Left atrial appendage occlusion in patients with atrial fibrillation and intracerebral haemorrhage associated with cerebral amyloid angiopathy: a multicentre observational study and pooled analysis of published studies

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Abstract

Background: Cerebral amyloid angiopathy (CAA) is a common cause of intracerebral haemorrhage (ICH) with a high recurrence risk. Left atrial appendage occlusion (LAAO) is a method for ischaemic stroke prevention in patients with atrial fibrillation (AF), potentially reducing the risk of intracranial bleeding in CAA-associated ICH. We aimed to determine the outcomes of AF patients with CAA-associated ICH undergoing LAAO.

Methods: We conducted a multicentre study of patients with CAA-associated ICH who underwent LAAO for stroke prevention. We pooled our findings with data from a systematic review of relevant published studies of LAAO for AF in ICH survivors reporting CAA diagnosis.

Results: We included data from 2 published studies (n=65) with CAA-specific data and our cohort study (n=37), providing a total of 102 participants (mean age 76.2 ± 8.0 years, 74.6% male) with CAA-related symptomatic ICH and AF treated with LAAO. The median follow-up period was 9.4 months [interquartile range (IQR) 4.2-20.6)]. Post-procedural antithrombotic regimens varied between single (73.0%) or dual antiplatelet therapy (16.2%), or direct oral anticoagulant (DOAC) (10.8%), with a median duration of 42 days (IQR 35–74). Post-procedural complications were uncommon, transient arrhythmias (2.1%) and non-life-threatening tamponade (2.1%). Pooled incidence rates of ischaemic stroke and ICH during follow-up were 5.16 (95% confidence interval (CI) 1.36-17.48) and 2.73 (95% CI 0.41-13.94) per 100 patient-years, respectively.

Conclusions: LAAO followed by short-term antithrombotic therapy might be a safe and effective ischaemic stroke preventive strategy in people with CAA-associated ICH and AF. However, randomised controlled trials are needed to determine how LAAO compares with long-term DOAC in this population.

PROSPERO registration number CRD42023415354.

Keywords: cerebral amyloid angiopathy, intracerebral haemorrhage, atrial fibrillation, left atrial appendage occlusion

Key messages

What is already known on this topic

- Cerebral amyloid angiopathy (CAA) is associated with a high annual risk of recurrent intracerebral haemorrhage (ICH)
- Atrial fibrillation (AF) is frequent in people with ICH, generating a clinical dilemma regarding the safety of long-term oral anticoagulation.

What this study adds

- Among AF patients with CAA-associated ICH who undergo left atrial appendage occlusion (LAAO), post-procedural antithrombotic regimens were heterogeneous, but approximately three-quarters received single antiplatelet therapy. Post-procedural annual ischaemic stroke and ICH rates were lower than predicted by CHA_2DS_2-VASc and HAS-BLED scores.

How this study might affect research, practice or policy

- Our study suggests that LAAO might be a promising option for ischaemic stroke prevention in patients with CAA-related intracerebral haemorrhage and AF; however, randomised controlled trials are needed to definitively establish its safety and effectiveness compared with the use of direct oral anticoagulants or other antithrombotic drug regimens.

Introduction

Cerebral amyloid angiopathy (CAA) is a common cause of lobar intracerebral haemorrhage (ICH) in older people, characterised by the deposition of amyloid beta peptides in cerebral cortical and leptomeningeal arteries, arterioles, and capillaries.[1 2] CAA has a high annual recurrent ICH risk, ranging 7.4% to 8.6%.[3-5] Approximately 20% to 30% of patients with ICH have non-valvular atrial fibrillation (AF),[6 7] for which, the principal treatment to prevent ischaemic cardioembolic stroke is long-term anticoagulation with a direct oral anticoagulant (DOAC).[8] A recently published individual participant data meta-analysis (IPDMA) evaluating the effects of oral anticoagulant (OAC) in patients with AF and spontaneous ICH demonstrated inconclusive effects on the risk of ischaemic or haemorrhagic major adverse cardiovascular outcomes.[9] Furthermore, a recent trial (ENRICH-AF, which was testing the use of the DOAC edoxaban versus avoiding edoxaban in survivors of intracranial haemorrhage and AF) has stopped enrolment of patients with intracranial bleeding patterns associated with CAA (i.e., lobar ICH or convexity subarachnoid haemorrhage (cSAH)) due to an unacceptably high risk of intracranial bleeding in patients assigned to edoxaban.

