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Impact of Echocardiographic Guidance on Safety and Efficacy of Left Atrial Appendage Closure: An Observational Study

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ABSTRACT

Objectives. We sought to evaluate the impact of echocardiographic guidance on the safety and efficacy of left atrial appendage (LAA) closure (LAAC).

Background. Expert consensus documents recommend intraprocedural imaging by means of either transesophageal echocardiography (TEE) or intracardiac echocardiography (ICE) to guide LAAC. However, no evidence exists that intraprocedural echocardiographic guidance in addition to fluoroscopy improves the safety and efficacy of LAAC.

Methods. Consecutive LAAC procedures performed in a high-volume center between January 2009 and October 2020 were stratified based on intraprocedural imaging modalities, including fluoroscopy guidance only (FG) or intraprocedural echocardiographic guidance (EG) in addition to fluoroscopy. The primary safety endpoint was the composite of procedural related complications occurred within 7 days after the procedure. Technical success at 7 days and at follow-up were secondary endpoints.

Results. Among 811 LAAC procedures, 549 (67.7%) and 262 (32.3%) were assigned to the FG and EG group, respectively. After adjusting for confounders, EG remained associated to a lower rate of the primary safety endpoint (3.4% vs. 9.1%; p= 0.004; adjusted Odds Ratio [adjOR]:0.31; 95% Confidence Interval [CI]: 0.11-0.90; p=0.030). Technical success trended higher at 7 days (92.1% vs. 87.2%; p=0.065; adjOR: 1.68; CI: 0.95-3.01; p=0.079) and was significantly improved with EG compared to FG (87.6% vs. 79.9%; p=0.018; OR: 4.06; CI: 1.60-10.27; p=0.003) after a median follow-up of 4.9 (IQR: 3.4-6.2) months.

Conclusions. In a large cohort of consecutive LAACs, the use of intraprocedural echocardiography to guide intervention in addition to standard fluoroscopy was associated with lower risks of procedural complications and higher mid-term technical success rates.

KEY WORDS: left atrial appendage closure, procedure guidance, procedural safety, transesophageal echocardiography, technical success

CONDENSED ABTRACT

811 left atrial appendage closures consecutively performed in a high-volume center between 2009 and 2020 were divided in 2 groups: 549 (67.7%) procedures performed by means of fluoroscopy Guidance (FG) only and 262 (32.3%) procedures guided by intraprocedural echocardiography guidance (EG) in addition to standard fluoroscopy. After adjusting for potential confounders, a lower rate of safety endpoint (3.4% vs. 9.1%; p= 0.004; adjusted Odds Ratio [adjOR]:0.31; 95% Confidence Interval [CI]: 0.11 - 0.90; p=0.030) and a higher rate of long-term (87.6% vs. 79.9%; p=0.018; adjOR: 4.06; CI: 1.60-10.27; p=0.003) technical success were observed in EG group.

ABBREVIATIONS AND ACRONYMS

AdjOR Adjusted odds ratio
ACP Amplatzer Cardiac Plug
AF Atrial fibrillation
CI Confidence interval
CCTA Cardiac computed tomography angiography
ICE Intracardiac echocardiography
IFU Instructions for use
LAA Left atrial appendage

LAAC Left atrial appendage closure
OAC Oral anticoagulation
RCT Randomized clinical trial
TEE Transesophageal echocardiography

INTRODUCTION

Left atrial appendage (LAA) closure (LAAC) has been established in clinical practice as a therapeutic option for patients with atrial fibrillation (AF) and contra-indication to oral anticoagulation (OAC) (1,2).

As a preventive treatment, LAAC lacks an immediate benefit for patients and its stroke prevention effects become more evident over time (3). Therefore, measures that reduce the risk of procedural complications and improve short and long-term safety merit particular consideration (4-6). Both LAAC planning and guidance have evolved over time as there is greater understanding about the peculiar and variable LAA anatomy and how intraprocedural imaging should guide intervention. (2,7,8)

According to expert consensus statements on percutaneous LAAC, the use of imaging, by means of either transesophageal echocardiography (TEE) or intracardiac echocardiography (ICE), is recommended to guide the LAAC procedure (2). However, TEE is invasive and requires conscious sedation or general anesthesia (4) and the use of ICE is expensive, not free of risk, and demands dedicated expertise(9). Both additional imaging modalities prolong the procedure. No evidence currently exists that the use of these echocardiography techniques during LAAC is associated with lower complication or higher success rates. Therefore, fluoroscopy is or was the only intraprocedural imaging modality employed during LAAC in some centers (10).

We sought to investigate whether the use of intraprocedural echocardiography improves outcomes in terms of both safety and efficacy as compared to fluoroscopy guidance alone.

METHODS

Study design and population

The LAAC Bern Registry (NCT04628078) is a single center prospective observational study including all the LAAC procedures performed at the Bern University Hospital after August 2015. There are no formal exclusion criteria, and all patients who provided informed consent were included in this registry. The registry complies with the Declaration of Helsinki and was approved by the institutional ethics committee. The present study was designed with the aim to compare procedures performed at Bern University Hospital since August 2015 to those before that time. Since August 2015, LAAC at our institution is performed under echocardiographic guidance (EG) in addition to standard fluoroscopy. The LAACs before August 2015 constitute the historical cohort of only fluoroscopy guided (FG) procedures, prospectively collected between January 2009 and July 2015 **(Figure 1)**. All consecutive patients undergoing LAAC at Bern University Hospital between January 2009 and October 2020 were included in the present analysis. Patients participating in randomized clinical trials (RCT) and those who did not provide an informed consent were excluded from the analysis (**Figure 1**). Based on the imaging method used to guide the procedure, LAACs were classified as FG or EG. The few FG procedures with a preprocedural Cardiac Computed Tomography Angiography (CCTA) were excluded from the analysis. Demographic and clinical characteristics, information on performed interventions, and hospital outcome data were systematically collected.

Endpoint definitions

The study specified three combined endpoints. The safety endpoint was defined as the composite of procedural related complications including death, cerebrovascular event, clinically relevant pericardial effusion, device embolization, non–access site related major or life-threatening bleeding (BARC 3-5), acute kidney injury, need for urgent surgical bailout, and need for cardiopulmonary resuscitation. An event was defined as procedure related if it occurred

within 7 days of the procedure and the clinical endpoint committee members concurred that the event was likely device or procedure related. In cases where information was insufficient to establish a clear relation to the device or procedure, a conservative position (assuming a relation) was taken. Definitions of each components of the composite endpoint are described in the **Supplementary Appendix**. The short-term technical success was defined as adequate LAA exclusion, as evaluated by post device release LAA angiography and absence of periprocedural device complications. Adequate LAA sealing was defined as LAA ostium sealing at LAA angiography without a >5mm peridevice leak (PDL) or presence of patent lobe(s) (any recess with an ostium diameter greater than 1cm situated distal to LAA ostium which remains uncovered after device release). Device complications were previously defined (11). The long-term technical success was defined as adequate LAA sealing, as evaluated by TEE at follow-up and absence of device-related complications at follow-up.

