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# Left atrial appendage closure in very elderly patients in the French National Registry

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Collaborators, Affiliations

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## Abstract

### Objective:

Left atrial appendage closure (LAAC) is recommended to decrease the stroke risk in patients with atrial fibrillation and contraindications to anticoagulation. However, age-stratified data are scarce. The aim of this study was to provide information on the safety and efficacy of LAAC, with emphasis on the oldest patients.

### Methods:

A nationwide, prospective, multicentre, observational registry was established by 53 French cardiology centres in 2018-2021. The composite primary endpoint included ischaemic stroke, systemic embolism, and unexplained or cardiovascular death. Separate analyses were done in the groups <80 years and  $\geq$ 80 years.

### Results:

Among the 1053 patients included, median age was 79.7 (73.6-84.3) years; 512 patients (48.6%) were aged  $\geq$ 80 years. Procedure-related serious adverse events were non-significantly more common in octogenarians (7.0% vs 4.4% in patients aged <80 years, respectively;  $p=0.07$ ). Despite a higher mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score in octogenarians, the rate of thromboembolic events during the study was similar in both groups (3.0 vs 3.1/100 patient-years;  $p=0.85$ ). By contrast, all-cause mortality was significantly higher in octogenarians (15.3 vs 10.1/100 patient-years,  $p<0.015$ ), due to a higher rate of non-cardiovascular deaths (8.2 vs 4.9/100 patient-years,  $p=0.034$ ). The rate of the primary endpoint was 8.1/100 patient-years overall with no statistically significant difference between age groups (9.4 and 7.0/100 patient-years;  $p=0.19$ ).

### Conclusion:

Despite a higher mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score in octogenarians, the rate of thromboembolic events after LAAC in this age group was similar to that in patients aged <80 years.

### Trial registration number:

ClinicalTrials.gov Registry (NCT03434015).

# INTRODUCTION

The number of patients with atrial fibrillation (AF) is expected to double by 2030 due to the improved survival of patients with cardiovascular disease, intensified search for undiagnosed AF and ageing of the general population.<sup>1</sup> The proportion of patients with AF who are given appropriate anticoagulant therapy has expanded markedly in recent years, due mainly to more widespread prescription of direct oral anticoagulants.<sup>2</sup> In several studies, benefits from anticoagulant agents outweighed the bleeding risk in elderly patients, creating a favourable risk/ benefit ratio.<sup>3 4</sup> Nonetheless, around 20% of elderly patients with AF receive insufficient or, more rarely, excessive anticoagulant doses.<sup>5</sup>

Left atrial appendage closure (LAAC) has emerged as an option to reduce the thromboembolic risk in patients with AF. Several propensity-matched studies and a randomised trial have reported a reduction of all-cause mortality with LAAC compared with anticoagulation, at least in some groups of patients.<sup>6–8</sup> This may be due to a reduction in the bleeding risk. Furthermore, LAAC is a structural intervention, and its effects are not dependent on patient compliance as for anticoagulation.<sup>9</sup>

The French National Authority for Health approved LAAC devices in 2016 for patients with definitive contraindications to long-term anticoagulation and a high thromboembolic risk. Of note, the authority required the enrolment of these patients in a national, prospective, post-approval registry (French Left Atrial Appendage Closure Registry, FLAAC-2).

Most registry studies published to date included heterogeneous populations and failed to stratify outcomes on patient age.<sup>10 11</sup> More specifically, data on patients aged 80 years or over are scarce.<sup>12 13</sup> Such data are of considerable interest since very elderly patients may be at greater risk of both thromboembolic events and bleeding and represent a substantial proportion of patients with AF with contraindications to anticoagulants.

The objective of this study was to provide safety and efficacy data on LAAC by analysing the French nationwide prospective post-approval registry of LAAC devices. We also compared outcomes in patients younger than 80 years vs aged 80 years or over.

## METHODS

### Study design

This nationwide, prospective, multicentre, observational study was conducted in all centres (n=53) that performed LAAC in France during the period of inclusion (August 2018–December 2019). Inclusion criteria were as follows: patients referred for LAAC and aged 18 years or older.

In France, LAAC is approved since 2016 for patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 4$  and a definitive contraindication to anticoagulant agents validated by dedicated multidisciplinary staff. Inclusion in this registry did not affect the choice of the device, procedural process, antithrombotic treatment or follow-up imaging. Patients were followed from baseline to the 12-month visit.

This investigator-driven study was funded by a research grant from Abbott and Boston Scientific. The device manufacturers had no role in the design, conduct or reporting of this study.

### **Patient and public involvement**

Neither the patients nor the public were involved in the research.

