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ORIGINAL ARTICLE

Atrial appendage closure in patients with heart failure and atrial fibrillation: industry-independent single-centre study

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Abstract

Aims To evaluate outcomes of percutaneous left atrial appendage closure (LAAC) in patients with congestive heart failure (CHF) and non-valvular atrial fibrillation (AF) in a consecutive, industry-independent registry associated with periprocedural success and complications during long-term follow-up.

Methods and results For this analysis, we included patients who underwent transcatheter LAAC from January 2014 to December 2019 at the University Heart Center in Lübeck, Germany, and compared patients with presence of CHF defined as patients with a reduced left ventricular ejection fraction (LVEF $\leq$ 40%), patients with a mid-range LVEF (LVEF 41–49%), patients with diastolic dysfunction and preserved LVEF (LVEF $\geq$ 50%), and patients with right-sided heart failure and impaired right ventricular function (tricuspid annular plane systolic excursion $<$ 17) to patients undergoing LAAC with no CHF. Primary endpoints were defined as periprocedural complications, and complications during long-term follow-up presented as major adverse cardiac and cerebrovascular events (MACCE). A total of 300 consecutive patients underwent LAAC. Of these, 96 patients in the CHF group were compared with 204 patients in the non-CHF group. Implantation success was lower in CHF group in comparison with non-CHF group (99.5% vs. 96%, P = 0.038); otherwise, there were no differences in periprocedural complications between groups. Patients with CHF showed a significantly higher incidence of MACCE rate (31.9% vs. 15.1%, P = 0.002) and more deaths (24.2% vs. 7%, $P \leq 0.001$) during long-term follow-up. In Cox multivariable regression analysis, CHF was an independent predictor of mortality after LAAC implantation at long-term follow-up (hazard ratio 3.23, 95% confidence intervals 1.52–6.86, P = 0.002).

Conclusions Implantation of LAAC devices in patients with non-valvular AF and CHF is safe. The increased mortality in patients with CHF compared with patients without CHF during the long-term follow-up is mainly attributed to comorbidities associated with CHF.

Keywords Left atrial appendage closure; Congestive heart failure; Atrial fibrillation; Anticoagulation

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Introduction

Atrial fibrillation (AF) is an increasing healthcare challenge due to its increasing incidence in the ageing population and its association with elevated risks of cardiovascular events, in particular stroke and mortality.[1]

In large randomized clinical trials, all available new oral anticoagulants (OACs) have shown similar efficacy for stroke prevention in AF compared with warfarin, but with a more favourable safety profile, especially concerning intracranial bleeding.[2] However, a substantial proportion of eligible AF patients are treated either suboptimally or not at all with OAC mainly because of increased bleeding risk, bleeding complications such as intracranial haemorrhage, and the need for lifelong anticoagulation monitoring.[3] Left atrial appendage closure (LAAC) has emerged as an alternative approach in this patient group. The basis of this approach is that the majority of clots are formed in the left atrial appendage (LAA), and therefore, its obliteration will prevent clot formation.[4]

The ESC Guidelines indicate that LAAC may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (class IIb, level of evidence B).[5]

Both AF and congestive heart failure (CHF) are highly linked disorders in many patients because of common risk factors and causal relation between the entities. These shared factors include diabetes mellitus, hypertension, and ischaemic and valvular heart disease.[6] Data from the Framingham study showed that patients with CHF have two to three times higher risk of ischaemic stroke through multiple possible pathophysiologic mechanisms.[7] AF or left ventricular (LV) hypokinesis can result in thrombus formation and a cardioembolic source of stroke arising from the LAA or LV cavity.[8]

Theoretically, the higher rates of stroke and embolism observed in patients with CHF and AF are due to impaired LAA emptying velocities leading to LAA thrombus formation, even when patients are on oral anticoagulants.[9] Hence, device-based LAAC might be an elegant alternative for patients with AF, CHF, and high risk for stroke and bleeding.