Fluoroscopy guided LAAC

FG LAACs were procedures guided exclusively by means of fluoroscopy and contrast medium injections. In this group, a preprocedural TEE was usually performed with the purpose to exclude LAA thrombus. No further imaging exams, except for fluoroscopy with contrast medium injections, were performed before or during the procedure. Procedures were generally performed under local anaesthesia. Unfractionated heparin (5000 IU) was administered before the femoral venous puncture and activated clotting time (ACT) was not routinely assessed. The left atrium was accessed by fluoroscopically guided transseptal puncture, frequently using contrast medium staining of the atrial septum for targeting the inferoposterior part of the fossa ovalis. If present, the access was achieved through a patent foramen ovale or an atrial septal defect. A device-specific sheath was advanced over a stiff 0.035″ guidewire into the left atrium

and directed into the proximal part of the LAA. LAA angiography was performed with a contrast medium injection through the delivery sheath, showing the LAA usually in one or more right anterior oblique caudal and cranial and straight lateral projections. The device dimension was selected by eyeballing, using the sheath diameter (about 6 mm) in the LAA as a reference to estimate the landing zone width. Further LAA angiographies were performed just before and after the device release in order to confirm the correct device position and shape and LAA ostium sealing. Finally, a sustained tug test was performed before releasing the device in order to confirm optimal device stability. Concomitantly performed combined procedures in this group are shown in **Table 2**.

Echocardiography guided LAAC

The procedures guided by means of either TEE or ICE in addition to fluoroscopy were classified as EG. TEE was performed by expert echocardiographers with extensive experience in guiding LAAC. The ICE guided (2 of 262) cases were executed in presence of a proctor. EG procedures differed from FG LAACs in some points. Either conscious sedation or general anaesthesia was implemented in addition to local anaesthesia due to TEE related discomfort and protection of the airways. Heparin was given after the transseptal puncture and the doses were adjusted to achieve an ACT of 250-300 seconds. LAA thrombi were excluded by means of intraprocedural TEE before the procedure or, if ICE was used, by means of pre-procedural CCTA. Furthermore, echocardiography was used to guide the transseptal puncture, to confirm the correct positioning of the device and finally to assess the optimal LAA ostium sealing, in addition to standard LAA angiography (**Central Illustration**). Finally, device sizing was based on a multiimaging modality including both LAA angiography and TEE views. At the end of the

procedure, echocardiography assessed the presence of pericardial effusion and any possible interferences with the mitral valve.

Hospitalization and follow-up

Postprocedural management, and follow-up were identical for both groups, except that the FG group were generally admitted the day of the intervention and discharged the same or the following day whereas the EG group were generally admitted the day before and discharged the day after the procedure. All patients were only discharged after excluding clinically relevant pericardial effusion and documenting correct position of the device in the LAA by transthoracic echocardiography. Type and duration of antithrombotic treatment after discharge were left to the discretion of the operator according to the bleeding and the stroke risks. A TEE follow-up at 3-6 months after LAAC was planned.

Patients were followed by means of a standardized questionnaire, by phone and, if possible, by means of an outpatient visit. Source documentation of all adverse events were collected, and all the events were classified and adjudicated by a clinical event committee consisting of two cardiologists and, in case of disagreement by a third cardiologist. Cerebrovascular events were reviewed and adjudicated by a neurologist.

Statistical analysis

Continuous variables are expressed as mean ± SD or median as appropriate, and categorical variables as a percentage. Variables were compared using Student t tests, test Mann-Whitney or Chi-Square test as appropriate. Predictors of the endpoints were determined by univariable and multivariate logistic regression analyses; variables associated to the endpoint of interest with a P-value of ≤ 0.10 at univariate analysis were retained in the multivariable

regression models. Estimates of the odds ratios (OR) and 95% confidence intervals (CI) for each variable are presented. A statistical significance threshold of 0.05 was accepted for hypothesis testing. IBM SPSS Statistics version 25 was used.

RESULTS

Baseline and Procedural Characteristics

A total of 909 LAAC procedures were considered for the study. After excluding 89 patients participating in RCTs, 5 patients who refused participation and 4 patients in the FG group who had undergone preprocedural CCTA, a total of 811 patients were included in the present analysis of whom 549 (67.7%) patients underwent FG and 262 (32.3%) patients underwent EG **(Figure 1)**.

Patients of the EG group were older (76.0±7.4 vs. 73.6±9.7; p=0.005), with a higher prevalence of diabetes (32.8% vs. 21.3%; p<0.001), prior gastrointestinal (34.7% vs. 20.0%; p<0.001), intracranial (11.5% vs. 20.2%; p=0.001) hemorrhages, or bleeding in other regions (11.5% vs. 24.4%; p<0.001), but with a lower prevalence of coronary heart disease (50.8% vs. 58.8%; p=0.030)**.** The mean HAS-BLED score was higher (2.9±1.0 vs. 2.6±1.2; p =0.025) in the EG group (**Table 1**). Procedural characteristics are summarized in **Table 2**. The FG group had a higher prevalence of LAA thrombus (5.6% vs. 1.9%; p= 0.016) and of chicken wing LAA morphology (19.0% vs. 14.4%, p=0.019) and received higher amounts of contrast medium during the procedure (204 [148-301] ml vs. 70 [48-98] ml; p<0.001). The distribution of first operators and their expertise differed between the two groups. Almost all LAACs (95%) performed before August 2015 were FG; whereas 84% among those executed later were EG. Dual antiplatelet therapy was the most frequent antithrombotic treatment at discharge in both

groups, whereas single antiplatelet therapy or no antithrombotic drug were more common in the FG group (12.5% vs. 5.3% and 1.3% vs. 0% respectively). Three patients (0.4%) were lost to follow-up after hospital discharge.

Safety Endpoint

The composite safety endpoint occurred in 50 (9.1%) patients in the FG group and in 9 (3.4%) patients in the EG group (p=0.004) (**Table 3**). There was no procedure related fatality in the EG and 4 deaths occurred in the FG group, of which two were related to accidental puncture of the aorta, one to LAA perforation and one to air embolization. The rates of individual components of the composite endpoint were all numerically albeit not significantly in favour of the EG group with the exception for urgent bailout surgery which was significantly higher in the FG group (1.8% vs. 0%; p=0.028). Among all baseline and procedural characteristics, echocardiographic guidance remained the only independent predictor of the composite safety endpoint (adjusted odds ratio [AdjOD]: 0.31; 95%CI: 0.11-0.90; p=0.030) (**Table 4**).

Short-term technical success

Postimplant LAA angiography was not performed in overall 18.5% of the patients (18.2% in FG and 19.1% in the EG groups). Short-term technical success rates did not differ between groups (92.1% in the EG vs. 87.2% in the FG groups; p=0.065). The rate of device related complications was higher in the FG (9.0% vs. 5.0%; p= 0.047), mainly owing to a greater early device embolization rate in the FG group (2.0% vs. 0%; p=0.021) (**Table 3**). The rates of adequate LAA sealing, assessed either with exclusively angiography or with angiography and intraprocedural echocardiography did not differ. LAA device was successful in all patients in the EG group, whereas the procedure was aborted in 4 patients in the FG group, mainly due to

clinically relevant pericardial effusions. In 4 cases in the FG group, a second device had to be implanted, consisting of a second LAA occluder in 3 cases and a vascular plug in 1 case due to inadequate LAA sealing. At multivariable analysis, short term technical success trended higher in EG group but did not reach statistical significance (adjOR: 1.68; CI: 0.95 - 3.01; p=0.079) (**Supplemental Table 2**).

