

Clinical benefit of left atrial appendage closure in octogenarians

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ABSTRACT

OBJECTIVES Whether left atrial appendage closure (LAAC) in octogenarians yield similar net clinical benefit compared to younger patients, was the purpose of the present study.

METHODS Two real-world LAAC registries, enrolling 744 consecutive Amplatzer and Watchman patients from 2009 to 2018, were retrospectively analyzed.

RESULTS All events are reported per 100 patient-years. Two hundred and sixty one octogenarians and 483 non-octogenarians with a mean follow-up of 1.7 ± 1.3 and 2.3 ± 1.6 years, and a total of 1,502 patient-years were included. Octogenarians had a higher risk for stroke (CHA₂DS₂-VAsc score: 5.2 ± 1.2 vs. 4.3 ± 1.7 , $P < 0.0001$) and bleeding (HAS-BLED score: 3.3 ± 0.8 vs. 3.1 ± 1.1 , $P = 0.001$). The combined safety endpoint of major periprocedural complications and major bleeding events at follow-up was comparable (30/446, 6.7% vs. 47/1056, 4.4%; hazard ratio [HR] = 1.2; 95% confidence interval [CI]: 0.73–1.98; $P = 0.48$) between the groups. The efficacy endpoint of all-cause stroke, systemic embolism, and cardiovascular/unexplained death occurred more often in octogenarians (61/446, 13.7% vs. 80/1056, 7.6%; HR = 7.0; 95% CI: 4.53–10.93; $P < 0.0001$). Overall, octogenarians had a lower net clinical benefit, i.e., the composite of all above mentioned hazards, from LAAC compared to younger patients (82/446, 18.4% vs. 116/1056, 11.0%; HR = 4.6; 95% CI: 3.11–7.0; $P < 0.0001$). Compared to the anticipated stroke rate, the observed rate decreased by 41% in octogenarians and 53% in non-octogenarians. The observed bleeding rate was reduced by 10% octogenarians and 41% non-octogenarians.

CONCLUSIONS LAAC can be performed with similar safety in octogenarians as compared to younger patients. On the long-term, it both reduces stroke and bleeding events, although to a lesser extent than in non-octogenarians.

As the most frequent arrhythmia, atrial fibrillation (AF) is associated with an increased risk of cognitive decline, stroke, disability, and mortality. The prevalence of AF is 2% in the general population and rises steadily with age, 3.7%–4.2% of subjects are aged above 60 years and up to 17% are octogenarians (age ≥ 80 years).^[1] Stroke risk from AF increases exponentially with age and is estimated at 23.9% per year in patients aged 80 years and older.^[2] Additionally, patients ≥ 80 years with AF, who are treated with oral

anticoagulation (OAC), have a higher incidence of hemorrhagic events than younger patients.^[3] Therefore, octogenarians with AF are at highest risk for both thromboembolic and bleeding events. OAC is the standard of care for stroke risk. However, clinical evidence shows underuse of OAC in the elderly, who would have the highest benefit regarding ischemic stroke risk. This is mainly due to concerns about bleeding or prior bleedings. Factors of comorbidity, like impaired cognition, nonadherence, history of falls or bleedings, renal dysfunction,

as well as concomitant drugs are reasons for leaving a substantial fraction of patients without stroke protection by OAC.^[4] Left atrial appendage closure (LAAC) is recommended as an alternative strategy for stroke prevention in AF patients who are not suitable for long-term treatment with OAC.^[5,6] Therefore, LAAC might be an attractive option for elderly AF patients. Several studies reported similar feasibility and safety of LAAC in subjects aged > 75 years compared to younger patients.^[7-11] Furthermore, those studies showed favorable early clinical outcomes with regard to stroke and bleeding protection.

Whether elderly patients have persistent long-term effects of LAAC has not been studied yet. Therefore, the subject of the present study was to compare the clinical benefit of LAAC in octogenarians with non-octogenarians based on the results of two real-world registries.

METHODS

Study Cohort

Two real-world LAAC registries (University Hospital Bern, Switzerland and Coburg Hospital, Germany), enrolling consecutive patients from July 2009 to April 2018, were retrospectively analyzed. Indications for LAAC were based on current standard recommendations.^[5,6] Inclusion criteria comprised patients ≥ 18 years with nonvalvular atrial fibrillation with a high risk for cardioembolic events (CHA₂DS₂-VASc score ≥ 2) and relative or absolute contraindications to OAC. Exclusion criteria were any evidence of infection, pregnancy, and indications for OAC other than AF. All patients provided written informed consent according to the requirements and approval of the local ethics committees. Between September 2015 and March 2018, clinical follow-up was carried out by patient visits, hospital stays, and surveys. Due to meticulous tracking, follow-up information could be obtained from all patients. Adverse events underwent adjudication by a clinical event committee of two independent physicians, and in case of disagreement by a third referee. Analyses were performed according to the intention-to-treat principle. The study complies with the Declaration of Helsinki.