### **Data management and monitoring**

Demographic and clinical data were obtained by physical examination and medical record review. Patients unreachable were considered as lost to follow-up after a minimum of five unsuccessful contact attempts.

CT scan and echocardiography were analysed by the investigators, without centralised reading.

Events of interest were reviewed by an independent adjudication committee to ensure that the same criteria (Valve Academic Research Consortium 2 classification) were used to identify each event. Abnormal renal function was defined using the definition described in the HAS-BLED score.

### **Outcomes**

The primary efficacy outcome measure was a composite of ischaemic stroke, systemic embolism, and unexplained or cardiovascular death.

The main secondary efficacy outcome measures were the annual rates of ischaemic stroke, systemic embolism, transient ischaemic attack, unexplained or cardiovascular death, and all-cause death. The safety outcome measures were the rates of device-related thrombus (DRT), other adverse events related or possibly related to the device or procedure, and bleeding events. Adverse events were considered during two periods, the periprocedural period (from the start of the intervention until patient discharge or day 7 after the procedure, whichever came last) and the subsequent follow-up period (until the date of the last visit). The data are reported for the overall cohort and the subgroups defined based on age younger than 80 years or 80 years or over (octogenarian group).

### **Statistics**

Continuous variables are described as mean $\pm$ SD or median (IQR), depending on distribution, and categorical variables as number (%). Mortality and the cumulative incidence of thromboembolism were compared using the Kaplan-Meier method for censored data during the overall follow-up. For each endpoint, the data were censored after the first event in patients who experienced more than one event.

Baseline features in the subgroups with versus without clinical events (primary endpoint: stroke or systemic embolism) were compared using Cox proportional hazards regression models with estimation of the HRs and their 95% CIs. Variables associated with p values lower than 0.15 were selected as candidate variables to be entered in multivariable analysis. Final model selection was based on a stepwise variable selection procedure with bidirectional elimination method using Akaike's information criterion. The CHA2DS2-VASc score was not included in the multivariable analysis since it was redundant with other parameters tested. Two-sided p values lower than 0.05 were considered statistically significant. The statistical analyses were conducted using Stata V.16.0 (StataCorp, College Station, Texas, USA) for descriptive analyses and R V.4.0.3 (R Foundation, Vienna, Austria) for the multivariable analyses using the StepReg package.

## RESULTS

### Patient characteristics

Between August 2018 and December 2019, 1053 patients were included in the FLAAC-2 registry by 53 centres in France. These patients represented 92.8% of the 1135 patients treated with LAAC in France during the same period.

[Table 1](#) reports the main patient characteristics. Median age was 79.7 (73.6–84.3) years, and 512 (48.6%) patients were 80 years of age or over at inclusion. Cardiovascular and non-cardiovascular comorbidities were common in both groups, but their nature differed significantly: prevalences were higher for heart failure, coronary artery disease, and prior valvular surgery in octogenarians and for cirrhosis, smoking and diabetes in patients aged <80 years.

The risk of stroke predicted by the CHA2DS2-VASc score was significantly higher in octogenarians ( $5.1\pm 1.2$  vs  $4.5\pm 1.3$  in patients aged <80 years,  $p<0.0001$ ). The number of points assigned for comorbidities and sex (female) was similar in both groups. The higher value of the CHA2DS2-VASc score in octogenarians was due to the additional points assigned for age.

The overall bleeding risk predicted by the HAS-BLED score was similar in the two age groups. However, a history of gastrointestinal bleeding was more common in octogenarians.

Patients' history of cardiac rhythm disorders is summarised in [table 1](#). The proportion of patients with permanent AF or a paced rhythm was higher in octogenarians.

All these results suggest age-driven differences in the profile of patients offered LAAC.

### Outcomes of the procedure

The procedural success rate was high (99.0%), with no difference between age groups ([table 2](#)). [Table 3](#) reports the serious adverse events (SAEs) related or possibly related to the procedure or device. Pericardial effusion requiring pericardiocentesis was the most common periprocedural SAE. The proportion of patients with any SAE was 5.7% (n=60) overall and was non-significantly higher in octogenarians (7.0% (n=36) vs 4.4% (n=24),  $p=0.07$ ). This

difference was chiefly ascribable to higher frequencies of tamponade, periprocedural stroke/systemic embolism, and vascular or bleeding complications in octogenarians.