Long-term technical success

At a median follow-up of 4.9 (IQR: 3.4-6.2) months, a total of 105 patients presented device related complications of which 80 (19.4%) occurred in the FG and 25 (12.4%) in the EG groups (P=0.029) (**Table 3**). A total of 586 patients underwent follow-up TEE assessment and the rate of significant peri-device leak was similarly low in both study groups (1.5% in the FG and 1% in the EG groups). As a result, the long-term technical success rate was higher with EG (87.6%) compared with FG (79.9%; p=0.018). At multivariable analysis, echocardiography guidance remained independently associated with a four-fold greater odds of long-term technical success (adjOR: 4.06; CI: 1.60 – 10.27; p=0.003), together with male sex (adjOR: 2.29; CI: 1.35 – 3.85; p=0.002).

DISCUSSION

The safety and efficacy of LAAC have been assessed in the context of 2 RCTs (12,13) and are further supported by the results of several large multicentre observational studies (4,14-16). Yet, these studies included echocardiography guided procedures only. Berti et al. observed similar results in terms of procedural safety and efficacy by using either TEE or ICE (4). Therefore, recent guidelines recommend the use of such imaging methods to guide LAAC(2). Yet, no evidence exists that intraprocedural echocardiographic guidance in addition to

fluoroscopy improves LAAC safety and efficacy. Based on these considerations, it was customary practice at our institution to guide LAAC procedures by fluoroscopy alone, avoiding TEE discomfort and risk and obviating the need for sedation or general anaesthesia. From August 2015 onwards, LAAC procedures were performed by echocardiographic guidance, in addition to fluoroscopy, which provides a unique opportunity to assess the impact of the combination of the former and the latter versus the latter only imaging modality in a large and consecutive patient population.

Our findings can be summarized as follows:

1) Procedures guided by echocardiography in addition to fluoroscopy had lower rates of procedure related complications at 7 days after LAAC compared with fluoroscopy guided only procedures. After adjustment for all measured confounders, echocardiography guidance remained independently associated with a lower rate of the composite safety endpoint.
2) Echocardiographic guidance emerged as an independent predictor of greater long term technical success, which was not driven by improved complete closure rates but rather by a cumulative lower rate of device related complications.

To the best of our knowledge, only three studies have compared FG LAACs with procedures guided by an additional imaging method. Yuniadi et al. compared, in a small single center cohort of LAACs, 25 FG with 28 EG LAACs in terms of procedural complications and technical success (10). The LAA device was successfully implanted in 96% of the cases in both groups, with similarly low complication rates. Zhang et al. recently reported the results of a single center study including 208 LAACs (17) of whom 107 were guided by fluoroscopy and 101 by TEE. The rates of in hospital complications favoured, numerically, the TEE group but did not differ

significantly (17). Therefore, no clear conclusion could be drawn. Finally Kleinecke et al. used propensity matching to compare 266 LAAC patients with Amplatzer devices at our institution treated with exclusively fluoroscopy guidance with 266 LAAC patients with Watchman devices treated at another institution with echocardiographic guidance (20). There were no significant outcome differences with a combined hazard endpoint (efficacy and safety) of 10.7% vs. 9.8%, respectively (P=0.26, efficacy 6.2% vs. 6.4%, P=0.92, safety 5.1% vs. 4.4%, P=0.10).

The current study, based on a larger population, provides greater power to compare the occurrence of lower frequency, yet clinically significant, procedure-related complications in LAAC patients with or without echocardiography guidance. Our findings suggest to routinely use intra-procedural echocardiography imaging modalities to minimize the rates of procedural complications, and that FG procedure, when performed by expert operators, can provide comparable LAA sealing capabilities.

The predicted stroke and bleeding risks in our population were higher compared with patients included in the PROTECT AF (13)(average CHA2DS2-VASc of 3.4; all patients eligible for chronic OAC) or PREVAIL (12) (CHA2DS2-VASc of 4.0; all patients eligible for OAC) trials, but similar to the findings of large and recent observational populations (4,14-16).

The rate of procedural complications observed in our study (7.3%) may appear high compared to those observed (2.8%-4.8%) across large studies with an independent clinical event committee(12,13,15,16,18,19). On the other hand, the procedural complication rate observed in the EG group amounted to 3.4% and is entirely consistent with what has been observed in prior large registries, in which EG was the standard of care (**Figure 2**). In addition, it should be noted that in the current study the definition of procedural complications also included acute kidney injury, the need for urgent surgical bailout and cardio-pulmonary resuscitation. We observed a

very high sealing rate of LAA (99.6%), irrespective of the guidance strategy, which is consistent and favourably compares with the rates reported in previous large registries, ranging from 95.1% to 99.1% (12,14-16,20,21). This might reflect the expertise of the operators and the differential sealing capacity of the Amplatzer devices compared with Watchman devices. Amplatzer devices were used in both groups in our series but it was the only implanted device in the FG group. A prospective controlled study comparing the LAA sealing capability of these two devices is in progress(22). All aborted LAACs, and all procedures complicated by device embolization or requiring implantation of a second device were observed in the FG group. As a consequence, technical success trended higher at 7 days and was significantly improved after a median follow-up of roughly 5 months with EG compared to FG.

The short-term technical success rate observed in the EG group (92.1%) was lower than those reported in the previous observational studies, ranging from 93.3% to 97% (14-16). Many factors may explain these findings. Firstly, all residual patent proximal lobes were considered as technical failure; secondly, we included pericardial effusion among the device related complications as previously suggested (11); thirdly, we routinely performed transthoracic echocardiography in all patients before discharge, which has most likely increased the likelihood to detect new onset not clinically relevant pericardial effusion compared to previous studies; fourthly, due to study design and purpose, the imaging method used to evaluate the LAA ostium sealing was the LAA angiography in the current study instead of TEE, which is at variance with the majority of the previous studies.

In summary, our study confirms the safety and efficacy of EG LAAC procedures, in that the rate of hard clinical endpoint, such as the composite of death and stroke was at 0.4% and an adequate LAA sealing was observed in 99.0% of the patients at TEE follow-up in the EG group.

Limitations

Our study has several important limitations. The observational and partially retrospective nature of the study might have introduced bias and unmeasured confounders, which the multivariable analyses may have not accounted for. We corrected the analyses based on multiple imbalances between groups, including first operator and year of inclusion and yet we acknowledge that the FG group mainly comprised a more historical group of patients compared with EG. Hence, the difference mainly in terms of safety endpoints between the two groups may also, at least partially, reflect the improvement of the LAAC technique over time. Yet, a higher numerical rate of safety endpoints was consistently seen across more contemporary patients treated in the FG compared with EG groups. LAAC in the FG group was more frequently combined with other interventions. Yet, concomitant procedures did not seem to impact on the safety or the technical success rates of LAAC. The type of LAAC device was largely imbalanced between groups as Watchman was predominantly implanted under EG, which is consisting with the IFU of the device. However, the type of implanted device was included in the multivariable analyses and type of imaging guidance but not the implanted device remained associated with the occurrence of safety endpoints. Post-device LAA angiography and follow-up TEE were not performed in a sizable proportion of patients, which has limited the assessment of adequate LAA sealing in both study groups. Only 2 of the 262 EG procedures were ICE guided; therefore, our data cannot support the value of ICE as compared to TEE.

CONCLUSIONS

In a large, single center, all-comer LAAC registry, echocardiographic guidance in addition to fluoroscopy, as compared to fluoroscopy alone, was independently associated with

lower procedural complication, higher long-term technical success and similar LAA sealing rates. Our observational data lends support to echocardiographic guidance for LAAC.

PERSPECTIVES

WHAT IS KNOWN?

No evidence exists that intraprocedural echocardiographic guidance in addition to fluoroscopy improves the safety and efficacy of LAAC. Therefore, fluoroscopy is or was the only intraprocedural imaging modality employed during LAAC in some centers.