LAAC Procedure

Patients underwent LAAC with Amplatzer Cardiac Plug (ACP) and Amulet (Abbott, St. Paul, MN, US), or Watchman (Boston Scientific, Marlborough, MA, US) occluders. Procedural aspects of these devices were previously described in detail.^[12] LAAC was performed either as a single procedure or combined with diagnostic coronary angiography and patent foramen ovale (PFO) or atrial septal defect (ASD) closure. Most procedures were performed under local anesthesia and in conscious sedation only. Procedures were principally guided by fluoroscopy, intraprocedural transesophageal echocardiography (TEE) was used in some cases depending on the centers' routine. The devices were implanted via transseptal puncture or PFO/ASD by use of a delivery sheath. TEE was performed after 6 weeks to 6 months to document sufficient LAA closure without peri-device leak (minor leak < 5 mm, major leak ≥ 5 mm) or device-related thrombus. Postprocedural antithrombotic therapy was left at the discretion of the respective operator, accounting for medical history (e.g., recent percutaneous coronary intervention (PCI) or other intervention). It typically consisted of dual antiplatelet therapy with acetylsalicylic acid and clopidogrel for 1-6 months and single antiplatelet or no therapy thereafter.

Definitions and Endpoints

Demographic, clinical and procedural characteristics, as well as adverse events and endpoints were obtained according to the recommendations of the European Heart Rhythm Association European (EHRA) and the Associations of Percutaneous Coronary Interventions (EAPCI), the Bleeding Academic Research Consortium (BARC), the Valve Academic Research Consortium criteria (VARC), and the 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials.^[12-15] The three predefined endpoints were adopted from the PROTECT-AF study.^[16] The primary efficacy endpoint was a composite of all-cause stroke, systemic embolism, and cardiovascular/unexplained death. The primary safety endpoint consisted of major periprocedural complications and major bleeding events at follow-up. The combined hazard endpoint was a composite of all above mentioned hazards. Device success



was defined as correct deployment and implantation of the respective LAA occluder. Periprocedural major adverse events included procedural mortality (< 72 h after the index procedure), all-cause stroke, systemic embolism, device embolization, cardiac tamponade, major bleeding after BARC, myocardial infarction, and other relevant complications leading to prolonged hospital stay. According to the definition of the BARC, bleeding was defined as fatal (type 5) or major with hemoglobin drop of > 3 g/dL requirement of packed red blood cell transfusions or intracranial hemorrhage (type 3a-c). Minor bleeding was defined as not actionable (type 1) or actionable (type 2) requiring medical intervention, leading to prompt evaluation or hospitalization but not meeting the criteria of major bleeding.^[13]

Statistical Analysis

Statistical analysis was performed using GraphPad Prism software, Version 8.0 (GraphPad Software, LLC, San Diego, CA, USA). Continuous variables are presented as mean \pm SD. Those were compared using the unpaired *t*-test. Categorical variables are expressed as frequency (percentages) and were compared with the chi-square test. The Kaplan-Meier method was used for graphical assessment of time-dependent events. For comparison of event curves, the log-rank (Mantel-Cox) test was used. For determination of hazard ratio, the Mantel-Haenszel method was applied. All tests and confidence intervals are two-sided, and an alpha level of 0.05 was chosen to determine statistical significance of differences. Logistic regression analyses were performed to identify predictors for adverse clinical events. Odds ratios (OR) are presented with the corresponding confidence intervals calculated to the 95th percentile (95% CI). In both groups, stroke and bleeding rates were compared with the anticipated rate by the CHA₂DS₂-VASc and HAS-BLED scores.^[17,18] Stroke and bleeding reduction were calculated as (estimated event rate – actual event rate)/estimated event rate.

RESULTS

Patients Characteristics

A total of 744 patients underwent LAAC with

Amplatzer or Watchman occluders at two centers between 2009 and 2018. Of those 35.1% were octogenarians and 64.9% non-octogenarians. Baseline characteristics are shown in Table 1. The average age of octogenarians was 84.0 \pm 3.0 years and of non-octogenarians 70.4 \pm 7.8 years ($P < 0.0001$), respectively. Octogenarians were more likely to be of female gender (47.1% [octogenarians] vs. 31.7% [non-octogenarians], $P < 0.001$) and had a higher stroke and bleeding risk as shown in Figure 1 (CHA₂DS₂-VASc score: 5.2 \pm 1.2 vs. 4.3 \pm 1.7, $P < 0.001$; HAS-BLED score 3.3 \pm 0.8 vs. 3.1 \pm 1.1, $P = 0.001$). In addition, this group was affected more often from coronary artery disease (60.5% vs. 48.9%, $P = 0.002$) and prior PCI/coronary artery bypass grafting (CABG) (52.1% vs. 44.5%, $P = 0.047$). Also, the body mass index was lower in octogenarians (26.9 \pm 4.6 vs. 29.6 \pm 18.9 kg/m², $P = 0.035$). The increased risk for stroke in elderly patients was due to age and vascular disease, there were no significant differences between groups with regard to the prevalence of chronic heart failure, hypertension, or diabetes mellitus.

