Left atrial appendage occlusion in atrial fibrillation after intracranial hemorrhage

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ABSTRACT

Objective: To evaluate the safety and feasibility of percutaneous left atrial appendage occlusion (LAAO) in patients with atrial fibrillation (AF) and previous intracranial hemorrhage (ICH).

Methods: In an explorative, prospective, single-center, observational study, LAAO was performed in patients with previous ICH and AF using the Amplatzer Cardiac Plug device. Risks of ischemic strokes and hemorrhagic complications were estimated using the CHA₂DS₂Vasc score and the HAS-BLED score. Before and 1, 6, 12, and 24 months after the procedure, clinical status and complications were recorded. Major complications were predefined as periprocedural stroke, death, pericardial effusion, and device embolism.

Results: LAAO was performed in 20 patients. Based on CHA₂DS₂Vasc score (mean 4.5 ± 1.4) and HAS-BLED score (mean 4.7 ± 1.0), annual risks of stroke and hemorrhagic complications were 4.0%–6.7% and 8.7%–12.5%, respectively. No patient had a procedure-related complication. Minor postprocedural complications were observed in 4/20 patients (2 inguinal hematoma, 1 self-limiting asystole, and 1 thrombus formation on device). No ischemic or hemorrhagic stroke occurred during a mean follow-up of 13.6 ± 8.2 months.

Conclusions: In this first study of LAAO in patients with previous ICH, LAAO appears feasible and safe. A larger, controlled trial is needed to assess the efficacy and safety of the procedure compared to other preventive measures.

Classification of evidence: This study provides Class III evidence that in patients with a history of previous ICH and AF, percutaneous LAAO is safe and feasible. *Neurology*® 2014;82:135–138

GLOSSARY

ACP = Amplatzer Cardiac Plug; **AF** = atrial fibrillation; **ICH** = intracranial hemorrhage; **LAA** = left atrial appendage; **LAAO** = left atrial appendage occlusion; **mRS** = modified Rankin Scale; **OAC** = oral anticoagulation; **TEE** = transesophageal echocardiogram.

Oral anticoagulation (OAC) in patients with atrial fibrillation (AF) and previous intracranial hemorrhage (ICH) is associated with an increased risk of recurrent ICH, and its use in this setting is therefore controversial.¹ Left atrial appendage occlusion (LAAO) has a role in patients with thromboembolic risk who cannot be managed in the long term using any form of OAC.^{2–4} Remarkably, however, the sole randomized trial of LAAO (PROTECT AF) included only patients eligible for warfarin treatment, excluding patients with previous ICH⁵; no prospective data on this important patient population are available from registries. We hypothesize that percutaneous LAAO could be an alternative stroke prevention in these patient populations.

The purpose of our prospective study was to provide pilot data regarding the feasibility and safety of LAAO in patients with AF and previous ICH.

METHODS We conducted an explorative, prospective, observational, uncontrolled, single-center study at the University Hospital of Heidelberg. Between November 2010 and November 2012, patients aged ≥ 18 years with documented nonvalvular AF and a history of previous ICH (i.e., intracerebral, subdural, or subarachnoid hemorrhage) were included. Patients with another indication for OAC in addition to AF or with a premorbid modified Rankin Scale (mRS) score > 4 were excluded. To minimize selection bias, screening for enrollment was consecutive.

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The medical history, basic demographic variables, NIH Stroke Scale, mRS, CHA₂DS₂-Vasc score, and HAS-BLED score⁶ were recorded. The day after the procedure and 1, 6, 12, and 24 months thereafter, clinical status and intermittent complications were documented.

In accordance with the PROTECT AF trial,⁵ intervention-related major complications were predefined as ischemic or hemorrhagic stroke, death, pericardial effusion, and device embolism. Inguinal pseudoaneurysm, arteriovenous fistula, hematoma, thrombus formation on the device, and minor bleeding (single or repeated) not requiring intervention were predefined as minor complications.

Left atrial appendage occlusion. LAAO was performed under transesophageal echocardiographic and fluoroscopic guidance. Access to the left atrium was obtained via the right femoral vein and subsequent transseptal puncture. To prevent clot formation, heparin was given IV after transseptal puncture. A sheath was inserted into the orifice of the left atrial appendage (LAA) and the occluder (Amplatzer Cardiac Plug [ACP]; St. Jude Medical, St. Paul, MN) was implanted into the LAA using a self-expanding nitinol frame.

After the procedure, antithrombotic treatment using combined antiplatelet medication (aspirin 100 mg/day and clopidogrel 75 mg/day) was given for 3 months, followed by aspirin monotherapy thereafter. Device position was verified by transesophageal echocardiogram (TEE) at 1 and 6 months after the procedure.

Standard protocol approvals, registrations, and patient consents. The local ethics committee approved all study procedures. Each patient provided written informed consent for study participation.