WHAT IS NEW?

Echocardiographic guidance in addition to fluoroscopy, as compared to fluoroscopy alone, is independently associated with lower procedural complication, higher long-term technical success and similar LAA sealing rates.

WHAT IS NEXT?

Randomized clinical trial comparing echocardiographic guidance and fluoroscopy alone and larger multicenter observational studies including higher percentage of ICE are desirable.

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FIGURES LEGENDS

Figure 1. Participant Selection. Of the 909 patients submitted to LAAC in Bern between January 2009 and October 2020, 89 patients were excluded because enrolled in RCTs, 5 refused to participate to the study and 4 cases were excluded because fluoroscopy guided only but with a pre-procedural CCTA.

LAAC, left atrial appendage closure; UH, university hospital; RCT, randomized controlled trial; CCTA, cardiac computed tomography angiography.

AdjOR, adjusted odds ratio; CI, confidence interval; LAAC, left atrial appendage closure; FG, fluoroscopy guidance; LAA, left atrial appendage; EG, echocardiography guidance.

Figure 2. Overview of largest studies reporting LAAC related complications adjudicated by an independent clinical event committee. Only the EG arm of the current study, with a procedure related complication rate of 3.4%, falls within the range of event incidences reported so far (2.8-4.5%), after excluding the pilot trial Protect-AF. On the other hand, a rate of 9.1% was observed in the FG group.

Central Illustration. Comprehensive images showing the two different strategies used to guide LAAC. On the left side the only fluoroscopy guidance (FG) strategy where transseptal puncture, device sizing, device implantation assessment right before and right after device release are performed based exclusively on fluoroscopy and LAA contrast medium injections. The right side of the figure shows the echocardiography guidance (EG) strategy where a transesophageal or intracardiac echocardiography is performed, in addition to fluoroscopy, to guide the procedural phases. The majority of FG LAACs were performed before August 2015, later EG was routinely used by the majority of operators. After adjusting for potential confounders including year of

recruitment, echocardiography guidance resulted an independent predictor of procedure related complications and of long-term technical success. Furthermore, technical success trended higher at 7 days.

Table 1. Baseline Patient Characteristics

	All patients N = 811	**FLUOROSCOPY guidance Group** N = 549	**ECHOCARDIOGRAPHY guidance Group** N = 262	**p value**
Age (years), mean ±SD	n = 811, 74.4±9.1	n = 549, 73.6±9.7	n = 262, 76.0±7.4	0.005
Male sex, no. (%)	n = 811, 578 (71.3%)	n = 549, 393 (71.6%)	n = 262, 185 (70.6%)	0.774
BMI (kg/m²), mean ±SD	n = 811, 27.2±4.8	n = 549, 27.3± 4.9	n = 262, 26.9±4.5	0.651
Hypertension, no. (%)	n = 811, 688 (84.8%)	n = 549, 469 (85.4%)	n = 262, 219 (83.6%)	0.494
Diabetes mellitus, no. (%)	n = 811, 203 (25.0%)	n = 549, 117 (21.3%)	n = 262, 86 (32.8%)	<0.001
Chronic kidney disease *, no. (%)	n = 811, 114 (14.1%)	n = 549, 76 (13.8%)	n = 262, 38 (14.5%)	0.800
CHA2DS2Vasc score, mean ±SD	n = 811, 4.2±1.6	n = 549 4.2±1.7	n = 262, 4.3±1.5	0.685
HASBLED score, mean ±SD	n = 811, 2.7±1.1	n = 549, 2.6±1.2	n = 262, 2.9±1.0	0.025
Paroxysmal atrial fibrillation, no. (%)	n = 811, 426 (52.6%)	n = 549, 275 (50.1%)	n = 262, 151 (57.9%)	<0.001
History of cerebrovascular events, no. (%)	n = 811, 237 (29.2%)	n = 549, 155 (28.2%)	n = 262, 82 (31.3%)	0.370
Carotid artery disease †, no. (%)	n = 811, 46 (5.7%)	n = 549, 28 (5.1%)	n = 262, 18 (6.9%)	0.308
History of coronary heart disease, no. (%)	n = 811, 456 (56.2%)	n = 549, 323 (58.8%)	n = 262, 133 (50.8%)	0.030
Previous myocardial infarction, no. (%)	n = 811, 187 (23.1%)	n = 549, 132 (24.0%)	n = 262, 55 (21.0%)	0.335
History of arterial embolism, no. (%)	n = 811, 23 (2.8%)	n = 549, 19 (3.5%)	n = 262, 4 (1.5%)	0.121
History of intracranial bleeding, no. (%)	n = 811, 116 (14.3%)	n = 549, 63 (11.5%)	n = 262, 53 (20.2%)	0.001
History of gastrointestinal bleeding, no. (%)	n = 811, 201 (24.8%)	n = 549, 110 (20.0%)	n = 262, 91 (34.7%)	<0.001
History of bleeding in other regions ‡, no. (%)	n = 811, 127 (15.7%)	n = 549, 63 (11.5%)	n = 262, 64 (24.4%)	<0.001
History of anticoagulant therapy failure ¶, no. (%)	n = 811, 19 (2.3%)	n = 549, 9 (1.6%)	n = 262, 10 (3.8%)	0.055
Left ventricular function (%), mean ±SD	n = 721, 55.3±11.1	n = 461, 55.2±11.5	n = 260, 55.6±10.5	0.099

* Chronic Kidney Disease was defined if at least one of the following criteria was met: <30 eGFR mL/min per 1.73m2 (using the Modification of Diet in Renal Disease formula) and/or blood creatinine value >200 mcmol/l and/or dialysis or history of kidney transplantation.

† Carotid artery disease was defined as either presence of stenosis >50% in at least one carotid artery or previous carotid treatment.

‡ History of bleeding in other regions included history of genito-urinary bleeding, epistaxis, hemoptysis, intra-articular bleeding, intramuscular bleeding, cutaneous or subcutaneous hematoma/ecchymosis, or history of any type of bleeding requiring medical attention. Patients with previous intracranial and/or gastrointestinal bleeding were excluded from this group.

¶ History of anticoagulant therapy failure was defined as either thromboembolic event or documented presence of LAA thrombus despite adequate anticoagulant therapy.

BMI, Body Mass Index; SD, Standard Deviation.