The aim of this study was therefore to investigate the outcomes of LAAC in patients with CHF and AF in a consecutive, industry-independent registry regarding periprocedural success and complications during long-term follow-up.

Methods

Study population

Patients who underwent endocardial or epicardial LAAC from January 2014 to December 2019 at the University Heart Center Lübeck (Lübeck, Germany) were included in this study. Patients who were included in the present analysis were divided into two groups. One group included patients with no evidence of CHF, while the other group included patients with CHF and a previous history or an evidence of decompensation. The CHF group included patients with a reduced LV ejection fraction (LVEF $\leq$ 40%), patients with a mid-range LVEF (LVEF 41–49%), patients with diastolic dysfunction and preserved LVEF (LVEF $\geq$ 50%), and patients with right-sided heart failure and impaired right ventricular function (tricuspid annular plane systolic excursion $<$ 17 mm).

There were no exclusion criteria according to the type of device used for LAAC where determination of device type was left to operator discretion according to the anatomy of LAA and experience of the operator.

The implantation of LAAC devices was done by experienced implanters and according to the recommendation of the EHRA/EAPCI expert consensus statement for catheter-based LAAC.[10] The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics board. All patients provided informed consent to the procedure before intervention.

Primary endpoints

The primary endpoints of the study were periprocedural complications and complications during follow-up in both groups of patients with and without CHF. Procedural endpoints and adverse events were categorized according to the Munich consensus document on LAAC.[11]

Periprocedural complications included in-hospital death, pericardial tamponade, device embolization, stroke, major bleeding, and vascular access complications. Complications during follow-up included ischaemic stroke, haemorrhagic stroke, thromboembolism, device thrombus, bleeding, and deaths. Endpoints were analysed both individually and in combination as major adverse cardiac and cerebrovascular events (MACCE).

Periprocedural management of left atrial appendage closure

Indications of LAAC in our patients were AF and previous major bleeding, bleeding predisposition, or contraindications for oral anticoagulants, which is consistent with the recommendation of EHRA/EAPCI. For assessment of the bleeding risk and the indication of LAAC, the CHA2DS2VASC and HASBLED scores were calculated for all patients.

Before the procedure, all patients underwent both transthoracic echocardiography for assessment of LVEF, diastolic function, and right ventricular function, while transesophageal echocardiography (TEE) was done for exclusion of the presence of LAA thrombus. The LAAC procedure was

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performed in all patients under deep sedation using continuous infusion of propofol. The implantation was guided by contrast angiography and intraprocedural TEE. The size and type of the device were selected according to the assessment of maximum diameter of the intended landing zone on both two-dimensional TEE and contrast angiography in right anterior oblique caudal and cranial projections and in TEE in 0°, 45°, 90°, and 135° where it was measured from the left circumflex coronary artery to the LAA roof, 1 cm inward from the apex of the ridge separating the LAA and left superior pulmonary vein.

The size of the device was selected to be 10–20% larger than the diameter of the landing zone and was deployed under fluoroscopy and TEE guidance as recommended by the manufacturer's instructions for use, as well as visual assessment of the LAA.

After deployment of the closure device, device stability and position were tested in contrast angiography and TEE, and the device was released after confirmation of stability.

During all LAAC procedures, the radiation dose (cGy cm^2), fluoroscopic time (min), and the amount of contrast (mL) used were documented.

According to the indication and physician's choice, the post-procedural antithrombotic therapy was determined. OAC or dual anti-platelet therapy was usually continued until the next follow-up TEE, while in the absence of a mandatory indication for OAC, dual or single anti-platelet therapy was prescribed.

In-hospital assessment of adverse events

For 24 h after the procedure, all patients were followed up for periprocedural adverse events including deaths, transient ischaemic attacks, stroke, systemic embolization, device embolization, significant pericardial effusion or cardiac tamponade, and major bleeding.