Several studies have shown the left atrial appendage (LAA) to be the major source of thrombus leading to thromboembolism in over 90% of patients with AF. Left atrial appendage occlusion (LAAO) achieves mechanical closure of the LAA,[10] and is of similar efficacy to oral anticoagulation for ischaemic stroke prevention in AF.[11 12] Due to the high risk of recurrent ICH in patients with CAA, LAAO is, an attractive alternative to long-term oral anticoagulation for ischaemic stroke prevention.[13-15] However, there are limited data on outcomes post-LAAO in patients with CAA and uncertainty about the safest post-procedure antithrombotic regime. In some previous studies, LAAO post-procedural antithrombotic therapy has involved OAC for a month, then dual antiplatelet therapy (DAPT) for six months, and then life-long single antiplatelet therapy (SAPT).[16] In patients with CAA, a low-intensity antithrombotic regimen

would ideally be preferred due to the very high baseline ICH risk; however, such treatment might not adequately prevent device-related thrombosis or protect from future stroke risk. Of note, patients who underwent LAAO were not included in the ENRICH-AF trial.[17]

We report on pooled data from a multicentre cohort study of patients with CAA-associated ICH undergoing LAAO, together with published data from a systematic review of the literature. We aimed to: (1) determine the risk of ischaemic stroke and recurrent ICH in patients with ICH due to CAA and AF who underwent LAAO; and (2) characterise post-procedure antithrombotic regimens.

Methods

Multicentre cohort study

We identified patients from prospective tertiary centre databases of all referrals for LAAO to Barts Heart Centre (BHC), Cambridge University Hospital (CUH), and University College London Hospitals (UCLH), from February 2015 to June 2023, with probable and possible CAA status as per the Boston criteria v1.5, following a review of individual patient imaging; we did not use the more recent Boston criteria v2.0 because a recent paper suggested that patients reclassified using these criteria have a much lower ICH risk.[18] Briefly, CAA was diagnosed if the patient was ≥55 years, clinical data and magnetic resonance imaging (MRI) demonstrated multiple ICH or cerebral microhaemorrhages (CMBs), which restricted to lobar, cortical, or cortical-subcortical areas or single haemorrhage with focal or disseminated cortical superficial siderosis (cSS) (probable) or solitary lobar, cortical, or cortical-subcortical ICH, CMB, or cSS (possible) with the absence of other cause of ICH.[19 20]

Device and procedure

In our multicentre cohort, LAAO was performed by interventional cardiologists under general anaesthesia, with vascular access via the right femoral vein. Most patients of UCLH received clopidogrel 300 mg the night before the procedure. LAA imaging and device implantation was guided by transoesophageal echocardiography (TOE) and fluoroscopy. Some centres used pre-operative computed tomography (CT) imaging of the heart. Unfractionated heparin (UFH) was administered intravenously during the procedure (prior to transseptal puncture), aiming for an activated clotting time (ACT) >300 seconds. The Abbott Amplatzer™ Amulet™ has been the preferred device at participating centres since 2015. Follow-up TOE was scheduled six weeks post-procedure. Flow around the device implied a leak, with any leak >5 mm considered significant. TOE was also used to exclude device-related thrombus. There are no robust data to guide optimal management of either of these scenarios. Para-device leaks were routinely managed conservatively.