Procedural Characteristics

Procedural aspects and TEE follow-up are depicted in Table 2. Device success was high and similar for both groups as depicted in Figure 1 (96.2% [octogenarians] vs. 97.7% [non-octogenarians], $P = 0.34$). Less contrast volume (115.5 \pm 5.1 vs. 144.2 \pm 4.2 mL, $P < 0.001$) was used in octogenarians. Furthermore, in this group more procedures were guided by TEE (62.5% vs. 50.5%, $P = 0.001$). The rate of major periprocedural complications (3.4% vs. 4.8%, $P = 0.40$) was comparable between the groups. Due to the lack of a randomised design of this study and frailty of the elderly patient population, the TEE follow-up is incomplete and was performed less frequently in octogenarians (58.6% vs. 70.8%, $P = 0.001$). The rate of device-related thrombus was similar for both groups (3.1% vs. 3.1%, $P = 0.98$). In the octogenarian group, one patient with device-related thrombus suffered a transient ischemic attack (TIA) and another one a non-disabling ischemic stroke. Of the non-octogenarians, device-related thrombus was associated with two ischemic, disabling strokes. The rate of major peri-device leaks



Table 1 Baseline characteristics.

	Octogenarians, n = 261	Non-octogenarians, n = 483	P-value
Age at time of LAAC, yrs	84.0 ± 3.0	70.4 ± 7.8	< 0.0001
Body mass index, kg/m ²	26.9 ± 4.6	29.6 ± 18.9	0.035
Female gender	123 (47.1%)	153 (31.7%)	< 0.0001
Arterial hypertension	236 (90.4%)	434 (89.9%)	0.81
Diabetes mellitus	80 (30.7%)	159 (32.9%)	0.53
Coronary artery disease	158 (60.5%)	236 (48.9%)	0.002
Prior PCI/CAGB	136 (52.1%)	215 (44.5%)	0.047
Left ventricular ejection fraction	54.2% ± 12.6%	54.0% ± 12.3%	0.78
Congestive heart failure	91 (34.9%)	151 (31.3%)	0.32
GFR, mL/min	59.5 ± 24.7	69.6 ± 28.1	0.13
Prior all-cause stroke	68 (26.1%)	156 (32.3%)	0.067
Prior major bleeding	161 (61.7%)	269 (55.7%)	0.11
CHA ₂ DS ₂ -VASc score	5.2 ± 1.2	4.3 ± 1.7	< 0.0001
HAS-BLED score	3.3 ± 0.8	3.1 ± 1.1	0.001
Anti-thrombotic medical therapy prior to LAAC			
Any oral anticoagulation	175 (67.0%)	317 (65.6%)	0.65
Vitamin K antagonists	124 (47.5%)	227 (47.0%)	0.86
Non-vitamin K dependent oral anticoagulants	55 (21.1%)	97 (20.1%)	0.75
ASA	94 (36.0%)	175 (36.2%)	0.95
Platelet inhibitors other than ASA	46 (17.6%)	87 (18.0%)	0.90

Data provided as *n* (%) or mean ± SD. ASA: acetylsalicylic acid; CABG: coronary artery bypass grafting; LAAC: left atrial appendage closure; PCI: percutaneous coronary intervention.

(2.0% vs. 1.5%, *P* = 0.85) was also comparable. In non-octogenarians, one patient with a major pericardial leak suffered from a non-disabling, ischemic stroke at follow-up. Antithrombotic therapy following LAAC was similar for both groups and consisted mainly of a dual platelet inhibition with acetylsalicylic acid (92.7% vs. 94.0%, *P* = 0.50) and clopidogrel (93.9% vs. 95.0%, *P* = 0.50) for 1 to 6 months, followed by a single antiplatelet if there was an indication for it. In case of OAC following LAAC (2.7% vs. 2.3%, *P* = 0.73) given unsuccessful intervention or a combined intervention with a pulmonary vein isolation, Non-vitamin K dependent oral anticoagulants (NOACs) were more often administered in octogenarians (1.9% vs. 0.4%, *P* = 0.04).