**Table 1** Baseline clinical characteristics

	All patients (n=1053)	<80 years of age (n=541)	≥80 years of age (n=512)	P value*
<b>General characteristics</b>				
Age, years†	79.7 (73.6–84.3)	73.8 (69.4–77.0)	84.5 (82.3–87.7)	<0.0001
Males/females, n (%)	672 (63.8)/381 (36.2)	362 (66.9)/179 (33.1)	310 (60.5)/202 (39.5)	0.032
Body mass index, kg/m <sup>2</sup> †	25.6 (22.9–29.0)	26.2 (23.5–30.0)	25.0 (22.5–28.1)	<0.0001
SAP, mm Hg†	132 (120–147)	132 (120–146)	131 (119–149)	0.88
DAP, mm Hg†	71 (64–81)	74 (65–82)	70 (63–79)	<0.0001
Heart rate, bpm†	71 (62–80)	71 (62–81)	71 (62–80)	0.78
<b>Cardiovascular history, n (%)</b>				
Heart failure	232 (22.0)	104 (19.2)	128 (25.0)	0.024
Coronary artery disease	287 (27.4)	132 (24.6)	155 (30.4)	0.037
Myocardial infarction	117 (11.2)	67 (12.5)	50 (9.8)	0.17
Diabetes mellitus	286 (27.2)	179 (33.1)	107 (20.9)	<0.0001
Hypertension	849 (80.6)	438 (81.0)	411 (80.3)	0.78
Smoker	247 (23.8)	155 (29.0)	92 (18.2)	<0.0001
Dyslipidaemia	436 (41.8)	229 (42.9)	207 (40.7)	0.48
Valvular disease‡	112 (10.7)	47 (8.8)	65 (12.7)	0.041
Prosthetic heart valve	88 (8.4)	35 (6.6)	53 (10.4)	0.025
Deep vein thrombosis/pulmonary embolism	110 (10.6)	55 (10.3)	55 (10.9)	0.76
CHA <sub>2</sub> DS <sub>2</sub> -VASC score§	4.8±1.3	4.5±1.3	5.1±1.2	<0.0001
History of thromboembolic event, n (%)	575 (54.6)	308 (56.9)	267 (52.1)	0.12
History of bleeding event, n (%)	920 (87.4)	466 (86.1)	454 (88.7)	0.22
Intracranial haemorrhage	403 (39.4)	224 (42.3)	179 (36.3)	0.051
Microbleeds	105 (10.4)	53 (10.2)	52 (10.6)	0.85
Spontaneous haematoma	101 (9.9)	56 (10.6)	45 (9.1)	0.41
Haematuria	44 (4.3)	22 (4.2)	22 (4.4)	0.86
Epistaxis	35 (3.5)	13 (2.5)	22 (4.4)	0.09
Gastrointestinal bleeding	299 (29.1)	128 (24.5)	171 (33.9)	0.0009
Other bleeding event	111 (11.1)	52 (10.2)	59 (12.1)	0.35
HAS-BLED score§	3.1±1.0	3.1±1.1	3.1±0.9	0.96
<b>Comorbidities, n (%)</b>				
Cirrhosis	48 (4.6)	37 (6.9)	11 (2.2)	0.0002
COPD	126 (12.1)	65 (12.1)	61 (12.0)	0.93
Asthma	35 (3.4)	21 (3.9)	14 (2.8)	0.29
Thyroid dysfunction	149 (14.3)	74 (13.9)	75 (14.8)	0.69
Malignancy	139 (13.3)	75 (14.0)	64 (12.6)	0.49
Alcohol abuse	61 (5.8)	47 (8.7)	14 (2.7)	<0.0001
Dialysis	56 (5.4)	36 (6.7)	20 (3.9)	0.045
Platelet (10 <sup>9</sup> /L)†	217 (176–266)	224 (180–271)	214 (172–260)	0.039
Creatinine (μmol/L)†	95.0 (77.5–128.8)	92.0 (75.3–123.9)	99.5 (80.0–132.0)	0.005
Creatinine clearance (mL/min)†	63.4 (45.8–81.1)	70.1 (48.7–85.6)	58.0 (43.2–73.8)	<0.0001
Haemoglobin (g/L)†	125 (110–137)	127 (110–139)	123 (110–135)	0.032
<b>Cardiac rhythm history, n (%)</b>				
Sinus rhythm/AF at baseline	414 (39.5)/633 (60.5)	227 (42.2)/311 (57.8)	187 (36.7)/322 (63.3)	0.07
Paced rhythm at baseline	181 (17.3)	70 (13.1)	111 (21.7)	0.0002
Paroxysmal/persistent/permanent AF	448 (43.7)/119 (11.6)/458 (44.7)	232 (44.0)/76 (14.4)/219 (41.6)	216 (43.4)/43 (8.6)/239 (48.0)	0.008
History of AF ablation	109 (10.5)	74 (13.9)	35 (6.9)	0.0002
Dependent patients, n (%)	99 (9.7)	46 (8.7)	53 (10.8)	0.28

\*Comparison between patients <80 or ≥80 years of age.  
†Median (IQR).  
‡Clinically significant.  
§Mean±SD.  
AF, atrial fibrillation; bpm, beats per minute; COPD, chronic obstructive pulmonary disease; DAP, diastolic arterial pressure; SAP, systolic arterial pressure.