Outcomes and data collection

Baseline characteristics, study outcomes, and follow-up data were obtained through electronic hospital records. The outcomes of interest were ischaemic stroke (peri- or post-procedural) and symptomatic ICH during the follow-up period. Ischaemic stroke was defined by a neurological deficit of acute onset, lasting at least 24 hours, judged by the treating clinician to have no other likely cause than cerebral infarction, based on all available clinical information and neuroimaging. ICH was defined as a focal neurological deficit, headache, seizure, or change in level of consciousness attributed to ICH detected on brain imaging. The incidence rates in our study were compared with an expected rate in the literature computed from the published mean CHA_2DS_2-VASc score for each study.[21] The incidence of device-related thrombosis after implantation was recorded. Safety outcomes were documented by procedural complications and extracranial bleeding complications, according to major bleeding and clinically relevant non-major bleeding (CRNMB) as per the International Society on

Thrombosis and Haemostasis (ISTH) classification. The UCL Hospitals NHS Foundation Trust Governance Review Board approved the study as a Service Evaluation (registration reference 07-202324-SE) for the evaluation of brain imaging findings, clinical features, causes, and outcomes of people with different forms of intracranial haemorrhage treated in the UCLH Comprehensive Stroke Service. Other centres also registered this work as a service evaluation, including Cambridge University Hospitals NHS Foundation Trust and Royal Papworth Hospitals NHS Foundation Trust. The service evaluation approval reference is Clinical Project ID5425 PRN11425. Since data were collected as part of routine clinical care, the requirement for individual patient consent was waived.

Systematic review and meta-analysis:

We conducted a systematic review following the Cochrane Handbook for Systematic Reviews of Interventions, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, and the PRISMA extension statement for reporting of systematic reviews that incorporate network meta-analyses of healthcare interventions.[22 23] The study protocol was prospectively registered with PROSPERO (registration ID: CRD42023415354). A systematic search was done to find relevant studies on post-LAAO procedure outcomes in patients with CAA. Three independent reviewers (KT, JB, and SS) searched PubMed (Medline) from inception until November 2023, using the following search strategy:

"((atria OR atrial OR atrial appendage) AND (occlusion OR occluder OR closure)) OR (watchman OR amulet OR amplatzer OR "cardiac plug") AND (amyloid OR (intrac* AND (haemorr* OR hemorr* OR bleed*)))"

Three authors (KT, JB, and SS) independently screened abstracts and assessed the full-text articles of the retrieved records to select eligible studies. Discrepancies between results

were resolved through consensus discussion. We also searched the reference lists of included papers and consulted our personal libraries for relevant articles. Studies that included patients with CAA by the Boston criteria v1.5 (possible or probable) undergoing LAAO with any device and reporting the required outcomes for the CAA population were included. We noted the post-procedure antithrombotic regimen used and the key outcomes of ICH or ischaemic stroke, procedural complications, and mortality. Studies that selectively reported only pooled outcomes without reporting them specifically for patients with CAA were excluded. Supplemental Figure 1 shows the PRISMA flowchart for the study identification process. The risk of bias in non-randomised studies of interventions (ROBINS-I), according to the Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022), was used for assessing the risk of bias and the quality of the included studies (Supplemental Figure 2).[22]

Statistical analysis

Categorical variables were presented as numbers and proportions, whilst continuous variables were reported as mean corresponding with standard deviation (SD) or median corresponding with interquartile range (IQR) as appropriate. Continuous data reported as the median and interquartile range (IQR) were converted to mean and standard deviation (SD) using a method proposed by a previous study.[24] The pooled results of the outcomes were presented as the incidence rate (effect size with 95% confidence interval (CI)) using random-effects meta-analysis with a restricted maximum likelihood (REML) method.[25] Publication bias was investigated using the funnel plot, and the Egger regression-based test was applied to test for funnel-plot asymmetry. A *P* value less than 0.05 was considered statistically significant. All statistical analyses were performed using licensed Stata statistical software version 18 (StataCorp. 2023. *Stata Statistical Software: Release 18*. College Station, TX: StataCorp LLC).

Results

Multicentre cohort study

Thirty-seven atrial fibrillation patients with intracerebral haemorrhage attributed to probable (83.8%) or possible (13.5%) CAA underwent successful LAAO; their characteristics are summarised in Table 1. The mean age was 75.3 (±7.9) years, and 83.8% were male. cSS was documented in 13 (43.3%) of 30 participants with available brain imaging data (6 [20.0%] with focal cSS and 7 [23.3%] with disseminated cSS). The study population had high thromboembolic and bleeding risks with mean CHA_2DS_2-VASc and HAS-BLED scores of 4.4 (±1.4) and 3.5 (±1.0), respectively. Detailed data, including post-procedure antithrombotic management, are illustrated in Supplemental Table 1. Pre-operative antithrombotic regimens were varied, including aspirin (66.6%), clopidogrel (16.7%), and DOACs (16.7%). The Amulet™ was mainly used in 33 cases (89.2%), whilst the remaining four patients were implanted with Amplatzer and Watchman equally.