Table 2. Procedural Characteristics

	All patients N = 811	FLUOROSCOPY guidance Group N = 549	ECHOCARDIOGRAPHY guidance Group N = 262	p value
Presence of LAA thrombus, no. (%)	n = 811, 36 (4.4%)	n = 549, 31 (5.6%)	n = 262, 5 (1.9%)	0.016
LAA angiography performed, no. (%)	n = 811, 787 (97.0%)	n = 549, 537 (97.8%)	n = 262, 250 (95.4%)	<0.001
Chicken wing shape *, no. (%)	n = 787, 138 (17.5%)	n = 537, 102 (19.0%)	n = 250, 36 (14.4%)	0.019
General anesthesia, no. (%)	n = 811, 52 (6.4%)	n = 549, 6 (1.1%)	n = 262, 46 (17.6%)	<0.001
Sinus rhythm during procedure, no. (%)	n = 790, 412 (52.2%)	n = 532, 284 (53.4%)	n = 258, 128 (49.6%)	<0.001
Implanted device Amulet, no. (%)	n = 811, 296 (36.5%)	n = 549, 207 (37.7%)	n = 262, 89 (34.0%)	<0.001
ACP, no. (%)	n = 811, 353 (43.5%)	n = 549, 342 (62.3%)	n = 262, 11 (4.2%)	
Watchman 2.5, no. (%)	n = 811, 136 (16.8%)	n = 549, 0 (0%)	n = 262, 136 (51.9%)	
Watchman FLX, no. (%)	n = 811, 26 (3.2%)	n = 549, 0 (0%)	n = 262, 26 (9.9%)	
First operator Operator 1, no. (%)	n = 811, 307 (37.9%)	n = 549, 304 (55.4%)	n = 262, 3 (1.1%)	<0.001
Operator 2, no. (%)	n = 811, 165 (20.3%)	n = 549, 104 (18.9%)	n = 262, 61 (23.3%)	
Operator 3, no. (%)	n = 811, 39 (4.8%)	n = 549, 39 (7.1%)	n = 262, 0 (0%)	
Operator 4, no. (%)	n = 811, 23 (2.8%)	n = 549, 23 (4.2%)	n = 262, 0 (0%)	
Operator 5, no. (%)	n = 811, 54 (6.7%)	n = 549, 30 (5.5%)	n = 262, 24 (9.2%)	
Operator 6, no. (%)	n = 811, 21 (2.6%)	n = 549, 0 (0%)	n = 262, 21 (8.0%)	
Operator 7, no. (%)	n = 811, 20 (2.5%)	n = 549, 0 (0%)	n = 262, 20 (7.6%)	
Operator 8, no. (%)	n = 811, 118 (14.5%)	n = 549, 4 (0.7%)	n = 262, 114 (43.5%)	
Operator 9, no. (%)	n = 811, 20 (2.6%)	n = 549, 16 (2.9%)	n = 262, 4 (1.7%)	
Others (Operators <20 LAAC), no. (%)	n = 811, 44 (5.4%)	n = 549, 29 (5.3%)	n = 262, 15 (5.7%)	
Operator Expertise 1st tertile interventions, no. (%)	n = 772, 273 (35.4%)	n = 520, 208 (40.0%)	n = 252, 65 (25.8%)	<0.001
2nd tertile interventions, no. (%)	n = 772, 252 (32.6%)	n = 520, 189 (36.3%)	n = 252, 63 (25.0%)	
3rd tertile interventions, no. (%)	n = 772, 247 (32.0%)	n = 520, 123 (23.7%)	n = 252, 124 (49.2%)	
Concomitant interventions, no. (%)	n = 811, 343 (42.3%)	n = 549, 298 (54.3%)	n = 262, 45 (17.2%)	<0.001
PCI, no. (%)	n = 811, 157 (19.4%)	n = 549, 140 (25.5%)	n = 262, 17 (6.5%)	<0.001
Closure of PFO, no. (%)	n = 811, 132 (16.3%)	n = 549, 118 (21.5%)	n = 262, 14 (5.3%)	<0.001
TAVI, no. (%)	n = 811, 35 (4.3%)	n = 549, 29 (5.3%)	n = 262, 6 (2.3%)	0.050
Mitraclip, no. (%)	n = 811, 13 (1.6%)	n = 549, 1 (0.2%)	n = 262, 12 (4.6%)	<0.001
Contrast medium (ml), median (IQR)	n = 783, 157 (86 - 250)	n = 522, 204 (148 - 301)	n = 261, 70 (48 – 98)	<0.001
Days of hospitalization (days), median (IQR)	n = 807, 1 (1- 2)	n = 545, 1 (1- 2)	n = 262, 1 (1- 2)	0.632
Antiplatelet/anticoagulant therapy at discharge No antiplatelet/anticoagulant drugs, no. (%)	n = 807, 7 (0.9%)	n = 545, 7 (1.3%)	n = 262, 0 (0%)	0.011
Any SAPT, no. (%)	n = 807, 82 (10.2%)	n = 545, 68 (12.5%)	n = 262, 14 (5.3%)	
Any single anticoagulant therapy, no. (%)	n = 807, 25 (3.1%)	n = 545, 15 (2.8%)	n = 262, 10 (3.8%)	
Any DAPT, no. (%)	n = 807, 667 (82.7%)	n = 545, 440 (80.7%)	n = 262, 227 (86.6%)	
Any SAPT + anticoagulant therapy, no. (%)	n = 807, 21 (2.6%)	n = 545, 13 (2.4%)	n = 262, 8 (3.1%)	
Any triple therapy, no. (%)	n= 807, 5 (0.6%)	n = 545, 2 (0.4%)	n = 262, 3 (1.1%)	

* LAA shape evaluated by LAA angiography.

LAA, left atrial appendage; ACP, Amplatzer Cardiac Plug; LAAC, left Atrial appendage closure; PCI, percutaneous coronary intervention; PFO, patent foramen ovale; ASD, atrial septal defect; TAVI, transcatheter aortic valve implantation; SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy.

Table 3. Safety Endpoint and Short and Long-term Technical Success Endpoints

	All patients N = 811	**FLUOROSCOPY guidance Group** N = 549	**ECHOCARDIOGRAPHY guidance Group** N = 262	**p value**
Outcome at 7 days available, no. (%)	n = 811, 808 (99.6%)	n = 549, 547 (99.6%)	n = 262, 261 (99.6%)	0.970
LAA angiography at end of procedure, no. (%)	n = 811, 661 (81.5%)	n = 549, 449 (81.8%)	n = 262, 212 (80.9%)	0.766
TEE follow-up available, no. (%)	n = 811, 586 (72.3%)	n =549, 389 (70.9%)	n = 262, 197 (75.2%)	0.197
Time-TEE (days), median (IQR)	n = 586,146 (101-187)	n = 389, 148 (115 -188)	n = 197, 119 (49 -185)	0.641
SAFETY ENDPOINT	n = 808, 59 (7.3%)	n = 547, 50 (9.1%)	n = 261, 9 (3.4%)	0.004
Death, no. (%)	n = 808, 4 (0.5%)	n = 547, 4 (0.7%)	n = 261, 0 (0%)	0.166
Stroke, no. (%)	n = 808, 5 (0.6%)	n = 547, 4 (0.7%)	n = 261, 1 (0.4%)	0.555
TIA, no. (%)	n = 808, 2 (0.2%)	n = 547, 2 (0.4%)	n = 261, 0 (0%)	0.328
Pericardial effusion clinically relevant, no. (%)	n = 808, 21 (2.6%)	n = 547, 18 (3.3%)	n = 261, 3 (1.1%)	0.074
Need for cardio-pulmonary resuscitation, no (%)	n = 808, 7 (0.9%)	n = 547, 7 (1.3%)	n = 261, 0 (0%)	0.066
Bleeding BARC 3-5 not access related, no. (%)	n = 808, 24 (3.0%)	n = 547, 18 (3.3%)	n = 261, 6 (2.3%)	0.437
Need for urgent surgical bailout, no. (%)	n = 808, 10 (1.2%)	n = 547, 10 (1.8%)	n = 261, 0 (0%)	0.028
Acute Kidney Injury, no. (%)	n = 808, 25 (3.1%)	n = 547, 21 (3.8%)	n = 261, 4 (1.5%)	0.077
SHORT-TERM TECHNICAL SUCCESS*	n = 668, 593 (88.8%)	n = 454, 396 (87.2%)	n = 214, 197 (92.1%)	0.065
Adequate LAA exclusion as evaluated by post-implantation angiography, no. (%)	n = 661, 643 (97.3%)	n = 449, 435 (96.9%)	n = 212, 208 (98.1%)	0.364
Adequate LAA exclusion according to the imaging method used for procedural guidance, no. (%)	n = 695, 674 (97.0%)	n = 449, 435 (96.9%)	n = 246, 239 (97.2%)	0.841
Implantation of a second device, no. (%)	n = 811, 4 (0.6%)	n = 549, 4 (0.9%)	n = 262, 0 (0%)	0.166
Aborted procedure, no. (%)	n = 811, 4 (0.5%)	n = 549, 4 (0.7%)	n = 262, 0 (0%)	0.166
Device-related complication within 7 days after LAAC, no. (%)	n = 808, 62 (7.7%)	n = 547, 49 (9.0%)	n = 261, 13 (5.0%)	0.047
Early device embolization, no. (%)	n = 808, 11 (1.4%)	n = 547, 11 (2.0%)	n = 261, 0 (0%)	0.021
Any pericardial effusion within 7 days after LAAC †, no (%)	n = 808, 52 (6.4%)	n = 547, 39 (7.1%)	n = 261, 13 (5.0%)	0.244
LONG-TERM TECHNICAL SUCCESS §	n = 614, 506 (82.4%)	n = 412, 329 (79.9%)	n = 202, 177 (87.6%)	0.018
Adequate LAA exclusion as evaluated by TEE follow-up, no. (%)	n = 586, 578 (98.6%)	n = 389, 383 (98.5%)	n = 197, 195 (99.0%)	0.603
Device-related complication up to TEE follow-up, no. (%)	n = 614, 105 (17.1%)	n = 412, 80 (19.4%)	n = 202, 25 (12.4%)	0.029
Any pericardial effusion at follow-up, no. (%)	n = 586, 25 (4.3%)	n = 389, 19 (4.9%)	n = 197, 6 (3.0%)	0.298
Peri-device thrombus, no. (%)	n = 586, 27 (4.6%)	n = 389, 20 (5.1%)	n = 197, 7 (3.6%)	0.386

