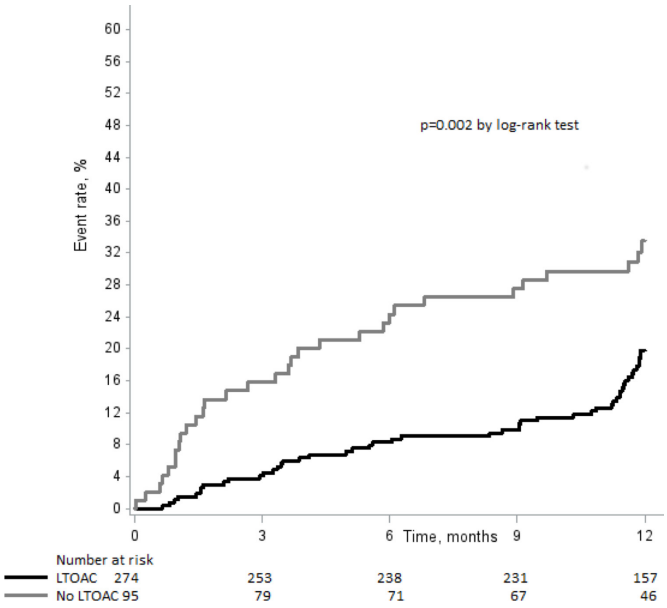

Figure 1 Twelve-month risk of death or dependency (from stroke onset to 12 months) according to treatment groups: long-term oral anticoagulant strategy (LTOAC) versus not on an LTOAC (no LTOAC).

33.5% of patients not on a long-term oral anticoagulant strategy (p=0.002).figure 1 At 12 months, brain infarction or brain haemorrhage occurred in 9.9% of patients on a long-term oral anticoagulant strategy and in 27.2% of patients not on a long-term oral anticoagulant strategy (p<0.001) (table 4).

Predictors of outcomes

Death and dependency

Online supplementary table 1 shows variables associated with the risk of death or dependency in univariable analysis.

In multivariable analysis, Rankin score ≥2 (almost threefold increase for mRS 2 and 3, and 14-fold increase for mRS 4 and 5), haemoglobin level, treatment groups (long-term oral anticoagulant strategy vs not on a long-term oral anticoagulant strategy), age, total cholesterol level and presence of small vessel disease (with a fourfold increase) were predictors of death or dependency (online supplementary table 2). The adjusted risk of death or dependency was onefold and half higher in patients not on a long-term oral anticoagulant strategy as compared with patients on a long-term oral anticoagulant strategy (HR 1.65; 95% CI 1.05 to 2.61; p=0.032).

Table 4 Outcomes events rates according to treatment groups: long-term oral anticoagulant strategy (LTOAC) versus not on an LTOAC (no LTOAC)

	LTOAC (n=274)	No LTOAC (n=95)	P value
Death and dependency Death	49 (17.9) 39/49 (79.6)	31 (32.6) 29/31 (93.5)	0.003
Brain infarction brain haemorrhage	26 (9.5)	25 (26.3)	<0.001
Brain infarction	18/26 (69.2)	15/25 (60.0)	
Brain haemorrhage	8/26 (30.8)	10/25 (30.0)	
Major bleeding	37 (13.5)	19 (20.0)	0.13
Aspiration pneumonia	35 (12.8)	29 (30.5)	<0.001
Pulmonary embolism	3 (1.1)	3 (3.2)	0.14
Deep venous thrombosis	5 (1.8)	0 (0)	0.19

Data are Kaplan-Meier estimates.

Recurrent brain infarction/brain haemorrhage

Online supplementary table 3 shows variables associated with brain infarction or brain haemorrhage in univariable analysis.

In multivariable analysis, Rankin score 4 or 5 (with a fivefold increase), glucose level, haemoglobin A1C, diastolic blood pressure, abnormal aortic valve, C reactive protein level, presence of atherothrombosis and treatment groups were predictors of brain infarction or brain haemorrhage (online supplementary table 4).

As compared with patients on a long-term oral anticoagulant strategy, the adjusted risk of brain infarction/brain haemorrhage was twofold and half higher in patients not on a long-term oral anticoagulant strategy (HR 2.46; 95% CI 1.36 to 4.44; p=0.003).