Table 1 Summary characteristics of successfully LAAO-implanted patients from the UK multicentre cohort

Number of patients	37
Age, year, mean ±SD	75.3 ± 7.9
Sex (M:F)	5.2:1
CAA diagnosis, n (%)	- Probable 31 (83.8%) - Possible 5 (13.5%) - CAA-related inflammation 1 (2.7%)
cSS, n (%)	- None 17 (56.7%) - Focal cSS 6 (20.0%) - Disseminated cSS 7 (23.3%)
CHA_2DS_2-VASc, mean ±SD	4.4 ± 1.4
HAS-BLED, mean ±SD	3.5 ± 1.0
Device used, n (%)	- Amulet 33 (89.2%)

	- Amplatzer Cardiac Plug 2 (5.4%) - Watchman 2 (5.4%)
Follow-up, months, median (IQR)	11 (6-19.5)
Post-procedural antithrombotic regimens and duration, n (%)	- SAPT 27 (73.0%) - DAPT 2 (5.4%) - DAPT, then SAPT 3 (8.1%) - DAPT, then DOAC 1 (2.7%) - DOAC 1 (2.7%) - DOAC, then SAPT 2 (5.4%) - DOAC, then DAPT 1 (2.7%) Overall median duration of 42 days (IQR 41–76)
Ischaemic strokes per 100 patient-years (95% CI)	5.99 (1.93-18.59)
ICH per 100 patient-years (95% CI)	2.00 (0.28-14.18)

Abbreviations: CAA, cerebral amyloid angiopathy; CI, confidence interval; cSS, cortical superficial siderosis (data available in 30 pf 37 participants); DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; ICH, intracerebral haemorrhage; IQR, interquartile range; LAAO, left atrial appendage occlusion; SAPT, single antiplatelet therapy; SD, standard deviation; UK, the United Kingdom.

In our cohort, the rates of ischaemic stroke and ICH following LAAO in those individuals were 5.99 (95% CI 1.93-18.59) and 2.00 (95% CI 0.28-14.18) per 100 patient-years, respectively. Figure 1 depicts the Kaplan-Meier curve of survival analysis for ischaemic stroke and ICH occurrence from our cohort. Most patients were treated with single antiplatelet therapy (SAPT) (27 of 37; 73.0%) with a median duration of 42 days (IQR 41–76). During follow-up (median 11 months (IQR 6-19.5)), there were three asymptomatic device-related thromboses in patients receiving SAPT and DAPT, a single lobar ICH in a patient with HAS-BLED score of 5 who were taking SAPT, and three cardioembolic ischaemic strokes in patients (all with a high CHA_2DS_2-VASc score of 5) receiving SAPT or DAPT. The device-related thrombus resolved after four months of treatment with a DOAC (apixaban 2.5 mg and 5 mg BID), after which antithrombotics were stopped.

Systematic review and meta-analysis

Our systematic review search identified eight studies. Another study was identified following the consultation of our personal libraries (see Table 2 for details). Only three of the

identified published studies had CAA-specific data for the required outcomes, providing 107 patients with CAA with data on our outcomes of interest, giving a total of 144, with our multicentre study included (Table 2). Demographics were similar in the included studies, with a mean age of 74.5 (±8.3) years, and 68% of patients were male. Mean CHA_2DS_2-VASc and HAS-BLED scores were 4.7 ± 1.5 and 3.9 ± 1.1, respectively. The Amulet™ was common device used across all the studies (55.5%). Of the nine included studies, two studies with CAA-specific data and our cohort (n=102, mean age 76.2 ± 8.0 years, 74.6% male) were selected to perform a meta-analysis.