Post-procedural echocardiographic follow-up of the patients

A follow-up TEE was performed 6–12 weeks after LAAC to assess the stability of the device to detect potential thrombus and/or peri-device leaks, where a major leak was defined as a leak of more than 5 mm and a minor leak was defined as a leak of less than 5 mm.

Post-procedural clinical follow-up of the patients

Patients were scheduled for regular follow-ups every 6–12 months at the outpatient clinic or the referring clinic for detection of complications including deaths, transient ischaemic attacks, stroke, and systemic embolization. Mortality was documented based on hospital visits, scheduled follow-up visits, and communication with ambulatory physicians.

Statistical analysis

Continuous data were expressed as a median with an interquartile range. Differences between groups were assessed by Fisher's exact or the X^2 test for categorical variables and were evaluated using the nonparametric Mann–Whitney *U* test for continuous data. The Kaplan–Meier graph was used to illustrate the long-term cumulative survival rates during the long-term follow-up in the two groups. All tests were two-tailed, and a P value < 0.05 was considered statistically significant. Predictors for mortality were identified by univariate and multivariable Cox regression analysis. Variables with a $P < 0.1$ in the univariate analysis were incorporated into the multivariable model. Multivariable regression was performed for mortality using a model containing CHF, age, body mass index, history of hypertension, CHA2DS2VASC score, and history of major bleeding. Statistical analysis was performed using SPSS Statistics 7.0.0.0 (IBM, Armonk, New York).

Results

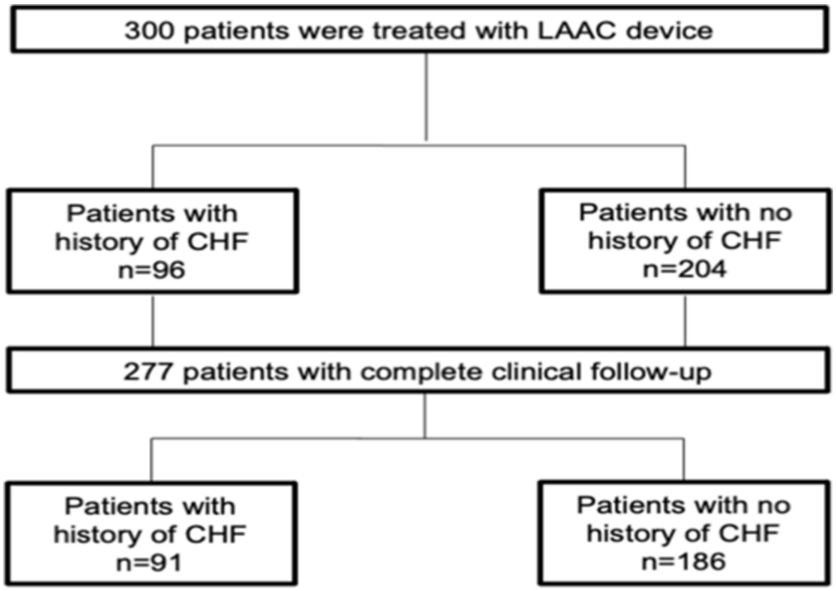
Baseline characteristics

In the period from January 2014 to December 2019, 300 patients underwent endocardial or epicardial LAAC with various types of devices at the University Heart Center Lübeck (Lübeck, Germany). Of these, 204 patients had no history of CHF while 96 patients had a history of CHF. A total of 277 patients had available follow-up data, and of those, 186 patients had no history of CHF while 91 patients had history of CHF. Median follow-up occurred at 176 (72–385) days for the non-CHF group and 101 (62–413) days for CHF group (*Figure 1*). Although patients with CHF were younger in age, they had higher incidence of ischaemic heart disease, peripheral vascular disease, and chronic kidney dysfunction and suffered more haemorrhagic strokes than patients with no evidence of CHF. Procedural device implantation success was achieved in 99.5% of the non-CHF group and 96% of the CHF group ($P = 0.038$) (*Table 1*).