Statistical analysis. Due to the explorative character of the study, all statistical analyses are descriptive. Data were analyzed using the statistical software package SPSS version 18.0. Categorical data are reported in absolute and relative frequencies. Continuous variables are presented as mean $\pm$ SD.

Classification of evidence. This study aimed to obtain Class III evidence that in patients with a history of previous ICH and AF, percutaneous LAAO is safe and feasible.

RESULTS The figure illustrates a flow diagram of the study population. A total of 24 patients with AF and previous ICH agreed to undergo LAAO. In 3 patients, TEE revealed that the LAA was too large for device placement, and in 1 patient a thrombus was detected in the LAA before the intervention (table 1). Hence, LAAO was performed in 20 patients (table 1).

Patient characteristics and baseline variables are shown in table 2. According to the mean CHA₂DS₂-Vasc score (table 2), the estimated subsequent annual stroke risk was 4.0%–6.7%. Based on the mean HAS-BLED score, the annual bleeding risk was 8.7%–12.5% for major hemorrhage and 1.2%–1.6% for ICH. No patient had a periprocedural major complication. Four patients had a postprocedural minor complication (2 inguinal hematoma, 1 self-limiting asystole, 1 thrombus formation on the occluder). Device-associated thrombus resolved without ischemic complications after 2 months of OAC with rivaroxaban.

The clinical efficacy of LAAO was evaluated during a mean follow-up period of 13.6 ± 8.2 months. No ischemic or hemorrhagic strokes and no TIAs were observed. Disability scores were unchanged at the follow-up visits (table 2).

DISCUSSION This pilot study of LAAO dedicated exclusively to patients with AF and previous ICH suggests that LAAO is feasible and safe in these patients.

While adverse events during long-term pharmacologic therapy with OAC usually develop continuously over time, interventions such as LAAO can cause early procedure-related events.⁷ The only prospective randomized controlled trial (PROTECT AF) comparing the efficacy and safety of LAAO and warfarin in patients with AF⁵ reported periprocedural complications in 7.4% of patients. The adverse events encompassed pericardial effusion (4.8%), periprocedural stroke (1.1%), and device embolism (0.6%). A subsequent study registry (CAP) also using the Watchman device documented substantially lower complication rates (pericardial effusion 2.2% and periprocedural stroke 0%).⁷ Limited data obtained using the ACP device initially showed complication rates of 7.3%,⁸ but the incidence of complications has decreased considerably with increasing experience of those performing the intervention.^{7,9} We observed no major and only 4 minor complications in our patients.

Patients with AF have an increased risk of hemorrhagic complications, particularly when under treatment with antithrombotics or anticoagulants. The HAS-BLED score was introduced to estimate the bleeding risk and it correlates with ICH risk.¹⁰ The mean HAS-BLED

Figure Flow diagram of study population

AF = atrial fibrillation; ICH = intracranial hemorrhage; LAAO = left atrial appendage occlusion; mRS = modified Rankin Scale; OAC = oral anticoagulation.

Table 1 Case series of patients with AF and previous ICH treated with LAAO

Patient sex/ age, y	Type of previous ICH	CHA ₂ DS ₂ Vasc score	HAS-BLED score	Secondary prevention before LAAO	Presumed etiology of bleeding	Time from ICH to LAAO, mo	Major complication ^a	Minor complication ^b
M/76	ICH	5	5	Clopidogrel	Hypertensive	56	—	—
M/66	ICH	5	6	Aspirin 100	Hypertensive	69	—	—
F/70	ICH	6	6	Aspirin 100	Unknown	68	—	—
M/66	SDH	3	5	Aspirin 300	OAC, INR 2.3	43	—	—
M/76	ICH	3	4	Phenprocoumon	Hypertensive	13	—	—
M/74	ICH	5	5	—	OAC, INR 2.3	13	—	—
M/78	SDH	6	5	—	Fall	4	—	—
F/71	ICH	6	6	Aspirin 100	Unknown	97	—	—
F/77	ICH	5	5	Aspirin 100	OAC, INR 2.7	3	—	—
M/70	SDH	5	6	Aspirin 100+, clopidogrel	OAC, INR 2.9	1	—	Self-limiting asystole
M/68	SDH	4	5	Dabigatran	Spontaneous	12	—	Inguinal hematoma
F/70	ICH	6	5	Aspirin 100	OAC, INR 2.5	5	—	—
M/78	ICH	3	4	—	Amyloid angiopathy	2	—	—
M/59	ICH	1	3	—	Amyloid angiopathy	4	—	—
F/69	ICH	4	3	—	OAC, rivaroxaban	5	—	—
M/80	ICH	3	4	Rivaroxaban	OAC, INR 5.2	11	—	—
M/73	ICH	5	5	—	Hypertensive	1	—	—
F/78	ICH	4	4	Rivaroxaban	Cavernoma, OAC, INR 2.3	5	—	Thrombus on device
M/83	SAH	6	4	—	Unknown	10	—	Inguinal hematoma
M/70	ICH	4	3	Aspirin	Hypertensive	39	—	—

Abbreviations: AF = atrial fibrillation; ICH = intracranial hemorrhage; INR = international normalized ratio; LAAO = left atrial appendage occlusion; OAC = oral anticoagulation; SAH = subarachnoid hemorrhage; SDH = subdural hemorrhage.