Table 2 Published studies: study and patient characteristics

Author	Year of publication	Study design	Number of patients	CAA-specific data	Patients with CAA (probable or possible)	Age (mean ± SD)	Sex ratio (M:F) (%)	CHA_2DS_2-VASc (or $CHADS_2$) score (mean/median with SD/IQR)	HAS-BLED score (mean/median with SD/IQR)
Horstman et al. [26]	2014	Prospective, observational, single-centre	20	No	2 (Not mentioned)	72.6 ± 5.8	70:30	4.5 ± 1.4	4.7 ± 1
Llull et al. [27]	2014	Individual case report	1	Yes	1 (probable)	70	Male	Not mentioned	Not mentioned
Hawkes et al. [28]	2016	Case series	7	No	1 (Not mentioned)	73 ± 6	57:43	5.6 ± 0.7	4.1 ± 0.3
Renou et al. [29]	2017	Prospective, observational, single-centre, cohort	46	No	25 (68% probable, 32% possible)	73.7 ± 8.4	63:37	5.2 ± 1.1	4.0 ± 1.0
Korsholm et al. [30]	2017	Prospective, observational, single-centre, non-randomised	107	No	3 (Not mentioned)	73.2 ± 9.9	72:28	4.4 ± 1.6	4.1 ± 1.1
Fayos-Vidal et al. [31]	2017	Retrospective, observational, single-centre	9	No	1 (probable)	72.7 ± 8.2	78:22	Median 4 (IQR, 2.5)	Median 3 (IQR, 0)
Hucker et al.[32]	2020	Retrospective analysis, multicentre (3)	63 (with previous ICH)	No	9 (100% probable)	75.3 ± 6.0	59:41	4.9 ± 1.7	3.5 ± 1.1

Author	Year of publication	Study design	Number of patients	CAA-specific data	Patients with CAA (probable or possible)	Age (mean ± SD)	Sex ratio (M:F) (%)	CHA_2DS_2-VASc (or $CHADS_2$) score (mean/median with SD/IQR)	HAS-BLED score (mean/median with SD/IQR)
Schrag et al. [33]	2021	Prospective, observational, multicentre (2)	26	Yes	26 (92% probable, 8% possible)	73 ± 8.5	62:38	4.6 ± 1.5	3.8 ± 1.0
Blanc et al. [34]	2021	Retrospective, cohort study	39	Yes	39 (82% probable, 18% possible)	79.3 ± 6.6	Not mentioned	2	Not mentioned
The present study	N/A	Multicentre cohort study	37	Yes	37 (84% probable, 14% possible)	75.3 ± 7.9	84:16	4.4 ± 1.4	3.5 ± 1.0
Total			**355**		**144 (80% probable, 15% possible)**	**74.5 ± 8.3**	**68:32**	**4.7 ± 1.5**	**3.9 ± 1.1**

Abbreviations: CAA, cerebral amyloid angiopathy; ICH, intracerebral haemorrhage; IQR, interquartile range; SD, standard deviation.

The pooled analysis showed that the overall incidence rate of post-procedure ischaemic stroke was 5.16 (95% CI 1.36-17.48; Figure 2A) per 100 patient-years. The expected rate of ischaemic stroke based on the CHA_2DS_2-VASc score was 7.2% per year. The sensitivity analysis using Egger's statistical test showed no publication bias (P = 0.92), which corresponded with the funnel plot (Supplemental Figure 3A), suggesting that no single study dominated the combined proportion and heterogeneity. Regarding ICH, the reported incidence from all studies demonstrated the pooled incidence rate of post-procedure ICH of 2.73 (95% CI 0.41-13.94) per 100 patient-years (Figure 2B). The sensitivity analysis using Egger's statistical test showed no publication bias (P = 0.96), corresponding with the funnel plot (Supplemental Figure 3B).

Post-procedural outcomes and complications

Table 3 presents outcomes of ischaemic stroke, ICH, and device-related thrombosis from included studies. Two studies with CAA-specific data and the present study resulted in a total of 102 CAA patients. Most of the published studies used a single antithrombotic drug regimen post-procedure for a median duration of 42 days (IQR 35-74), with or without a period of DAPT before. Device-related thrombus rates were low in all studies (4 from 102 cases, 3.9%). Regarding common procedural complications from pooled data, transient arrhythmias occurred in 2.1%, as well as non-life-threatening tamponade (2.1%). Cardiac CT produced a high yield in peri-device leakage detection (37%).[35] Extracranial bleeding occurred in eight cases (gastrointestinal in 75% (Figure 3)).