Clinical Outcomes

Clinical outcomes are listed in Table 3. All events are reported per 100 patient-years. The mean follow-up was 1.7 ± 1.3 (octogenarians) and 2.3 ± 1.6 (non-octogenarians) years and included a total of 1,502

patient-years. Kaplan-Meier curves of the primary endpoints and their components are shown in Figure 2. As expected, the primary efficacy endpoint occurred more often in octogenarians. It was reached in 61/446, 13.7% (octogenarians) vs. 80/1056, 7.6% (non-octogenarians), HR = 7.04; 95% CI: 4.53–10.9; *P* < 0.001. Octogenarians were more likely to suffer from all-cause stroke (19/446, 4.3% [octogenarians] vs. 22/1056, 2.1% [non-octogenarians]; HR = 2.1; 95% CI: 1.0–4.44, *P* = 0.049), as well as cardiovascular and unexplained deaths (58/446, 13.0% vs. 70/1056, 6.6%; HR = 2.3; 95% CI: 1.55–3.36, *P* < 0.0001). The primary safety endpoint did not differ significantly between the groups (30/446, 6.7% vs. 47/1056, 4.4%; HR = 1.2; 95% CI: 0.73–1.98; *P* = 0.48). However, a higher rate of major bleeding events at follow-up was observed in octogenarians (21/446, 4.7% vs. 26/1056, 2.5%; HR = 2.1; 95% CI: 1.10–3.88; *P* = 0.025). Considering all above-mentioned components of the primary efficacy and safety endpoint, the combined hazard endpoint, i.e., the net clinical benefit

Table 2 Procedural characteristics and TEE follow-up.

	Octogenarians, n = 261	Non-octogenarians, n = 483	P-value
Anesthesia			
Conscious sedation	248 (95.0%)	467 (96.7%)	0.89
General	8 (3.1%)	18 (3.7%)	0.67
TEE guidance	163 (62.5%)	244 (50.5%)	0.001
Amplatzer occluder	188 (72.0%)	397 (82.2%)	0.0012
Watchman occluder	73 (28.0%)	86 (17.8%)	0.0012
Fluoroscopy time, min	14.2 ± 0.1	13.1 ± 8.8	0.59
Total contrast volume, mL	115.5 ± 5.1	144.2 ± 4.2	<0.0001
Device success	251 (96.2%)	472 (97.7%)	0.34
Major periprocedural complication			
Death	1 (0.4%)	1 (0.2%)	0.66
Stroke	0 (0.0%)	2 (0.4%)	0.55
Cardiac tamponade	5 (1.9%)	14 (2.9%)	0.42
Major bleeding	6 (2.3%)	17 (3.5%)	0.36
Major access vessel complication	0 (0.0%)	1 (0.2%)	1.0
Need for bailout surgery	3 (1.2%)	4 (0.8%)	0.67
Device embolization	2 (0.8%)	4 (0.8%)	0.47
Severe kidney injury	2 (0.8%)	9 (1.9%)	0.24
Need for cardio-pulmonary resuscitation	5 (1.9%)	7 (1.4%)	0.63
Anti-thrombotic medical therapy post LAAC			
Any oral anticoagulation	7 (2.7%)	11 (2.3%)	0.73
Vitamin K antagonists	2 (0.8%)	9 (1.9%)	0.24
Non-vitamin K antagonists	5 (1.9%)	2 (0.4%)	0.04
ASA	242 (92.7%)	454 (94.0%)	0.50
Platelet inhibitors other than ASA	245 (93.9%)	459 (95.0%)	0.50
TEE follow-up			
TEE performed	153 (58.6%)	342 (70.8%)	0.001
Thrombus on device	6 (3.1%)	12 (3.1%)	0.98
Peri-device leak ≥ 5 mm	3 (2.0%)	5 (1.5%)	0.85

Data provided as *n* (%) or mean ± SD. ASA: acetylsalicylic acid; LAAC: left atrial appendage closure; TEE: transesophageal echocardiography.

was lower for octogenarians (82/446, 18.4% vs. 116/1056, 11.0%; HR = 4.6; 95% CI: 3.11–6.70; *P* < 0.0001).

Logistic Regression For Factors Associated With Adverse Clinical Events (Combined Hazard Endpoint)

In multiple logistic regression age (odds ratio [OR] = 1.04, 95% CI: 1.01–1.06, *P* = 0.01) and congestive heart failure (OR = 2.09, 95% CI: 1.25–3.49, *P* = 0.01) were identified as predictors for adverse clinical events (combined hazard endpoint) at follow-up (Table 4).

DISCUSSION

The purpose of the present study was to determine the net clinical benefit of LAAC in octogenarians compared to younger patients based on the results of a large, real-world cohort. The main findings were: (1) acute periprocedural outcomes, such as device success and the rate of periprocedural complications were comparable between the groups; (2) in the long-term, LAAC was less effective for prevention of all-cause stroke, cardiovascular/unexplained death and overall mortality in oc-



Table 3 Long-term clinical outcome.