## Antithrombotic treatment at discharge

Table 4 reports the antithrombotic treatments prescribed at discharge. In octogenarians, therapeutic-dose anticoagulation was used significantly less often (n=50, 9.9% vs n=95, 17.8% in patients aged <80 years; p<0.001) and antiplatelet therapy without anticoagulation significantly more often (n=417, 82.9% vs n=409, 76.6% in patients aged <80 years; p=0.012).



## Device-related thrombus

After hospital discharge, CT scan or transoesophageal echocardiography were performed in 350 octogenarians (69.0%) and 389 patients aged <80 years (72.7%,  $p=0.19$ ). A DRT developed in 36 (3.5%) patients. This event was not more common in octogenarians ( $n=18$ , 3.6% vs  $n=18$ , 3.4% in patients aged <80 years;  $p=0.87$ ). DRT was associated with an eightfold increase in the occurrence of thromboembolism overall (19.4% vs 2.5%; HR 8.95; 95% CI 3.9 to 20.8;  $p<0.0001$ ). The increased risk of stroke and/or systemic embolism was observed in both age groups (HR 11.9; 95% CI 3.7 to 38.1;  $p<0.0001$  in octogenarians; and HR 6.7; 95% CI 1.9 to 23.6;  $p<0.001$  in patients aged <80 years).

Data per device family are presented in online supplemental table 1. DRT occurred in 6.1% of patients with Watchman vs only 0.8% with Amulet.

	All patients (n=1053)	<80 years of age (n=541)	≥80 years of age (n=512)	P value*
<b>Technical data</b>				
Endotracheal intubation, n (%)	736 (74.0)	392 (77.3)	344 (70.5)	0.014
Intubation duration (min)†	60 (50–78)	60 (50–76)	60 (50–80)	0.88
Volume of contrast agent (mL)†	30.0 (15.0–60.0)	30.0 (15.0–59.5)	30.0 (15.0–60.0)	0.19
Fluoroscopy time (min)†	8.0 (5.0–13.0)	8.0 (5.0–13.0)	8.0 (5.0–13.0)	0.76
Procedure duration (min)†	42.0 (30.0–60.0)	43.0 (30.0–60.0)	40.5 (30.0–60.0)	0.39
<b>Echocardiographic monitoring, n (%)</b>				
Transoesophageal echocardiography	962 (93.5)	492 (93.0)	470 (94.0)	0.52
Intracardiac echocardiography	89 (9.0)	51 (10.1)	38 (7.9)	0.23
None	22 (2.1)	11 (2.1)	11 (2.2)	0.88
<b>Device implantation, n (%)</b>				
Device used (Amulet/Watchman)‡	525 (49.9)/528 (50.1)	274 (50.6)/267 (49.4)	251 (49.0)/261 (51.0)	0.60
Procedural success	1042 (99.0)	535 (98.9)	507 (99.0)	0.83

\*Comparison between patients <80 or ≥80 years of age.  
†Median (IQR).  
‡The large majority of the Watchman device are first-generation Watchman devices.

## Follow-up

Median follow-up after successful LAAC was 374 (352–415) days. Only five patients were lost to follow-up. The primary endpoint occurred in 85 patients (8.1/100 patient-years) including 47 patients in the octogenarian group and 38 patients aged <80 years (9.4 vs 7.0/100 patient-years, respectively;  $p=0.19$ ) ([figure 1A](#) and online supplemental table 2). Predictors of the primary endpoint identified by univariate analysis are reported in online supplemental tables 3 and 4. A multivariable analysis is presented in [table 5](#).