Table 3 Ischaemic stroke and ICH outcomes, device-related thrombosis, and antithrombotic regimens post-LAAO in studies with CAA-specific data (published studies and the present study)

Author (reference)	Schrag et al. [33]	Blanc et al. [34]	The present study	Overall
CAA-specific data	Yes	Yes	Yes	**Yes**
Number of patients	26	39	37	**102**
Follow-up (months), median (IQR)	23.5 (14.5-33.5)	12 (3–18)	11 (6-19.5)	**Mean 14.6 ± 13.2**
Device	Amulet (7.7%); Watchman (65.4%); Lariat procedure (15.4%); surgical repair (11.5%)	Not mentioned	Amulet 33 (89.2%); ACP 2 (5.4%); Watchman 2 (5.4%)	**Amulet 55.5%, Watchman 30.2%, ACP 3.2%, others 11.1%**
Main antithrombotic regimen	Post procedure for ≥ 6 weeks: SAPT (46.2%) or DAPT (7.7%) for anticoagulation naïve; or warfarin/ DOAC (42.3%) or none (3.8%) Long term: SAPT (69.2%) or DAPT (3.8%) or none (26.9%)	SAPT for at least 1 month	Post procedure: SAPT (73.0%); DAPT 5.4%); DAPT, then SAPT or DOAC (10.8%); DOAC, then SAPT or DAPT (10.8%) Long term: SAPT (20.7%); none (79.3%)	**Duration: median 42 days (35-74)**
Device-related thrombosis	1	Not mentioned	3	**4**
Ischaemic strokes	1 (in patient with device-related thrombosis)	3	3 (1 in patient with device-related thrombosis)	**7**
Ischaemic strokes per 100 patient-years (95% CI)	1.80 (0.26-12.95)	7.70 (1.90-20.90)	5.99 (1.93-18.59)	**5.16** **(1.36-17.48)**
ICH	1 (traumatic)	2	1	**4**

Author (reference)	Schrag et al. [33]	Blanc et al. [34]	The present study	Overall
ICH per 100 patient-years (95% CI)	1.80 (0.26-12.95)	4.40 (0.70-14.70)	2.00 (0.28-14.18)	**2.73** **(0.41-13.94)**

Abbreviations: ACP, AMPLATZER Cardiac Plug; CAA, cerebral amyloid angiopathy; CI, confidence interval; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; ICH, intracerebral haemorrhage; IQR, interquartile range; LAAO, left atrial appendage occlusion; SAPT, single antiplatelet therapy.

Discussion

Balancing the risk of intracerebral haemorrhage with the risk of an ischemic stroke is a challenging clinical dilemma for patients with ICH associated with cerebral amyloid angiopathy and atrial fibrillation. In our observational study from prospective specialist centre databases and a systematic review of patients with a history of CAA-related ICH and AF who underwent LAAO, the observed annual incidence rate of ischaemic stroke was 5.16% compared to an expected annual risk of ischaemic stroke of the pooled population (according to the CHA_2DS_2-VASc score) of 7.2%.[21] The observed incidence rate of ICH following LAAO in those individuals was 2.73 per 100 patient-years compared to an expected rate of 7.0-8.5% based on observational studies.[4] Post-procedure antithrombotic regimens were heterogeneous; however, most patients were prescribed either single or dual antiplatelet therapy for antithrombotic management in the first six months following the procedure, with a median duration of 42 days.

Large randomised controlled trials have already shown LAAO utility in nonvalvular AF (NVAF) patients compared with long-term warfarin therapy, but there is very limited evidence in ICH patients, especially in CAA-associated ICH in whom the benefit of LAAO might be greatest. The PROTECT AF trial randomised NVAF with at least one additional risk factor for stroke ($CHADS_2$ score ≥ 1) to receive warfarin or LAAO and demonstrated that LAAO was both non-inferior and superior to warfarin for the combined outcome of stroke, systemic embolism, and cardiovascular death.[15] The PREVAIL trial further showed non-inferiority for ischaemic stroke prevention in a higher-risk patient cohort, defined by a $CHADS_2$ score of at least 2 or 1 and another risk factor, as well as a significant decrease in peri-procedural complications.[13] LAAO was also non-inferior to DOACs in the PRAGUE-17 trial, which studied the efficacy and safety of LAAO compared to OAC in high-risk patients with NVAF, including CHA_2DS_2-VASc of ≥ 3 plus HAS-BLED of ≥ 2, previous bleeding with