	Octogenarians, n = 261 446 patient-years		Non-octogenarians, n = 483 1056 patient-years		P-value
Age at follow-up, yrs	86.1 ± 3.3		73.2 ± 7.6		< 0.0001
Time from study inclusion to follow-up in years	1.7 ± 1.3		2.3 ± 1.6		< 0.0001
	Events/Patient-years	Observed rate	Events/Patient-years	Observed rate	
Primary efficacy endpoint	61/446	13.7 (10.8-17.12)	80/1,056	7.6 (6.1-9.3)	<0.0001
Primary safety endpoint	30/446	6.7 (4.8-9.4)	47/1,056	4.4 (3.4-5.9)	0.48
Combined hazard endpoint	82/446	18.4 (15.1-22.2)	116/1,056	11.0 (9.2-13.0)	<0.0001
All-cause death	83/446	18.6 (15.3-22.5)	101/1,056	9.6 (7.9-11.5)	<0.0001
Cardiovascular/unexplained death	58/446	13.0 (10.2-16.4)	70/1,056	6.6 (5.3-8.3)	<0.0001
Stroke and TIA (any)	19/446	4.3 (2.7-6.6)	22/1,056	2.1 (1.4-3.1)	0.01
Stroke without TIA (any)	15/446	3.4 (2.0-5.5)	20/1,056	1.9 (1.2-2.9)	0.049
Disabling stroke	9/446	2.0 (1.1-3.8)	12/1,056	1.1 (0.7-2.0)	<0.0001
Non-disabling stroke	7/446	1.6 (0.8-3.2)	7/1,056	0.7 (0.3-1.4)	<0.0001
Ischemic stroke	15/446	3.3 (2.0-5.5)	18/1,056	1.7 (1.1-2.7)	<0.0001
Hemorrhagic stroke	0/446	0	2/1,056	0.2 (0.1-0.7)	0.005
TIA	4/446	0.9 (0.3-2.3)	2/1,056	0.2 (0.1-0.7)	0.02
Systemic embolism	1/446	0.2 (0.3-2.3)	3/1,056	0.3 (0.1-0.8)	0.35
Any bleeding	40/446	9.0 (6.7-12.0)	58/1,056	5.5 (4.3-7.0)	0.020
Major bleedings	21/446	4.7 (3.1-7.1)	26/1,056	2.5 (1.7-3.6)	0.025
Anti-thrombotic therapy at time of follow-up					
Any oral anticoagulation	25 (7.3%)		42 (8.7%)		0.77
Vitamin K antagonists	5 (1.9%)		17 (3.5%)		0.20
NOACs	18 (6.9%)		23 (4.8%)		0.26
ASA	172 (65.9%)		310 (64.2%)		1.0
Platelet inhibitors other than ASA	40 (15.3%)		63 (13.0%)		0.90

Data provided as n (%) or mean ± SD. ASA: acetylsalicylic acid; NOACs: non-vitamin K dependent oral anticoagulants; TIA: transient ischemic attack.

togenarians; (3) in terms of safety, the rate of bleedings at follow-up was also higher in this group; and (4) altogether, octogenarians had a lower net clinical benefit from LAAC than younger patients.

Efficacy and safety of LAAC in elderly patients have been examined in previous studies. Gafoor, *et al.*^[7] reported in 75 patients with an average age of 83.4 years and a mean CHA₂DS₂-VASc score of 5.2 a procedural success of 90.1% and 4.0% periprocedural complications. At 1-year follow-up, two non-cardiovascular deaths (2.7%) and one stroke (1.3%) were documented. A subgroup analysis of the ACP multicenter registry with 1 053 subjects, which compared patients < 75 vs. ≥ 75 years showed similar procedural success for both groups, although older patients had a higher incidence of cardiac tamponade. After a median follow-up of 16.8 months,

stroke and major bleeding rates were similar among groups.^[9] In a sub-analysis of the EWOLUTION registry with 1 025 patients, 84 patients ≥ 85 years of age were compared with the younger cohort. Procedural success and major periprocedural complications were similar in both groups. Despite the higher baseline stroke and bleeding risk in the elderly, there was no difference between the groups in the annualized stroke and major bleeding rates (0.8/100 patient-years in ≥ 85 years vs. 1.3/100 patient-years in < 85 years, *P* = 0.65).^[10] Finally, Yu, *et al.*^[11] documented in 351 patients, who underwent LAAC and were analyzed according to age (age ≥ 75 years [58.7%] vs. < 75 years [41.3%]), no significant differences with regard to procedural success rates and procedure-related complications. After a nearly 2-year follow-up, there was an increased trend of