Periprocedural complications

Periprocedural complications, which were defined as major bleeding complications, in-hospital death, pericardial tamponade, and device embolization, did not differ between the two groups (*Table 2*).

Figure 1 Flow chart of patients who received LAAC devices. CHF, congestive heart failure; LAAC, left atrial appendage closure.



Clinical outcomes during follow-up

During long-term follow-up, patients in the CHF group who received an LAAC had more statistically significant MACCE than patients in the non-CHF group (31.9% vs. 15.1%, respectively; $P = 0.002$) with significantly higher rates of death (24.2% vs. 7%, respectively; $P \leq 0.001$) (*Table 3*). In univariate Cox regression analysis, CHF (hazard ratio 3.83, 95% confidence intervals 1.93–7.60, $P \leq 0.001$) was a significant predictor of increased mortality. After multivariable adjustment for other established markers of patient risk, CHF remained a significant and independent predictor of mortality (hazard ratio 3.23, 95% confidence intervals 1.52–6.86, $P = 0.002$) (*Table 4*). The Kaplan–Meier graph was used to illustrate the impact of CHF on long-term cumulative survival (*Figure 2*).

These results were consistent in the subgroup analyses including patients with heart failure with reduced ejection fraction (Supporting Information, *Table S1*), patients with heart failure with a mid-range ejection fraction (*Table S2*), and patients with heart failure with preserved ejection fraction (*Table S3*).

Discussion

To the best of our knowledge, this is the first study evaluating a long-term follow-up in high-risk patients with CHF and non-valvular AF undergoing LAAC. The results of our study show that patients with CHF who were treated with an LAAC had more statistically significant MACCE and more deaths during long-term follow-up compared with patients with normal cardiac function. In the multivariable analysis, CHF was a significant and independent predictor of mortality. However, our data also underline that LAAC in patients with CHF is a safe procedure without increasing peri-interventional complications but with a lower implantation success rate. The unsuccessful implantations were related mainly to device dislocation in three patients in CHF group and one patient in non-CHF group with successful snaring of the devices and implantation of larger or smaller devices. Another unsuccessful implantation in the CHF group was due to failed implantation of a Lariat device due to periprocedural formation of an LAA thrombus and occurrence of pericardial effusion.

Periprocedural complications

In our study, the presence of CHF did not affect the periprocedural outcome, as shown in a comparable numbers of hospital deaths, major bleeding, and MACCE in both groups. The in-hospital stoke rate was 1% in patients with CHF, while none of the patients in the non-CHF group experienced a stroke. These results were comparable with the reported 0.5% periprocedural ischaemic stroke rate after LAAC in the Continued Access Left Atrial Appendage Closure Registry 2, where 27.1% of the included patients had history of CHF.[12] In the National Cardiovascular Data Registry LAAO Registry, the major in-hospital ischaemic stroke rate was only 0.17%.[13] Regarding pericardial

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Table 1 Baseline and procedural characteristics