* Patients without post-implantation angiography assessment who experienced device-related complication within 7 days after LAAC were adjudicated as "short-term technical failure".

† Any pericardial effusions (included those not clinically indicated) detected close after the procedure, at the pre-discharge TTE and/or during the 7 days after LAAC.

§ Patients without TEE follow-up who experienced device-related complication after LAAC were adjudicated as "long-term technical failure".

LAA, left atrial appendage; TEE, transesophageal echocardiography; LAAC, left atrial appendage closure; IQR, interquartile range.

Table 4. Baseline Univariate and Multivariate Predictors of Safety Endpoint

	Univariate		Multivariate	
Safety Endpoint	**OR (95% CI)**	**p-value**	**AdjOR (95% CI)**	**p-value**
Age (y)	1.04 (1.01 – 1.08)	0.019	1.03 (0.99 – 1.06)	0.203
Male sex	0.66 (0.38 - 1.14)	0.133		
BMI	1.01 (0.96 - 1.07)	0.719		
Hypertension	1.36 (0.60 - 3.07)	0.457		
Diabetes mellitus	1.34 (0.75 - 2.39)	0.323		
Chronic kidney disease *	1.62 (0.83 - 3.16)	0.157		
HASBLED score	1.11 (0.88 - 1.41)	0.386		
CHA2DS2Vasc score	1.28 (1.08 - 1.52)	0.004	1.17 (0.95 - 1.42)	0.135
Paroxysmal atrial fibrillation	0.91 (0.53 - 1.57)	0.736		
History of cerebrovascular events	1.08 (0.61 - 1.92)	0.802		
Carotid artery disease	0.27 (0.04 - 2.00)	0.199		
History of coronary heart disease	1.33 (0.77 - 2.30)	0.305		
Prior MI	1.51 (0.85 - 2.71)	0.158		
History of arterial embolism	0.57 (0.08 - 4.30)	0.586		
History of anticoagulant therapy failure	2.45 (0.69 - 8.68)	0.163		
History of intracranial bleeding	0.31 (0.09 – 0.99)	0.048	0.34 (0.10 – 1.11)	0.074
History of gastrointestinal bleeding	0.76 (0.39 - 1.46)	0.404		
History of bleeding in other regions †	1.10 (0.54 – 2.24)	0.787		
Ejection fraction	0.99 (0.97-1.01)	0.431		
LAA thrombus	2.15 (0.80 - 5.74)	0.129		
LAA shape (chicken wing)	1.13 (0.46 - 2.80)	0.794		
Sinus rhythm during procedure, no. (%)	1.42 (0.82 - 2.47)	0.212		
Type of implanted device	1.36 (1.02 - 1.81)	0.036	1.22 (0.88 – 2.04)	0.26
First operator	0.91 (0.82 - 1.04)	0.123		
Expertise operator (third tertile)	0.56 (0.27 - 1.15)	0.114		
Concomitant Intervention	1.26 (0.74 – 2.14)	0.397		
Echocardiography guidance	0.36 (0.17 - 0.73)	0.005	0.31 (0.11 – 0.90)	0.030
Discharge antiplatelet therapy group	1.17 (0.82 - 1.66)	0.383		
Year of recruitment	0.87 (0.79 – 0.97)	0.011	0.95 (0.83 – 1.09)	0.461

* Chronic Kidney Disease was defined if at least one of the following criteria was met: <30 eGFR mL/min per 1.73m2 (using the Modification of Diet in Renal Disease formula) and/or blood creatinine value >200 mcmol/l and/or dialysis or history of kidney transplantation.

† History of bleeding in other regions included history of genito-urinary bleeding, epistaxis, hemoptysis, intra-articular bleeding, intramuscular bleeding, cutaneous or subcutaneous hematoma/ecchymosis, or history of any type of bleeding requiring medical attention. Patients with previous intracranial and/or gastrointestinal bleeding were excluded from this group.

OR, odds ratio; AdjOR, adjusted odds ratio; CI, confidence interval; BMI, body mass index; MI, myocardial infarction; LAA,Left atrial appendage.