hospitalisation, or history of a cardioembolic event during OAC.[14] Recent patient-level meta-analysis of 3 randomised trials, combining 1,516 patients with AF (933 treated with LAAO), indicated that LAAO gave comparable rates of all stroke and systemic embolism compared to vitamin K antagonist or DOAC together with a considerable decline in haemorrhagic stroke, all-cause, and cardiovascular mortality. Notably, a 78% reduction in haemorrhagic stroke and a 47% decrease in nonprocedure-related bleeding seemed to be the primary contributors to the mechanism of mortality benefit.[36] These findings indicate a potential benefit of LAAO in individuals with AF and CAA-associated ICH, who carry a substantial risk of recurrent ICH.

However, uncertainty remains on the indications and optimal strategy for LAAO in patients with previous ICH, including in patients with CAA. Some data indicate that the use of antiplatelet therapy alone after LAAO might be associated with high event rates (ischaemic strokes, ICH, and mortality);[30] however, the authors of that study suggest that ischaemic strokes were attributable to a high cerebral atherosclerotic burden rather than cardiac embolism. In the present study, recurrent ischaemic events occurred in patients with high or very high thromboembolic risk and a CHA_2DS_2-VASc score of more than 5 or 6 receiving SAPT as an antithrombotic regimen. The high ischaemic risk in our cohort is likely associated with the high CHA_2DS_2-VASc score (4.4), and most individuals referred for LAAO would have had DOAC discontinued. However, it remains unclear whether post-procedure DOAC use rather than SAPT or DAPT is any safer. Randomised studies are therefore needed to establish the optimal post-procedural management in patients with CAA-ICH undergoing LAAO.

Nevertheless, in both our study and published case series, the rates of ischaemic stroke or ICH were lower compared with the expected annual risks from existing scores and observational data.[21] The aim of post-procedure antiplatelet or anticoagulation regimen is to prevent device-related thrombus and its possible consequences and minimise stroke risk. Rates

of these complications were low in all studies, along with low rates of ICH, signifying this is possibly a safe approach and may balance the risks of device-related thrombus vs. ICH for patients with CAA-associated ICH undergoing LAAO. However, in our cohort, the survival curve (Figure 1) does not suggest that ischaemic strokes were early and related to device implantation since none occurred in the early post-procedural period. It is important to acknowledge that our protocol of minimising the use of OAC or antiplatelet therapy shortly after LAAO in individuals with CAA might contribute to the low incidence of ICH in the cohort. An additional important consideration is that in the high bleeding risk CAA group, peri-procedural bleeding could also be a consequence of heparin used during the procedure.[30] Moreover, some studies highlight the importance of maintaining multidisciplinary and individualised clinical post-procedure antithrombotic plans in patients with CAA.[32 33] Some peri- or post-procedural complications seen during the previously mentioned randomised trials[13-15 37] and the studies in this systematic review may be reduced with optimisation of follow-up, e.g., echocardiography protocols post LAAO can support medical management of device-related thrombus via early detection.[38] The incidence of procedural complications decreases with operator experience.[39 40]

Limitations

Many publications did not explicitly report CAA-specific outcomes, meaning they were excluded. As patients with CAA are at very high risk of ICH, we recommend that future LAAO studies in people with ICH should systematically describe the causes of ICH (including CAA) and report outcomes for specific diagnostic groups separately. Additionally, cSS has been recognised as a significant determinant for ICH in patients with CAA, especially with disseminated cSS or high multifocal cSS scores (annual ICH recurrence rate at 26.9% for a score of 4).[41 42] The rate of cSS in our cohort was 44.8%, which is less than the prevalence in the original cohort of patients with pathologically-confirmed CAA included in the Boston