Variable	No CHF (n = 204)	CHF (n = 96)	P
Age (years)	75 (70–79)	73 (64–80)	**0.009**
Male sex	122/204 (60%)	66/96 (69%)	0.160
Hypertension	173/204 (85%)	88/96 (92%)	0.140
Diabetes mellitus	54/204 (27%)	34/96 (35%)	0.135
Body mass index (kg/m^2)	26 (24–28)	28 (24–32)	0.842
Ischaemic heart disease	79/199 (40%)	60/94 (64%)	<**0.001**
Peripheral vascular disease	51/204 (25%)	53/96 (55%)	<**0.001**
Chronic kidney dysfunction	101/204 (50%)	64/96 (67%)	**0.006**
Liver dysfunction	4/204 (2%)	3/96 (3%)	0.684
History of ischaemic stroke	46/204 (23%)	19/96 (20%)	0.654
History of TIA	11/204 (5%)	7/96 (7%)	0.603
History of haemorrhagic stroke	75/204 (37%)	51/96 (53%)	**0.009**
History of major bleeding	97/204 (48%)	50/96 (52%)	0.536
LVEF	55 (54-55)	45 (35–50)	<**0.001**
Classification of CHF			<**0.001**
HEpEF	—	22/96 (23%)	
HFrEF	—	37/96 (39%)	
HFmEF	—	31/96 (32%)	
Right-sided HF	—	6/96 (6%)	
NYHA class			<**0.001**
1	182/200 (91%)	15/89 (17%)	
2	8/200 (4%)	28/89 (32%)	
3	9/200 (5%)	44/89 (49%)	
4	0/200 (0%)	2/89 (2%)	
CHA2DS2VASC score	3 (2–4)	4 (4–5)	<**0.001**
HASBLED score	2 (1–3)	2 (2–3)	0.107
LAA-flow	45 (20–55)	30 (15–60)	0.283
Serum creatinine	86 (72–102)	101 (84–166)	0.169
GFR	72 (58–82)	59 (36–75)	**0.008**
Hospital stay (days)	4 (3–5)	4 (3–11)	<**0.001**
Device implanted			0.114
Watchman	116/204 (57%)	45/96 (47%)	
Amulet	73/204 (36%)	47/96 (49%)	
Lariat	14/204 (7%)	3/96 (3%)	
Lambre	1/204 (0%)	1/96 (1%)	
Device size (mm)	27 (24–28)	24 (24–27)	0.088
Contrast volume (mL)	60 (40–80)	70 (60–90)	0.729
Radiation time (min)	9 (6–13)	11 (7–14)	0.825
Radiation dose	1668 (1216–3031)	2386 (1191–3644)	0.289
Implantation success	203/204 (99.5%)	92/96 (96%)	**0.038**
Major leak (>5 mm)	1/204 (0.5%)	1/94 (1%)	0.532
Minor leak (<5 mm)	4/204 (2%)	6/95 (6%)	0.079
Follow-up duration (days)	176 (72–385)	101 (62–413)	0.304

CHF, congestive heart failure; GFR, glomerular filtration rate; HFmEF, heart failure with a mid-range ejection fraction; HFpEF, heart failure with a preserved ejection fraction; HFrEF, heart failure with a reduced ejection fraction; LAA, left atrial appendage; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; TIA, transient ischaemic attack.

Table 2 Procedural complications

Variable	No CHF	CHF	P
MACCE, *n* (%)	12/204 (5.9)	7/96 (7.3)	0.620
In-hospital death, *n* (%)	3/204 (1.5)	2/96 (2.1)	0.657
Pericardial tamponade, *n* (%)	4/204 (2.0)	2/96 (2.1)	1.000
Device embolization, *n* (%)	2/204 (1.0)	2/96 (2.1)	0.595
Stroke, *n* (%)	0/204 (0.0)	1/96 (1.0)	0.320
Major bleeding, *n* (%)	4/204 (2.0)	3/96 (3.1)	0.684
Blood transfusion, *n* (%)	5/204 (2.5)	3/96 (3.1)	0.714
Major vascular access complications	3/204 (1.5)	1/96 (1.0)	1.000
Minor vascular access complications	4/203 (2.0)	2/96 (2.1)	1.000

CHF, congestive heart failure; MACCE, major adverse cerebral and cardiovascular events.

tamponade, there were also no significant differences between the two groups (2% in each group). In the National Cardiovascular Data Registry, the most common major adverse event was pericardial effusion requiring intervention, which was a common cause for procedural cancellation.[11]