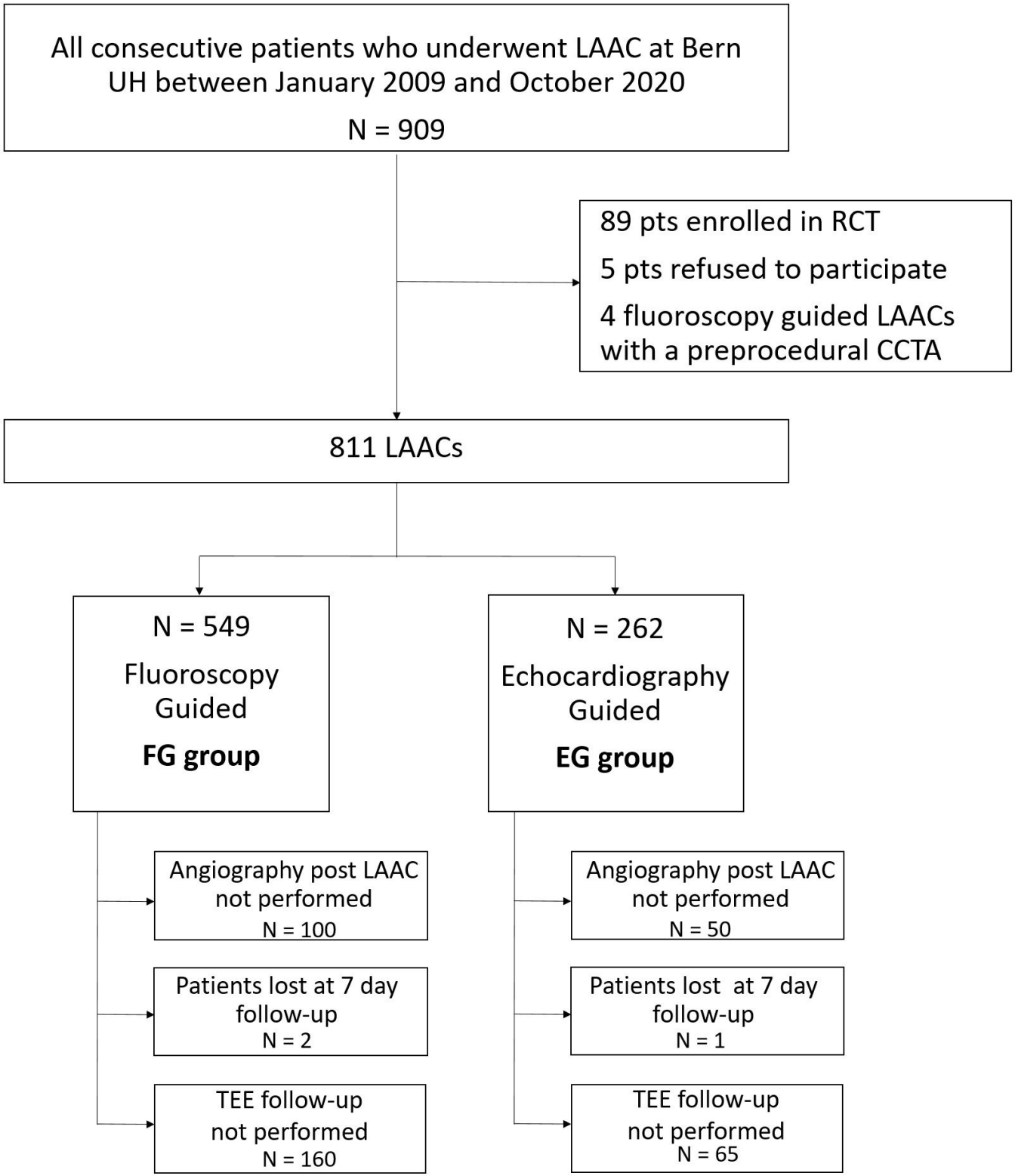
Table 5. Baseline Univariate and Multivariate Predictors of Long-term Technical Success

	Univariate		Multivariate	
Long Term Technical Success	**OR (95% CI)**	**p-value**	**Adj OR (95% CI)**	**p-value**
Age (y)	0.97 (0.95 - 0.99)	0.016	0.97 (0.94 - 1.01)	0.105
Male sex	2.07 (1.34 - 3.20)	0.001	2.29 (1.35 - 3.85)	0.002
BMI	0.99 (0.95 - 1.04)	0.887		
Hypertension	0.97 (0.54 - 1.74)	0.916		
Diabetes mellitus	0.93 (0.58 - 1.51)	0.776		
Chronic kidney disease *	1.49 (0.76 - 2.91)	0.247		
HASBLED score	1.07 (0.89 - 1.28)	0.492		
CHA2DS2Vasc score	0.78 (0.69 - 0.90)	<0.001	0.94 (0.78 - 1.13)	0.506
Paroxysmal atrial fibrillation	0.91 (0.59 - 1.40)	0.664		
History of cerebrovascular events	0.79 (0.51 - 1.24)	0.302		
Carotid artery disease	1.03 (0.42 - 2.55)	0.943		
History of coronary heart disease	1.14 (0.75 - 1.73)	0.541		
Prior MI	0.71 (0.44 - 1.14)	0.176		
History of arterial embolism	0.63 (0.20 - 2.00)	0.434		
History of anticoagulant therapy failure	0.50 (0.17 - 1.45)	0.202		
History of intracranial bleeding	1.73 (0.87 - 3.47)	0.121		
History of gastrointestinal bleeding	1.44 (0.89 - 2.60)	0.182		
History of bleeding in other regions†	0.80 (0.47 – 1.38)	0.425		
Ejection fraction	1.020 (1.001 - 1.040)	0.040	1.02 (0.99 - 1.04)	0.125
LAA thrombus	0.38 (0.17 - 0.88)	0.024	0.52 (0.20 - 1.34)	0.173
LAA shape (chicken wing)	1.01 (0.51 - 2.01)	0.982		
Sinus rhythm during procedure, no. (%)	0.62 (0.40 – 0.97)	0.034	0.60 (0.34 – 1.06)	0.079
Type of implanted Device	0.77 (0.61 - 0.97)	0.026	0.82 (0.63 -1.07	0.148
First operator	0.97 (0.91 - 1.03)	0.260		
Expertise operator (third tertile)	1.49 (0.82 – 2.70)	0.192		
Concomitant Intervention	1.18 (0.77 – 1.80)	0.453		
Echocardiography-guidance	1.79 (1.10 - 2.90)	0.019	4.06 (1.60 - 10.27)	0.003
Discharge antiplatelet therapy group	0.94 (0.72 - 1.23)	0.650		
Year of recruitment	1.06 (0.98 – 1.15)	0.133		

* Chronic Kidney Disease was defined if at least one of the following criteria was met: <30 eGFR mL/min per 1.73m2 (using the Modification of Diet in Renal Disease formula) and/or blood creatinine value >200 mcmol/l and/or dialysis or history of kidney transplantation.

† History of bleeding in other regions included history of genitourinary bleeding, epistaxis, hemoptysis, intra-articular bleeding, intramuscular bleeding, cutaneous or subcutaneous hematoma/ecchymosis, or history of any type of bleeding requiring medical attention. Patients with previous intracranial and/or gastrointestinal bleeding were excluded from this group.

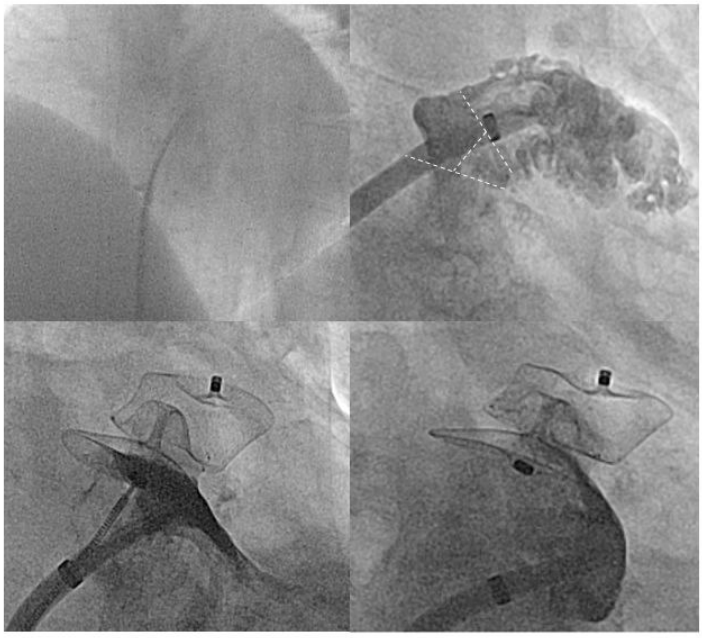
OR, odds ratio; AdjOR, adjusted odds ratio; CI, confidence interval; BMI, body mass index; MI, myocardial infarction; LAA, left atrial appendage.