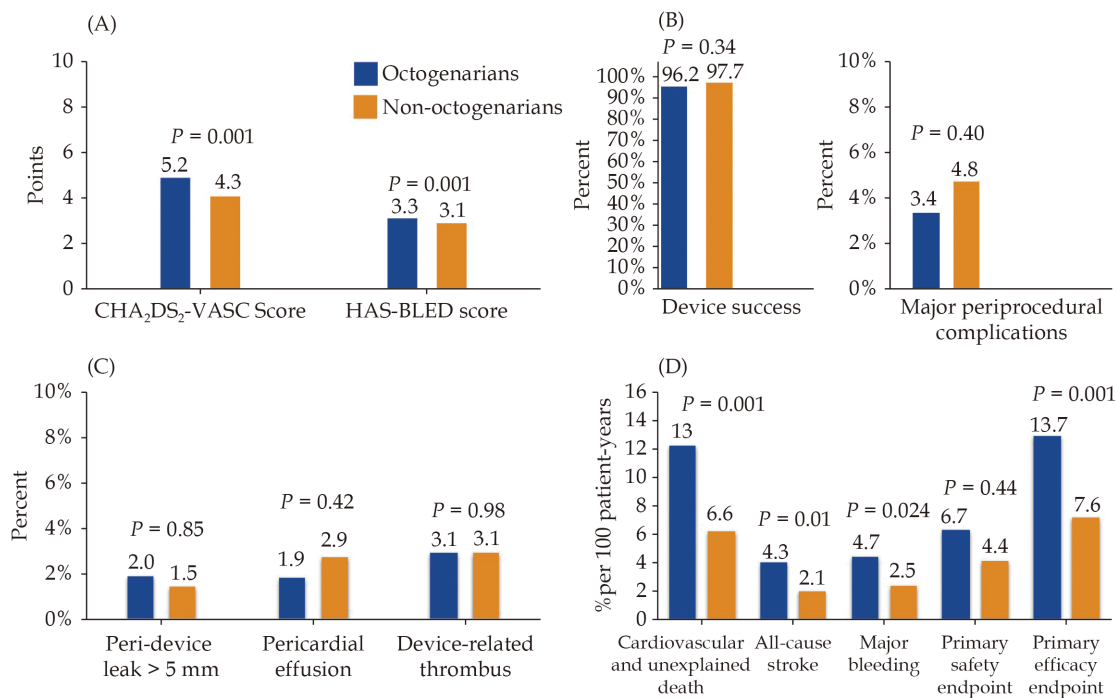


Figure 1 Comparison of key variables, TEE findings and clinical outcomes after LAAC in octogenarians vs. non-octogenarians. (A): Baseline risk for stroke and bleeding; (B): device success and major periprocedural complications; (C): TEE at follow up; and (D): long-term efficacy and safety. LAAC: left atrial appendage closure; TEE: transesophageal echocardiography.

bleeding events in the group aged ≥ 75 years, but there were no significant differences between both groups in all-cause death, cardiovascular death, stroke/TIA/system embolism, device thrombus and major peri-device leaks.^[13] The rate of successful device implantation and major periprocedural complications in the present study was similar between the groups, and comparable to other real-world registries that included different LAAC devices (Italian registry: device success of 95.4%; major complication rate of 6.2%; German registry: technical success of 98.1%, major complication rate of 4.5%).^[19,20] With regard to the occurrence and rate of device-related thrombi, which are associated with ischemic strokes, no differences were observed between octogenarians and younger patients. This is in contrast to other studies, which identified older age, history of stroke, smoking and female gender as risk markers for device-related thrombus.^[21,22] However, the rate of device-related thrombi in the octogenarian group may be underestimated because this study arm underwent less frequently TEE follow-up. Besides stroke prevention, LAAC also prevents bleedings by avoiding oral an-

ticoagulation. Bleeding events accumulate over the lifespan and lead to an increased overall mortality. Randomised trials and propensity score matched studies, which compared LAAC to oral anticoagulation, demonstrated that LAAC is associated with a significant reduction in bleeding events and all-cause mortality.^[23-25] Similarly to previous reports, bleeding events at follow-up were low in the younger patient group (Italian registry: 2.2% per 100 patient-years; German registry: annual bleeding rate of 1.6%),^[19,20] but significantly higher in octogenarians with higher HAS-BLED scores. Compared to the anticipated rate of the HAS-BLED score, the observed bleeding rate was reduced by 10% in octogenarians and 41% non-octogenarians (Figure 3). Nine (42.9%) octogenarian patients with a major bleeding event were on a single and three (14.3%) on a dual antiplatelet therapy, one patient was treated with a vitamin K antagonist and eight patients (38.1%) received no antithrombotic medication. Fourteen (66.7%) of those patients suffered from gastrointestinal bleedings. This illustrates the clinical challenge in every day practice when treating elderly patients with antithrombotic medication.