Table 3 Complications during long-term follow-up

Variable	No CHF	CHF	*p*
MACCE, *n* (%)	28/186 (15.1)	29/91 (31.9)	**0.002**
Ischaemic stroke, *n* (%)	6/185 (3.2)	1/91 (1.1)	0.432
Haemorrhagic stroke, *n* (%)	2/185 (1.1)	1/91 (1.1)	1.000
Thromboembolism, *n* (%)	4/185 (2.2)	1/91 (1.1)	1.000
Device-related thrombus, *n* (%)	6/183 (3.3)	2/90 (2.2)	1.000
Bleeding, *n* (%)	13/185 (7)	11/91 (12.1)	0.177
Death, *n* (%)	13/185 (7)	22/91 (24.2)	<**0.001**
Cardiac death, *n* (%)	3/13 (23.1)	6/22 (27.3)	1.000

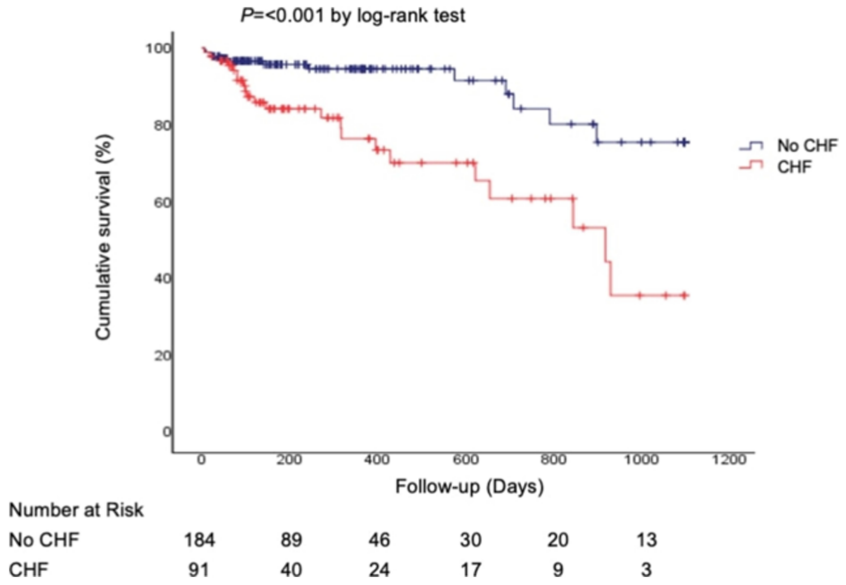
CHF, congestive heart failure; MACCE, major adverse cerebral and cardiovascular events.

Table 4 Predictors of mortality at long-term follow-up in Cox regression analysis

	Univariate		Multivariable	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Congestive heart failure	3.83 (1.93–7.60)	<**0.001**	3.23 (1.52–6.86)	**0.002**
Ischaemic heart disease	0.57 (0.28–1.15)	0.115	—	
Peripheral vascular disease	1.68 (0.87–3.24)	0.123	—	
Age (years)	1.07 (1.02–1.12)	**0.007**	1.04 (0.99–1.11)	ns
Female sex	0.95 (0.47–1.91)	0.885	—	
Body mass index (kg/m^2)	0.93 (0.87–1.01)	0.071	0.96 (0.89–1.03)	ns
Diabetes mellitus	0.72 (0.35–1.48)	0.367	—	
Hypertension	1.15 (0.35–3.79)	0.082	1.94 (0.43–8.76)	ns
CHA2DS2VASC score	1.18 (0.97–1.44)	0.099	0.89 (0.68–1.16)	ns
HASBLED score	1.03 (0.77–1.38)	0.860	—	
Chronic renal failure	1.38 (0.71–2.68)	0.337	—	
History of ischaemic stroke	0.755 (0.33–1.74)	0.509	—	
History of haemorrhagic stroke	1.39 (0.72–2.69)	0.327	—	
History of major bleeding	2.33 (1.12–4.86)	**0.024**	1.87 (0.85–4.15)	ns

CI, confidence interval; LAAC, left atrial appendage closure device; LVEF, left ventricular ejection fraction.