DISCUSSION

The WATCH-AF registry shows that, among patients with stroke and AF, one-fourth cannot receive a long-term oral anticoagulation strategy. One-third of these patients were dead or dependent at 12 months with an adjusted risk multiplied by 1.65 compared with patients who received a long-term oral anticoagulant strategy, and one-fourth had a recurrent brain infarction or brain haemorrhage

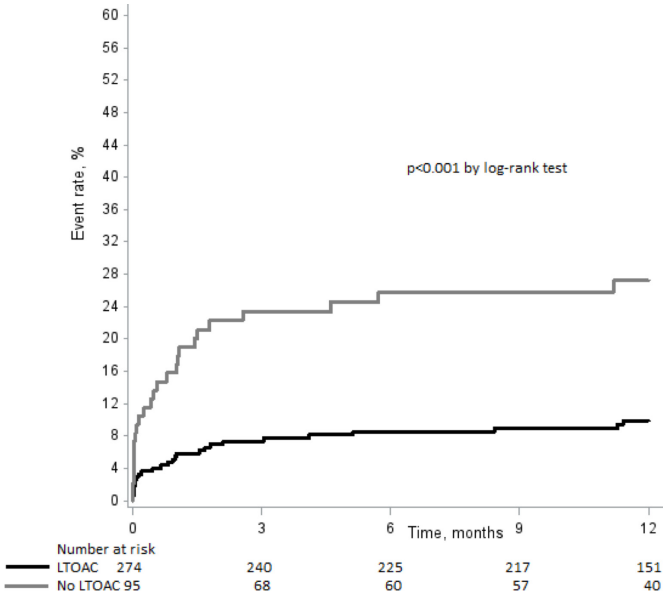

Figure 2 Twelve-month risk of brain infarction or brain haemorrhage (from stroke onset to 12 months) according to treatment groups: long-term oral anticoagulant strategy (LTOAC) versus not on an LTOAC (no LTOAC).

with an adjusted risk multiplied by 2.5. The new finding of this prospective registry is the proportion of patients with contraindication to long-term oral anticoagulation after a stroke, based on precise assessment using scores of disability, severity, cognitive functions and functional independence after the stroke event, as well as the 1-year risk of this group. These high proportions and risks question the necessity of finding therapeutic alternatives to long-term oral anticoagulant for these patients.

Beside treatment groups, independent predictors of death or dependency included the presence of small vessel disease (either multiple small deep infarcts or severe—Fazekas III—leukoaraiosis or microbleeds) with a fourfold increase and, not surprisingly, a Rankin score more than 1 (any degree of disability) with an almost threefold increase for a discharge mRS of 2 or 3 (needing some help but functionally independent), and a 14-fold increase for a mRS of 4 or 5 (needing permanent help or bedridden). Apart from not being on a long-term oral anticoagulant strategy, discharge Rankin score 4 or 5 was also the best independent predictor of recurrent brain infarction or brain haemorrhage.

This real-life, prospective registry, without any patient selection, shows that the risk of recurrent brain infarction or brain haemorrhage is still very high, even in the group on a long-term oral anticoagulant strategy with a 9.9% annual risk, showing that beside the antithrombotic treatment, other treatment strategies need to be found to decrease this risk, including risk factors control and strategies to improve adherence to treatments such as therapeutic education programme. The 27.2% annual risk of recurrent brain infarction or brain haemorrhage in patients not on a long-term oral anticoagulant strategy strengthens the case for alternative preventive strategies in these patients to be trialled such as left atrial appendage closure. According to figure 2, this risk is maximum during the first 3-month period postindex stroke. The reasons for not being on a long-term anticoagulant strategy were patient refusal, contraindication to long-term oral anticoagulant, comorbidity, frailty, patient bedridden or with severe dementia, history of bleeding precluding a long-term oral anticoagulant strategy or adherence to treatment (table 3).

The strengths of this registry were that (1) both stroke centres were primary care with a dedicated catching area, (2) inclusions have been consecutive and exhaustive with systematic verification that no patient with stroke and AF have been missed, (3) in every individual patient we retrospectively collected information about knowledge of AF, chosen treatment strategies by their primary care physician or cardiologist, risk factor stratification including CHA_2DS_2VASC, HAS-BLED, ATRIA, STRATIFY, IADL and about treatment adherence to VKA (eg, INR and TTR), over the previous 6 months, (4), using a high level of precision, we thoroughly evaluated patients at baseline and during a 1-year follow-up at four visits concerning concurrent underlying causes of stroke (eg, all patients had a brain MRI, extracranial and intracranial artery assessment, transthoracic and transoesophageal echocardiography) such as associated atherosclerotic disease and cerebral small vessel disease, risk stratification (CHA_2DS_2VASC, HAS-BLED, ATRIA scores), index stroke severity (NIHSS), disability (mRS), functional independence (IADL), risk of fall (STRATIFY risk assessment tool), cognitive function (MMSE), in order to precisely determine treatment strategy according to ESC/EHRA guidelines and (5) the very large sample size for this kind of precisions.