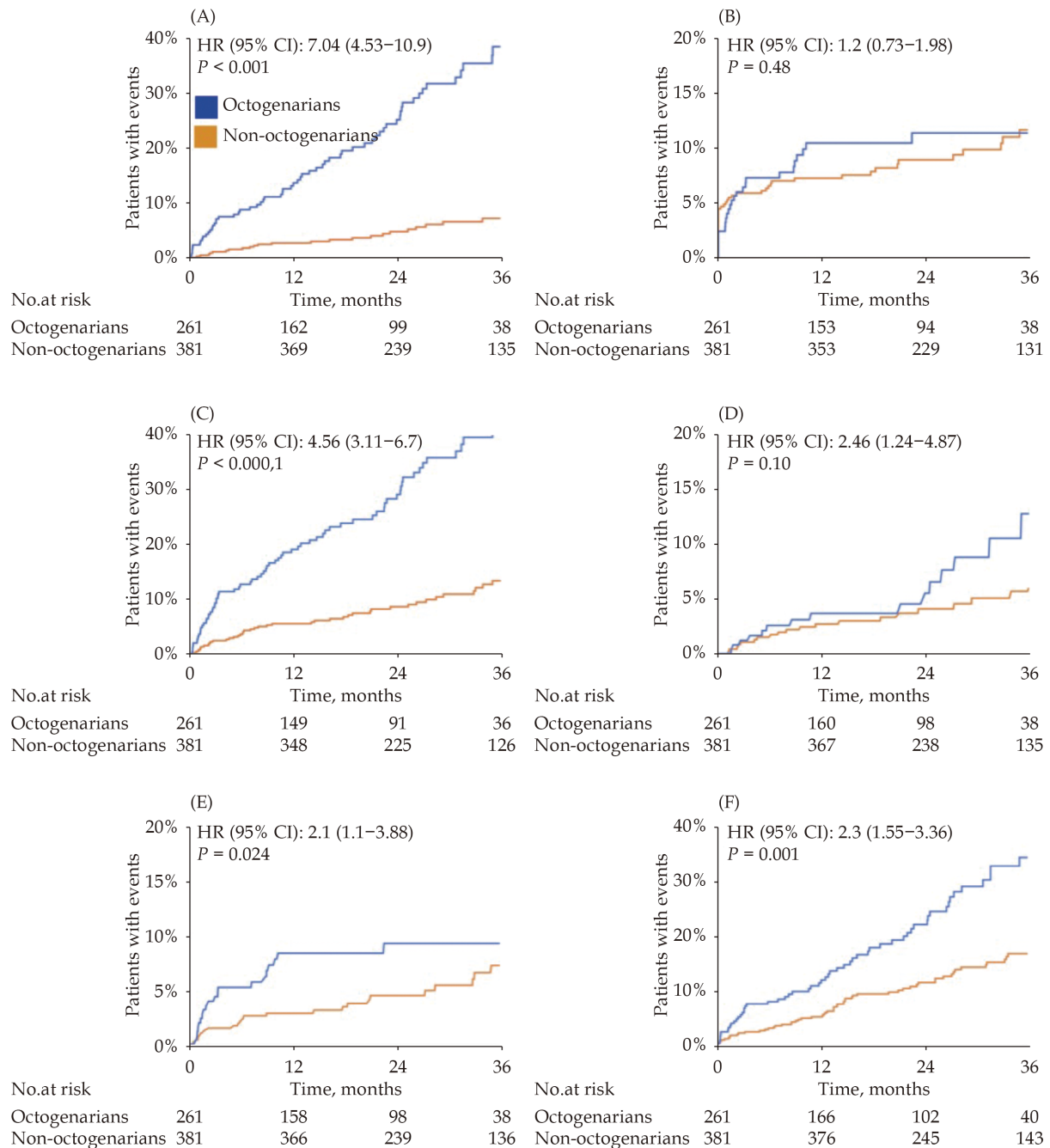


Figure 2 Kaplan-Meier curves. (A): Primary efficacy endpoint; (B): primary safety endpoint; (C): combined hazard endpoint (net clinical benefit); (D): all-cause stroke; (E): major bleeding event; and (F): cardiovascular or unexplained death at 36 months. HR: hazard ratio.

Due to the higher $\text{CHA}_2\text{DS}_2\text{-VASc}$ scores of the older group, the rate of all-cause stroke at follow-up was twice as high in octogenarians than in younger patients. However, compared to the anticipated stroke rate of the $\text{CHA}_2\text{DS}_2\text{-VASc}$ score, the observed stroke rate was still reduced by 41% in octogenarians versus 53% in non-octogenarians (Figure 3). In contrast, a subanalysis of the EWOLUTION re-

gistry in patients older than 85 years, reported no differences in the annual rates of stroke with a relative risk reduction of 80% in both groups.^[9] With regard to all-cause mortality, the rates of death in the non-octogenarian group is comparable to the Spanish multicenter registry with a comparable patient population (598 patients, median 75.4 years, death rate: 7.0%).^[26] As expected, in the octogenarian

Table 4 Predictors for adverse clinical events (combined hazard endpoint).

	OR (95% CI)	P value
Age at LAAC	1.04 (1.01–1.06)	0.01
Female	1.03 (0.68–1.58)	0.88
Body mass index	0.99 (0.96–1.01)	0.64
Diabetes mellitus	1.20 (0.78–1.84)	0.40
Arterial hypertension	1.38 (0.72–2.79)	0.36
Coronary artery disease	1.21 (0.57–2.48)	0.61
Prior PCI/CABG	0.84 (0.42–1.75)	0.64
Congestive heart failure	2.09 (1.25–3.49)	0.01
Glomerular filtration rate	0.99 (0.90–1.0)	0.10
Kidney disease	0.88 (0.46–1.66)	0.70
Liver disease	1.18 (0.54–2.53)	0.67
CHA ₂ DS ₂ -VASc score	1.01 (0.83–1.23)	0.94
HAS-BLED score	1.29 (0.99–1.67)	0.06

CABG: coronary artery bypass grafting; LAAC: left atrial appendage closure; PCI: percutaneous coronary intervention.