^aStroke, death, pericardial effusion, device embolism.

^bInguinal pseudoaneurysm, inguinal arteriovenous fistula, inguinal hematoma, minor bleeding not requiring intervention, thrombus formation on Amplatzer Cardiac Plug device.

score in our study is associated with an increased annual risk of major (8.7%–12.5%) and intracranial bleeding (1.2%–1.6%) under treatment of OAC. We observed no ICH or major systemic bleeding events during follow-up. These findings regarding periprocedural and hemorrhagic complications suggest that it is safe to perform LAAO in AF patients with previous ICH.

Due to the limited number of patients and the study design, our data do not permit firm conclusions regarding the efficacy of the procedure. During a mean follow-up period of 13.6 ± 8.2 months, however, no strokes or systemic embolism were noted in our study. Post hoc analysis of the PROTECT AF and CAP registry data showed the greatest net clinical benefit of LAAO in patients at a higher risk of stroke according to the CHADS₂ score and in patients with increased risk of bleeding.⁹ The annual risk of stroke according to the CHA₂DS₂Vasc score in our study was at least twice as high as the annual stroke rates reported in previous LAAO studies (2.2% and 2.0%, respectively).^{5,7}

New oral anticoagulants may help to prevent stroke in AF patients with previous ICH, because they have been consistently associated with a lower risk of ICH complications than warfarin.^{3,4} Moreover, the AVERROES trial reported no excess risk of major bleeding in AF patients treated with apixaban compared to aspirin.³ However, no data are yet available for new oral anticoagulants in patients with previous ICH.

Our study has strengths and limitations. It was prospective, patient enrollment was consecutive, and the patients were followed up for 2 years. The major limitations of the study are performance at a single center and the small number of patients, meaning that it lacks adequate power for robust conclusions regarding safety and efficacy. We therefore caution against uncritical alteration of routine clinical practice on the basis of our data. Moreover, our cohort encompassed heterogeneous subtypes with different latencies since the index ICH and differing risks of recurrent ICH.

Table 2 Patient characteristics

	Mean $\pm$ SD or n (%)	95% CI
Total patients	20 (100)	
Age, y	72.6 $\pm$ 5.8	70.1–75.1
Sex		
Male	14 (70.0)	49.9–90.1
Female	6 (30.0)	9.9–50.1
AF		
Paroxysmal	12 (60.0)	38.5–81.5
Permanent	8 (40.0)	18.5–61.5
Previous TIA	1 (5.0)	0.0–14.6
Previous ischemic stroke	8 (40.0)	18.5–61.5
Time from ICH to LAAO, mo	23.1 $\pm$ 28.6	10.6–35.6
CHA ₂ DS ₂ Vasc score	4.5 $\pm$ 1.4	3.8–5.2
HAS-BLED score	4.7 $\pm$ 1.0	4.3–5.1
NIHSS baseline	2.1 $\pm$ 2.7	1.4–23.9
mRS baseline	2.0 $\pm$ 1.2	1.5–2.5
Complication		
Major ^a	0 (0)	
Minor ^b	4 (20.0)	2.5–37.5

Abbreviations: AF = atrial fibrillation; CI = confidence interval; ICH = intracranial hemorrhage; LAAO = left atrial appendage occlusion; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale.

^aPeriprocedural stroke, pericardial effusion, device embolization, death.

^bInguinal pseudoaneurysm, inguinal arteriovenous fistula, inguinal hematoma, minor bleed-
ing not requiring intervention, thrombus formation on Amplatzer Cardiac Plug device.

This pilot study of LAAO in patients with AF and previous ICH suggests that LAAO may be an alternative to oral anticoagulation for stroke prevention in these patients. Further evaluation of the efficacy and safety of LAAO in large prospective, controlled trials is necessary to evaluate the value of the procedure.

AUTHOR CONTRIBUTIONS

S. Horstmann: data collection, analysis and interpretation of the data, drafting of the manuscript. C.Z.: LAAO procedure, revision of the manuscript. U.K.: LAAO procedure, revision of the manuscript. T.R.: data collection, revision of the manuscript. G.R.: statistical analysis, revision of the manuscript. N.G.: LAAO procedure, revision of the manuscript. S. Hardt: LAAO procedure, revision of the manuscript. R.V.: design and conceptualization of the study, analysis and interpretation of the data, drafting and revision of the manuscript.

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