Generalisability of this study was limited as it involved only two centres, although busy stroke centres acting as primary care centres with a dedicated catching area, however, for the kind of precision that we set up in this registry we needed highly motivated centres, and a multicentre assessment with such a precision and numerous scales would have made the registry not feasible or with a lot of missing data. Our sample size can be viewed as rather small for an AF cohort. However, for the precision in scales and workup that the study needed, a sample size of 400 was an enormous effort. A much larger sample size with additions of other centres could have improve the overall generalisability, but at the expense of lack of precision.

In conclusions, we found that patients with stroke and AF not suitable to a long-term oral anticoagulant strategy represented one-fourth of the cohort and that they were at a very high 1-year risk of death and dependency and of brain infarction/brain haemorrhage recurrence. Alternative treatment options, such as left atrial appendage closure, should be trialled in these patients.

Acknowledgements This study was conducted by an academic research organisation 'Charles Foix group for clinical trial and registry in stroke' at University of Paris, Paris, France.

Contributors CG collected the data, interpreted the data and wrote the first draft of the manuscript. PA designed the study, obtained funding, interpreted the data and wrote the first draft of the manuscript. HC did the statistical analysis, generated tables and figures. Other authors collected the data, revised the draft and contributed for important intellectual content of the manuscript.

Funding This study was funded by SOS-ATTAQUE CEREBRALE (a not-for-profit stroke survivors association) via an unrestrictive grant from Boston Scientific (the maker of a left atrial appendage closure device).

Competing interests NN reports the following relationships: receipt of research grants support from Pfizer, Sanofi, from The French National Research Agency and consultancy fees from Boehringer-Ingelheim, Bayer et Amgen. PA reports receipt of research grant support from Pfizer, Sanofi, Bristol-Myers-Squibb, Merck, AstraZeneca, Boston Scientific and from the French government, and consulting fees from Pfizer, BMS, Merck, Boehringer-Ingelheim, AstraZeneca, Bayer, Daiichi-Sankyo, Edwards, Boston Scientific, Kowa, GSK, Fibrogen, Amgen, Shin Poong, Gilead, and lecture fees from Bayer, St-Jude Medical, Amgen, Pfizer, Sanofi.

Patient consent for publication Not required.

Ethics approval The study complies with the Declaration of Helsinki, the locally appointed ethics committee has approved the research protocol (Comité de Protection des Personnes Ile de France 5).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

ORCID iD
Pierre Amarenco http://orcid.org/0000-0002-3842-1236

REFERENCES

1 Lin HJ, Wolf PA, Kelly-Hayes M, *et al*. Stroke severity in atrial fibrillation. The Framingham study. *Stroke* 1996;27:1760–4.
2 Connolly SJ, Eikelboom JW, Ng J, *et al*. Net clinical benefit of adding clopidogrel to aspirin therapy in patients with atrial fibrillation for whom vitamin K antagonists are unsuitable. *Ann Intern Med* 2011;155:579–86.
3 Marini C, De Santis F, Sacco S, *et al*. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. *Stroke* 2005;36:1115–9.
4 Kelly-Hayes M, Beiser A, Kase CS, *et al*. The influence of gender and age on disability following ischemic stroke: the Framingham study. *J Stroke Cerebrovasc Dis* 2003;12:119–26.
5 Hart RG, Benavente O, McBride R, *et al*. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;131:492–501.
6 Ruff CT, Giugliano RP, Braunwald E, *et al*. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383:955–62.
7 Holmes DR, Reddy VY, Turi ZG, *et al*. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;374:534–42.
8 Boersma LV, Ince H, Kische S, *et al*. Efficacy and safety of left atrial appendage closure with Watchman in patients with or without contraindication to oral anticoagulation: 1-year follow-up outcome data of the EWOLUTION trial. *Heart Rhythm* 2017;14:1302–8.
9 Amarenco P, Bogousslavsky J, Caplan LR, *et al*. The ASCOD phenotyping of ischemic stroke (updated ASCO phenotyping). *Cerebrovasc Dis* 2013;36:1–5.
10 Amarenco P, Albers GW, Denison H, *et al*. Efficacy and safety of ticagrelor versus aspirin in acute stroke or transient ischaemic attack of atherosclerotic origin: a subgroup analysis of SOCRATES, a randomised, double-blind, controlled trial. *Lancet Neurol* 2017;16:301–10.
11 Meier B, Blaauw Y, Khattab AA, *et al*. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. *Europace* 2014;16:1397–416.
12 Tzikas A, Holmes DR, Gafoor S, *et al*. Percutaneous left atrial appendage occlusion: the Munich consensus document on definitions, endpoints, and data collection requirements for clinical studies. *Europace* 2017;19:4–15.
13 Camm AJ, Lip GYH, De Caterina R, *et al*. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. developed with the special contribution of the European heart rhythm association. *Eur Heart J* 2012;33:2719–47.