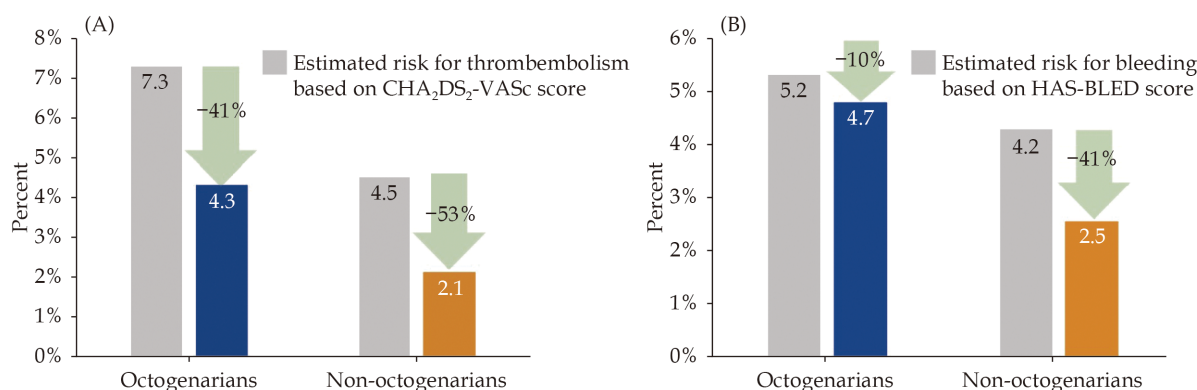


Figure 3 Effectiveness of LAAC in reduction of stroke and TIA based on annual rate predicted by CHA₂DS₂-VASc score (A) and major bleeding based on annual rate predicted by HAS-BLED score (B). LAAC: left atrial appendage closure; TIA: transient ischemic attack.

group, a higher rate of all-cause mortality, as well as cardiovascular and unexplained death at follow-up was observed. This result is reasonable since patients with advanced age have more comorbidities including congestive heart failure, coronary artery disease, prior PCI/CAGB and renal impairment. In the multiple logistic regression analysis, age and congestive heart failure were identified as predictors for adverse clinical events. Besides age, in the Spanish study also the occurrence of intracranial hemorrhage and stroke were significantly associated with higher mortality at follow-up.^[26] The relatively high rates of cardiovascular and all-cause mortality in the present study reflect a polymorbid patient population. Therefore, when considering LAAC in octogenarians, individual aspects like co-morbidities,

quality of life, and anticipated residual life expectancy should be taken into account.

LIMITATIONS

Limitations of the present study include the observational, retrospective and nonrandomized design. It has a moderate sample size and was not powered to detect differences in age groups. Differences in baseline characteristics like gender, body mass index and the prevalence of coronary artery disease are substantial confounders. Also, disparities in procedural characteristics, e.g., occluder type, the rate of TEE guidance, and total contrast volume represent a relevant bias.

Other major limitations are a missing random-



ized control group for event reduction but only a calculated stroke and bleeding risk to estimate the benefit of LAAC. The rate of TEE follow-up was incomplete and lower in octogenarians, which may have led to an over- or under-estimation of device-related thrombi and peri-device leaks in this group.

CONCLUSIONS

This study suggests that LAAC can be performed with similar procedural success and safety in octogenarians compared to younger patients. It also reduces stroke and bleedings events in the long-term, although to a lesser extent than in non-octogenarians.

COMPLIANCE WITH ETHICAL STANDARDS

The authors state that the study complies with the Declaration of Helsinki. The locally appointed ethics committee has approved the research protocol. Informed consent has been obtained from the subjects.

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Drs. Mohrez, Gloekler, Meier and Kleinecke took part in the data evaluation and in the planning, writing, revising, and reviewing the final draft of this manuscript. S. Achenbach participated in data analysis and interpretation and he critically revised the manuscript for important intellectual content. All co-authors contributed fully in terms of the design of the study, the evaluation of data, the actual manuscript preparation, and the revision and approval of the final submitted manuscript. As the corresponding author, Dr Kleinecke confirms that all authors have seen and approved the final text.

CONFLICT OF INTERESTS

Caroline Kleinecke has received speaker honoraria from Boston Scientific. Johannes Brachmann has received consulting fees from Abbott, Medtronic, Bayer, Liva-nova, Pfizer, Boston Scientific, Boehringer Ingelheim and Biotronik; Stephan Windecker has received grants to the institution from Abbott, Biotronik, Boston Scientific, Medtronic and Edwards Lifesciences; Bernhard Meier is a proctor for Abbott;

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