Figure 2 Kaplan–Meier graph showing long-term cumulative survival according to the presence and absence of congestive heart failure (CHF).



Clinical outcomes during long-term follow-up

On long-term follow-up, the incidence of MACCE in patients with CHF was significantly higher than in those without CHF, which was mainly caused by increased mortality in the CHF group. This is consistent with the fact that patients with CHF have a poor prognosis, with high rates of hospital admission and mortality despite the implementation of evidence-based treatments.[14] In our cohort, the overall mortality rate was estimated to be 12.7% (35/276), which was nearly similar to that published in other LAAC studies.[15–17] Consistent with our results, the mortality rate in the PROTECT-AF trial was 12.3% in the LAA device group.[18] However, compared with our results, all-cause mortality rates in the CAP and CAP 2 registries were much lower (4.27% and 6.24%, respectively).[12] The explanation for this is that our patients were older and had higher prevalence of diabetes, CHF, transient ischaemic attack, and ischaemic and haemorrhagic stroke.[19]

Interestingly, cardiac mortality did not differ between patients with and without CHF with an overall cardiac mortality rate of 3.3% (9/276). In the PREVAIL trial, the cardiovascular/unexplained death rate was 2.6% in the LAAC group.[19] The increased mortality in the CHF patients may be explained by comorbidities that are normally associated with patients with CHF such as diabetes, hyperlipidaemia, anaemia, iron deficiency, kidney and hepatic dysfunction, chronic obstructive pulmonary disease, sleep-disordered breathing, obesity, cachexia, infection, electrolyte disturbances, infection, and depression. Furthermore, comorbidities are associated with increased severity of CHF symptoms, reduced tolerance to treatment, and worse prognosis.[14] In our cohort, despite patients with CHF being younger in age, they had more risk factors with higher incidence of ischaemic heart disease, peripheral vascular disease, and chronic kidney dysfunction and suffered more haemorrhagic strokes than patients with normal heart function.

Moreover, the CHA2DS2VASC score and the history of haemorrhagic stroke were significantly higher in the CHF group than in the non-CHF group. Gažová *et al*. reported that increasing CHA2DS2VASC scores were not only accompanied by an increase in the incidence of stroke but also by an increase in 3- to 5-year mortality.[20]

Regarding the safety of LAAC in CHF patients, our study showed non-inferiority in the efficacy of LAAC in stroke prevention in both groups, as the ischaemic stroke rate was 3.2% in the non-CHF group and 1.1% in the CHF group. Both haemorrhagic stroke and major bleeding showed no significant difference in both groups during follow-up. These results were consistent with other reports of Amplatzer registries[11,21,22] and with the 5-year outcomes of the PROTECT-AF and PREVAIL trials for the Watchman occluder.[23] We had an overall incidence of ischaemic stroke of 2.5% (7/276), which is lower in comparison with other studies reporting stroke rates of up to 4% in patients with non-valvular AF.[24,25]

Limitations

Potential selection bias cannot be excluded due to lack of randomization. The effect of different types of CHF on patients with non-valvular AF undergoing LAAC was not separately studied. Other limitations of this study include the small number of patients, selection of the LAAC device according to the operator decision, and expertise and different post-interventional anticoagulation strategies over the period of the study.

In conclusion, in our large, industry-independent, real-world registry, we found that the implantation of LAAC devices in patients with CHF and non-valvular AF was associated with comparable periprocedural efficacy and safety for patients without CHF but with a lower implantation success rate. Increased mortality at long-term follow-up was related to comorbidities normally associated with patients with CHF. Larger randomized studies or well-designed prospective registries will have to confirm these results.

Acknowledgements

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Conflict of interest

M. Saad is proctor for Boston Scientific and received honoraria for his proctoring sessions otherwise none declared.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Complications during long-term follow-up in patients with HFrEF.
Table S2. Complications during long-term follow-up in patients with HFmrEF.
Table S3. Complications during long-term follow-up in patients with HFpEF.

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