criteria (60.5%)[19] but higher than the rate of 34% reported in a pooled analysis of 1,239 patients with CAA from cohort studies.[43] The reasons for the low rate of recurrent ICH in our study thus remain uncertain, and could related to other unmeasured baseline factors or aspects of post-LAAO clinical care; we also note that the rate of 2% is similar to that reported in another cohort study of 26 patients with CAA and AF treated with LAAO, but the prevalence of cSS was not described in this study.[44] Further limitations include the nature of the studies, which were mostly small, observational, and non-randomised, leading to risks of bias and confounding by indication. According to the risk of bias assessment and analysis (Supplemental Figure 2), no study was graded as having a low risk of bias. Therefore, larger multicentre studies are needed to better explore LAAO and its outcomes in patients with CAA. Further randomised study of antithrombotic regimens post-implantation is also warranted. Longer follow-up is required; the study with the longest follow-up time of 27.6 months[30] in our systematic review had a high frequency of adverse events. However, it is important to acknowledge that the rates from risk factor-based approach stratification, predicated on AF identified using electrocardiography (ECG) or Holter monitoring, may not apply to individuals in whom transient episodes of AF are diagnosed with long-term cardiac monitoring. We do not have detailed data on how AF was detected in all of the participants included in our pooled analysis. Additionally, the CHA_2DS_2-VASc score is not validated for patients with CAA and ICH, and the lack of a comparator group does not allow us to determine the effect of LAAO compared to oral anticoagulation LAAO in patients with CAA-associated ICH and AF, which will require randomised trial data.

The main conclusion of the present study is that LAAO appears to be a promising option in patients with CAA-related ICH with rates of ischaemic stroke and ICH lower than expected from risk scores and observational data. These data show that LAAO in this cohort appears to be both feasible and safe. Nevertheless, due to the limitations inherent in observational data

our findings emphasise the need for further large randomised controlled trials of stroke prevention in ICH survivors with AF. Such ongoing studies include STROKECLOSE (NCT02830152) and CLEARANCE (NCT04298723) to determine the effectiveness of LAAO in reducing the occurrence of stroke, bleeding, and cardiovascular mortality in patients with NVAF who have previously experienced ICH. We recommend that future studies should phenotype intracerebral haemorrhage (including CAA status) to better establish safety and efficacy in this high-risk population.

Contributors

Conceptualisation: KT, JB, SS, and DJW; Data curation: KT, JB, SS, IP, SA, ST, PAC, and AC; Formal analysis: KT, JB, SS, IP, and DJW; Methodology: KT, JB, SS, IP, SA, PAC, RA, ORS, and DJW; Supervision: RA, ORS, and DJW; Visualisation: KT, JB, SS, IP, SA, and PAC; Writing – original draft: KT, JB, and SS; Writing – review & editing: SA, PAC, ORS, and DJW. DJW is the study guarantor. All authors read, critically revised, and approved the final manuscript.

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Competing interests

None declared.

Patient consent for publication

Not applicable.

Ethics approval

The UCL Hospitals NHS Foundation Trust Governance Review Board approved the study as a Service Evaluation (registration reference 07-202324-SE) for the evaluation of brain imaging findings, clinical features, causes, and outcomes of people with different forms of

intracranial haemorrhage treated in the UCLH Comprehensive Stroke Service. Other centres also registered this work as a service evaluation, including Cambridge University Hospitals NHS Foundation Trust and Royal Papworth Hospitals NHS Foundation Trust. The service evaluation approval reference is Clinical Project ID5425 PRN11425.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Supplemental materials

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Figure legends

Figure 1 Kaplan-Meier curve of survival analysis for ischaemic stroke and ICH occurrence from our cohort. ICH, intracerebral haemorrhage.

Figure 2 Meta-analysis of the pooled incidence rates of (A) ischaemic stroke and (B) ICH in patients with CAA-associated ICH and AF who were treated with LAAO. AF, atrial fibrillation; CAA, cerebral amyloid angiopathy; CI, confidence interval; ICH, intracerebral haemorrhage; LAAO, left atrial appendage occlusion.

Figure 3 Common procedural complications from pooled data. AF, atrial fibrillation; CAA, cerebral amyloid angiopathy; ICH, intracerebral haemorrhage; LAAO, left atrial appendage occlusion.