All consecutive patients who underwent LAAC at Bern UH between January 2009 and October 2020
N = 909
89 pts enrolled in RCT
5 pts refused to participate
4 fluoroscopy guided LAACs with a preprocedural CCTA
811 LAACs
N = 549
Fluoroscopy Guided
FG group
N = 262
Echocardiography Guided
EG group
Angiography post LAAC not performed
N = 100
Patients lost at 7 day follow-up
N = 2
TEE follow-up not performed
N = 160
Angiography post LAAC not performed
N = 50
Patients lost at 7 day follow-up
N = 1
TEE follow-up not performed
N = 65

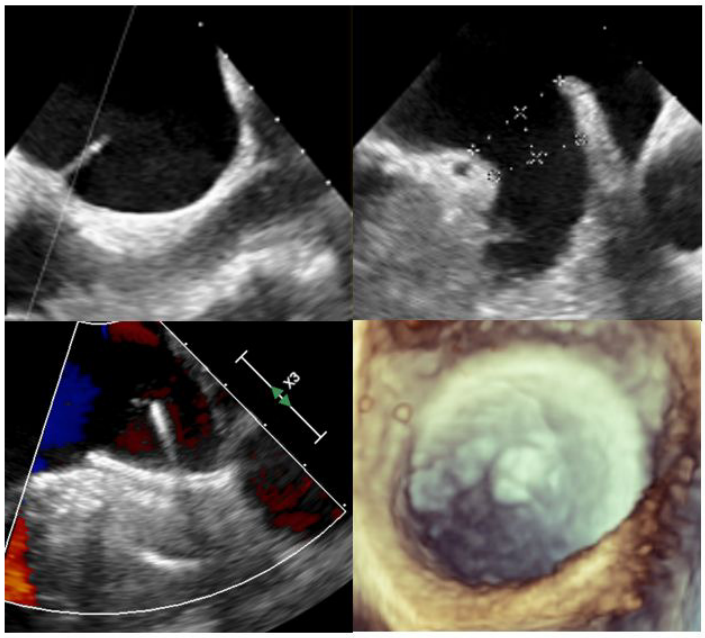
Consecutive LAAC Procedures at Bern Hospital-Switzerland Between 2009-2020 (N=811)

2009 — 2015 — 2020

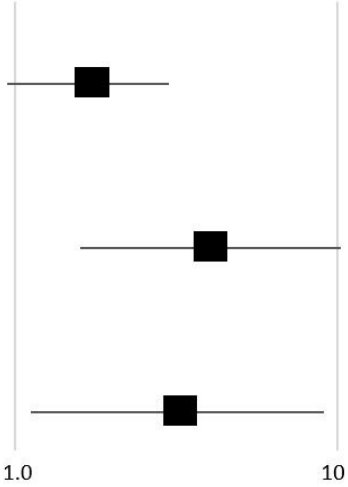
Fluoroscopy Guidance

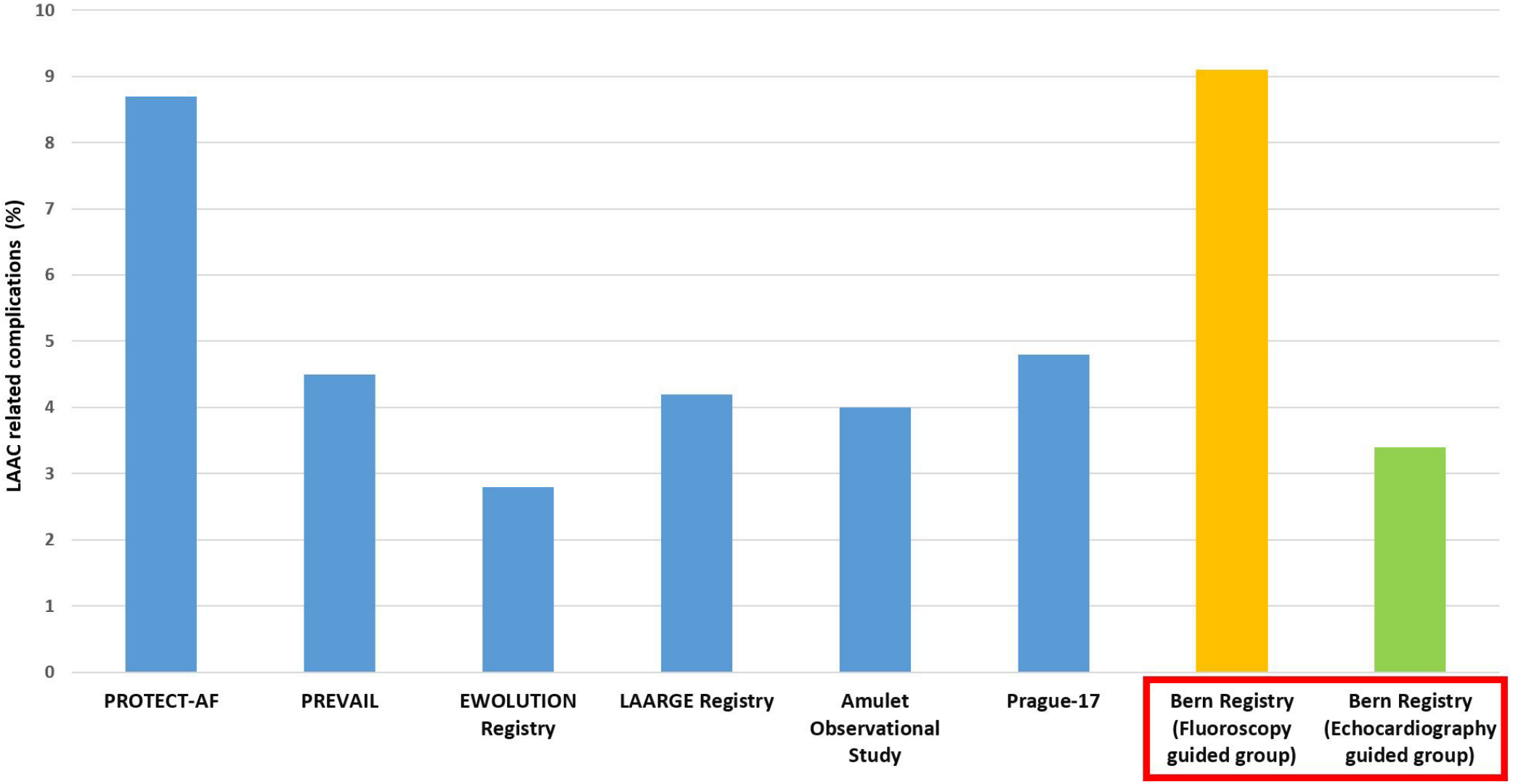


Echocardiography Guidance



	Better Fluoroscopy Guidance	*Better Echocardiography Guidance*	*adjOR (95% CI)*	*p value*
Short-Term Technical Success			**1.68 (0.95 – 3.01)**	**0.079**
Long-Term Technical Success			**4.06 (1.60 – 10.27)**	**0.003**
Safety Endpoint			**3.18 (1.12 - 9.08)**	**0.030**




LAAC related complications (%)
10
9
8
7
6
5
4
3
2
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PROTECT-AF
PREVAIL
EWOLUTION Registry
LAARGE Registry
Amulet Observational Study
Prague-17
Bern Registry (Fluoroscopy guided group)
Bern Registry (Echocardiography guided group)