	All patients (n=1053)		<80 years (n=541)		≥80 years (n=512)	
	Periprocedural period*	Follow-up	Periprocedural period*	Follow-up	Periprocedural period*	Follow-up
Pericardial effusion requiring pericardiocentesis	21 (2.0)	2 (0.2)	6 (1.1)	2 (0.4)	15 (2.9)	0 (0.0)
Surgical pericardiocentesis	8 (0.8)	1 (0.1)	3 (0.6)	1 (0.2)	5 (1.0)	0 (0.0)
Subxyphoid pericardiocentesis	13 (1.2)	1 (0.1)	3 (0.6)	1 (0.2)	10 (2.0)	0 (0.0)
Recurrence of pericardial effusion	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Device embolisation	5 (0.5)	0 (0.0)	2 (0.4)	0 (0.0)	3 (0.6)	0 (0.0)
Requiring surgery	2 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Snared	3 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
Ischaemic stroke or systemic embolism	5 (0.5)	6 (0.6)†	1 (0.2)	3 (0.6)†	4 (0.8)	3 (0.6)†
Transient ischaemic attack	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Vascular or haemorrhagic complications	17 (1.6)	0 (0.0)	5 (0.9)	0 (0.0)	12 (2.3)	0 (0.0)
Life-threatening	4 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.6)	0 (0.0)
Major	13 (1.2)	0 (0.0)	4 (0.7)	0 (0.0)	9 (1.8)	0 (0.0)
Air embolism	3 (0.3)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Death	7 (0.7)	2 (0.2)‡	3 (0.6)	1 (0.2)‡	4 (0.8)	1 (0.2)‡
			<b>&lt;80 years</b>		<b>≥80 years</b>	
	Patients with any SAE		24 (4.4)		36 (7.0)	
						<b>P value</b>
						0.07

\*To day 7 or discharge.  
†Ischaemic stroke or systemic embolism in patients with a device-related thrombus during the study.  
‡Death related to ischaemic stroke or systemic embolism in patients with device-related thrombus during the study.  
SAE, serious adverse event.

During the overall study period, ischaemic stroke occurred in 24 patients (26 events) and systemic embolism in 8 patients (9 events), yielding a thromboembolism rate of 3.1/100 patient-years. Transient ischaemic attack was observed in four additional patients and an asymptomatic ischaemic lesion was discovered by routine imaging in another patient (figure 1B,C). While the mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score was significantly higher in octogenarians than in patients aged <80 years (5.1±1.2 vs 4.5±1.3, p<0.0001), the annual rate of thromboembolic events (stroke/ systemic embolism) was similar in the two groups (octogenarians: 3.0/100 patient-years; patients aged <80 years: 3.1/100 patient-years, p=0.85).

Online supplemental tables 5 and 6 list the predictors of stroke/systemic embolism identified by univariate Cox regression analysis. By multivariable analysis, a history of thromboembolic event was associated with a higher risk of stroke/systemic embolism after LAAC in the overall cohort and the younger group (table 5).

Life-threatening or major bleeding events unrelated to LAAC occurred in 54 patients, including 14 patients (16 events) with intracranial bleeds. The proportion of patients with these events was not higher in the group of octogenarians (5.5% vs 4.9% in patients aged <80 years, p=0.63).

Among the 1042 patients with successful LAAC, 133 died during the study, yielding a mortality rate of 12.6/100 patient-years. Of these 133 patients, 7 died before day 7 or discharge. Ischaemic stroke or systemic embolism was the direct cause of death in 12 patients. The risk of all-cause death was significantly higher in octogenarians (15.3 vs 10.1/100 patient-years; p<0.015; HR 1.04; 95% CI 1.01 to 1.06; p=0.002). This higher mortality in octogenarians was related to a significantly higher rate of non-cardiovascular death (8.2 vs 4.9/100 patient-years, p=0.034) (figure 1F) and to a non-significantly higher rate of death due to unknown or cardiovascular causes (7.1 vs 5.1/100 patient-years, p=0.19) (figure 1E).

Prognosis factors of all-cause mortality are presented in table 5 and online supplemental tables 7 and 8. In both subgroups, we observed a stepwise increase in mortality with the number of risk factors (online supplemental table 9).

## DISCUSSION

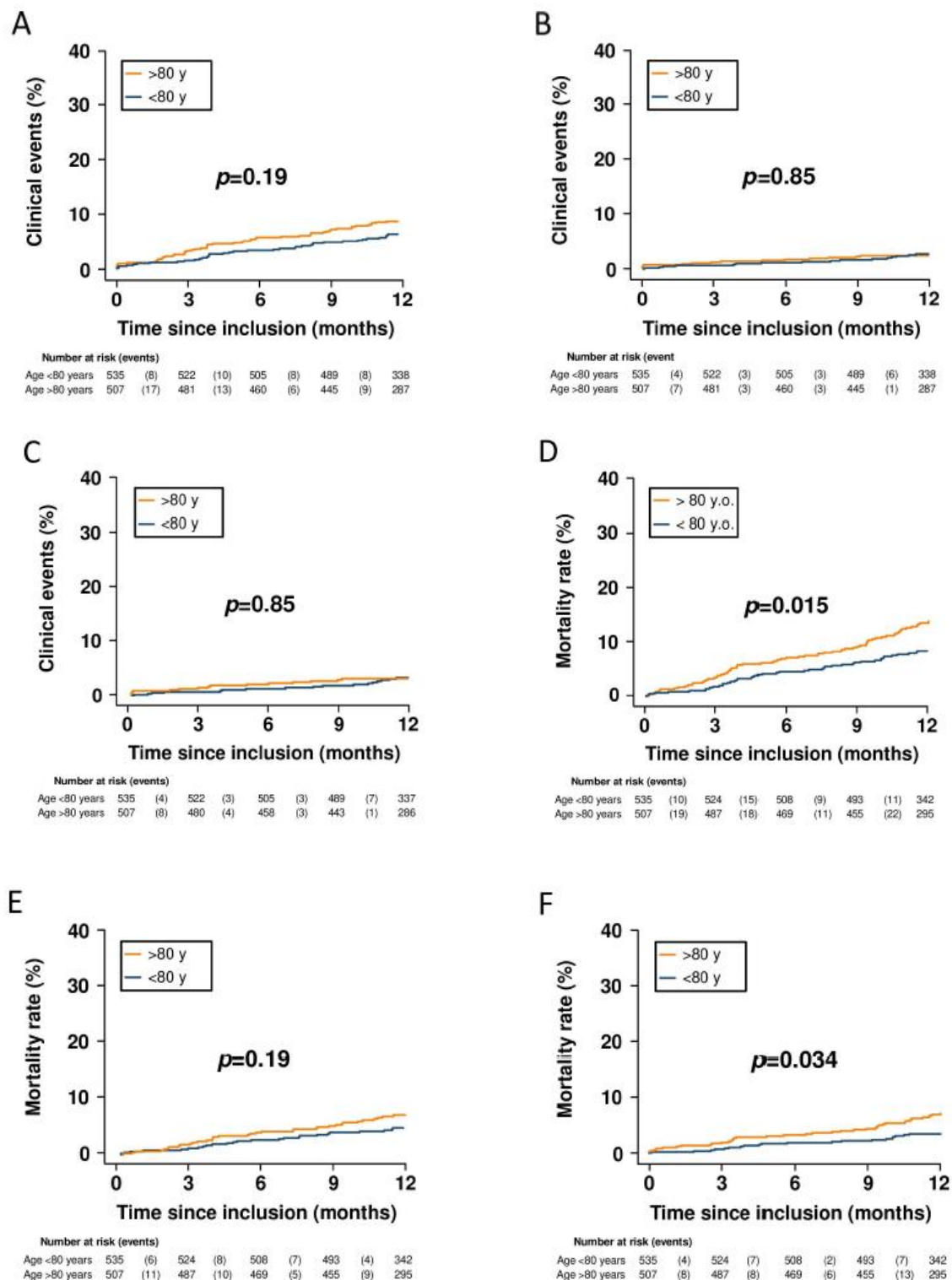
This analysis of a prospective, nationwide registry provides a picture of LAAC in France. Most patients (84%) were at very high risk of stroke, with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 4 or higher. The large sample size allowed a detailed comparison of patients aged 80 years or older, who contributed nearly half the cohort, with their younger counterparts. The outcomes collected over the study support LAAC for preventing thromboembolism in patients with AF, a high thromboembolic risk and a contraindication to long-term anticoagulation, notably those aged 80 years or over. The likelihood of experiencing any SAE was slightly greater in octogenarians, but the difference was not statistically significant. Thromboembolic events, serious bleeding events and DRT were not more common in the older patients. Although all-cause mortality was significantly higher in octogenarians, the main reason for this difference was a higher frequency of non-cardiovascular deaths.

Very elderly patients were under-represented in key randomised controlled trials assessing the efficacy of LAAC in preventing thromboembolism in patients with AF. In the PROTECT-AF and PREVAIL trials, mean age in the intervention group was 71.7 and 74.0 years, respectively.<sup>14 15</sup> The population in the PRAGUE-17 trial demonstrating the non-inferiority of LAAC compared with direct oral anticoagulant therapy had a mean age of 73.4 years.<sup>16</sup> Similarly, the mean age of the populations in the EWOLUTION registry, Amulet IDE trial and US National Cardiovascular Data Registry ranged from 73 to 76 years.<sup>10 17 18</sup> These studies grouped therefore patients with very different ages and clinical conditions and were not stratified on age.

Few stratified studies have compared the clinical outcomes after LAAC in different classes of age.<sup>12 13 19–23</sup> Two prospective studies demonstrated similar thromboembolic event rates in patients younger than 75 years and aged 75 years or over.<sup>20 22</sup> Data in older patients are sparse. Ischaemic stroke was not more common in the group aged 80 years or over in the Amplatzer Amulet Occluder observational study.<sup>12</sup> In contrast, a combined analysis of two real-world LAAC registries demonstrated a smaller decrease in the predicted stroke rate in patients aged 80 years or over (41%) compared with younger patients (53%).<sup>13</sup> The raw number of ischaemic stroke was higher in the elderly group in the PROTECT-AF/ PREVAIL trials.<sup>23</sup> These studies are summarised in online supplemental table 10. In our cohort, annual rate of thromboembolic event was similar in the two groups (3.0% in octogenarians, 3.1 in patients aged <80 years,  $p=0.85$ ). Moreover, by multivariable analysis, older age was not significantly associated with thromboembolism, although the CHA<sub>2</sub>DS<sub>2</sub>-VASc score was higher due to the additional points assigned for age. Of note, compared with a cohort of patients with AF and no anticoagulation previously reported in the literature,<sup>24</sup> the risk of stroke, systemic embolism or transient ischaemic attack was considerably lower in both our subgroups (65% in octogenarians and 61% in patients aged <80 years).

Adherence to follow-up imaging after LAAC was not significantly different between the two age groups and the rate of diagnosed DRT was similar. These imaging data confirm the favourable safety profile of LAAC devices in very elderly patients. DRT appeared to be more frequent in patients treated with a Watchman device. Of note, the rates of thromboembolic events were similar with the two device families. In the Amulet IDE or SWISS-APER0

Studies, there were no statistically significant differences in the incidence of DRT between device families.<sup>17 25</sup> The discrepancies between these studies may be explained by differences in the antithrombotic treatment prescribed after LAAC (table 4).



**Figure 1** Kaplan-Meier curves according to age for: (A) the primary endpoint (ischaemic stroke, systemic embolism or unexplained/cardiovascular death); (B) stroke and systemic embolism; (C) stroke, systemic embolism and transient ischaemic attack; (D) all-cause death; (E) unexplained or cardiovascular death; and (F) non-cardiovascular death.

<b>Primary composite endpoint</b>						
	All patients n=933		<80 years of age n=468		≥80 years of age n=467	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95%CI)	P value
Abnormal renal function	2.12 (1.30; 3.45)	0.003	2.74 (1.34; 5.60)	0.006	1.99 (1.06; 3.75)	0.032
Haemoglobin*	0.87 (0.77; 0.99)	0.033	0.82 (0.68; 0.98)	0.029	–	–
Cirrhosis	3.43 (1.71; 6.87)	0.0005	2.69 (1.10; 6.58)	0.030	4.09 (1.44; 11.65)	0.008
Age	1.04 (1.01; 1.07)	0.016	–	–	1.08 (1.00; 1.17)	0.061
Prosthetic heart valve	2.07 (1.10; 3.90)	0.024	4.05 (1.73; 9.50)	0.001	–	–
Heart failure	1.49 (0.91; 2.45)	0.112	–	–	–	–
<b>Thromboembolic event</b>						
	All patients n=1032		<80 years of age n=469		≥80 years of age	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Previous thromboembolic event	3.23 (1.38; 7.54)	0.007	5.69 (1.26; 25.64)	0.023	–	–
Abnormal renal function	2.40 (1.12; 5.13)	0.024	2.69 (0.88; 8.18)	0.082	–	–
Prosthetic heart valve	2.53 (0.97; 6.62)	0.058	3.92 (1.06; 14.52)	0.041	–	–
Haemoglobin*	–	–	0.77 (0.59; 1.02)	0.068	–	–
<b>All-cause death</b>						
	All patients n=932		<80 years of age n=468		≥80 years of age n=467	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Haemoglobin*	0.77 (0.70; 0.85)	<0.0001	0.76 (0.66; 0.88)	0.0001	0.77 (0.68; 0.87)	<0.0001
Heart failure	1.79 (1.22; 2.63)	0.003	2.32 (1.26; 4.26)	0.007	1.58 (0.96; 2.60)	0.075
Abnormal renal function	1.65 (1.12; 2.44)	0.011	–	–	1.80 (1.08; 3.00)	0.024
Age	1.04 (1.01; 1.06)	0.006	1.07 (1.01; 1.14)	0.032	–	–
Coronary artery disease	1.58 (1.09; 2.29)	0.016	1.62 (0.89; 2.98)	0.117	–	–
Cirrhosis	2.23 (1.21; 4.13)	0.010	2.69 (1.25; 5.80)	0.012	–	–
Prosthetic heart valve	1.60 (0.94; 2.74)	0.086	2.25 (1.02; 4.99)	0.046	–	–

\*HR (95% CI) per 1 g/dL increase.

The association between advanced age and periprocedural complications was evaluated in the US National In-patient Sample Database.<sup>26</sup> In the unadjusted analysis, major in-hospital complications were significantly more common in the group aged 80 years or over (6.7% vs 5.7% in patients aged <80 years,  $p < 0.01$ ). Hospital mortality was also higher in the older patients. Adjustment on comorbidities eliminated the difference in major complications, although not in hospital mortality. Thus, the burden of age-related diseases, rather than age itself, may influence the risk/benefit ratio. Similarly, in the US Readmissions Database, a modest increase in early readmission during the first post-procedural month has been reported in very elderly patients (9.9% vs 8.4%,  $p = 0.004$ ).<sup>27</sup> Our results are consistent with these findings, with a non-significant increase in procedure-related SAEs in octogenarians, the main events being pericardial effusion and vascular complications. In all these studies, the between-group differences were limited, supporting LAAC as reasonably safe in very elderly patients selected based on an individualised assessment of the risk/benefit ratio.

As most of the patients referred for LAAC have a history of bleeding, an important issue is whether older age is associated with a higher post-procedural bleeding risk. In our FLAAC-2 registry, non-procedure-related bleeding events occurred in similar proportions of patients in the two age groups. The data from previous studies are conflicting. In the Amplatzer Cardiac Plug multicentre registry and the LAARGE registry, no significant differences in major bleeding rates were observed between patients aged <75 or ≥75 years.<sup>20 22</sup> By contrast, other studies evidenced higher rates of bleeding events in the oldest patients.<sup>12 13 21</sup> These apparent discrepancies may be ascribable to differences across countries in the clinical profile of patients selected for LAAC. In our registry, the baseline bleeding risk as assessed by the



HAS-BLED score was similar in the two age groups. Of note, the proportion of patients prescribed anticoagulant therapy at discharge was lower in octogenarians. A propensity-adjusted analysis of the EWOLUTION Study suggested that antithrombotic treatment duration may be associated with the risk of bleeding.<sup>28</sup> Identification of the best post-procedural antithrombotic treatment for patients at high risk of bleeding awaits further studies.

Making decisions about interventional procedures in very elderly patients can be complex.<sup>29</sup> For LAAC, it may be difficult to convince elderly patients of the justification of a preventive intervention that is not without risk. The fact that stroke, if it occurs, may jeopardise their quality of life, must be explained to these patients. This requires an optimal physician–patient relationship.

### **Limitations**

This registry is one of the largest prospective registries reported to date. However, a few patients referred for LAAC during the inclusion period were not included. As for all registries, caution is needed when generalising results to a broader population, particularly in patients with multiple comorbidities. In addition, this study had no control group. The clinical outcomes after LAAC were therefore compared with previously published data.<sup>24</sup> Furthermore, the analysis of CT scan and echocardiography images was not centralised. The size of DRT was not taken into account. Therefore, we cannot exclude a centre effect on the rate of DRT. Finally, patients were categorised by chronological age and not based on comprehensive geriatric assessments.

## **CONCLUSION**

Our analysis of data from a nationwide post-approval registry suggests a favourable risk/benefit ratio of LAAC even in the very elderly. A small, non-significant increase in procedure-related adverse events was noted in the patients aged 80 years or over. LAAC should be considered in very elderly patients and decisions made on a case-by-case basis, according to the findings from a comprehensive and individualised clinical assessment.

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## **Contributors**

ET, EA, PD and PLC were responsible for the conception, design and planning of the study. All authors (ET, RE, NA, GR, GD, PG, AL, JB, ME, PD, EA, PLC) contributed to the conduct of the study and acquisition of data. ET and PLC were in charge of the global coordination of the study. EA was in charge of the statistical analysis. All authors contributed to the reporting of this work and revised the manuscript for important intellectual content. All authors approved the manuscript submitted. ET and PLC had full access to all the data and are responsible for the overall content as guarantors.

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## **Competing interests**

ET and PLC received unrestricted research grants from Boston Scientific and St Jude Medical for this study. PG is the medical director and shareholder of CERC (Cardiovascular European Research Center) and received speaker's and advisory fees from Abbott and Boston Scientific. GR is proctor for Boston Scientific. RE is consultant and has performed proctoring for Boston Scientific and Abbott. None for all other authors.

## **Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

## **Patient consent for publication**

Not required.

## **Ethics approval**

This study involves human participants. The study was conducted in accordance with the Declaration of Helsinki and was approved by the appropriate ethics committee (CPP Ile de France III, 3528-NI, 24/10/2017). All patients gave written informed consent before study enrolment.

## Provenance and peer review

Not commissioned; externally peer reviewed.

## Data availability statement

Data are available upon reasonable request.

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