



Influence of severe anemia on procedural safety and one-year outcome after left atrial appendage closure: Insights from a very high-risk cohort

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ABSTRACT

Introduction: Patients undergoing left atrial appendage closure (LAAC) are often severely anemic and close to the transfusion threshold. The aim was to investigate the prevalence of severe anemia in this cohort and if procedural safety is compromised compared with non-anemic patients.

Methods and results: Comparison of severely anemic patients (Hb < 80 g/l) vs. non-severely anemic patients in the prospective, multicentre observational LAARGE registry of patients undergoing LAAC. A total of 638 patients (anemia 22.3% vs non-anemic 77.7%) were included. Anemic patients were older (77.1 years \pm 7.9 vs 75.6 years \pm 7.9, $p = 0.014$), had more comorbidities, higher CHA₂DS₂-VASc (4.8 vs 4.4, $p = 0.017$) and higher HAS-BLED (4.3 vs 3.8, $p < 0.001$) scores. Implant success was not influenced by anemia (99.3% vs 97.2%). Severe in-hospital (0.7% vs 5.6%, $p = 0.01$) and overall complications (8.5% vs 13.7%, $p = 0.11$) were less common in patients with anemia, driven by fewer pericardial effusions. Mortality was higher in anemic patients and associated with an increased hazard ratio, albeit not significantly (16.0% vs 10.3%, HR 1.61 (95%-CI: 0.97–2.67), $p = 0.06$). In the one-year follow-up, composite outcome of death, stroke or systemic embolism occurred in 22/142 anemic and in 54/496 non-anemic patients with an adjusted HR of 1.04 (95%-CI 0.62–1.73, $p = 0.89$).

Conclusion: Severe anemia close to the transfusion threshold is common in patients undergoing LAAC. However, this does not influence in-hospital complications or implant success. One-year mortality is higher in anemic patients, mainly driven by co-morbidities.

1. Introduction

Atrial fibrillation (AF) is one of the most common causes of stroke and found in at least every fourth stroke patient [1]. Oral anticoagulation (OAC) is very effective for stroke prevention in patients with AF [2]. Yet, OAC is frequently discontinued, often due to bleeding or due to perceived or real risks of bleeding, including anemia [3]. In those cases, left atrial appendage closure (LAAC) can be attempted for stroke prevention. Existing data from randomized controlled trials point to non-inferiority of LAAC compared to OAC in patients eligible for either

Vitamin K antagonists (VKA) or Non-Vitamin K antagonist oral anti-coagulation (NOAC) [4,5]. In view of the lack of robust evidence supporting the use of LAAC as an alternative to OAC, LAAC is currently used as a second-line treatment in a clinically vulnerable population. For instance, in the prospective European EWOLUTION registry collecting baseline data from patients undergoing LAAC with one specific device, ca. 40% of a history of stroke, ca. 60% had a contraindication for OAC [6], and ca. 40% had a history of major bleeding or a predisposition to bleeding [6]. Anemia has been associated with major bleeding and all-cause-mortality in patients with AF on OAC [7]. Patients referred for

Abbreviations: AF, Atrial fibrillation; AV, Arteriovenous; LAAC, Left atrial appendage closure; MI, Myocardial infarction; NOAC, Non-vitamin K antagonist; NSAID, Non-steroidal anti-inflammatory drug; OAC, Oral anticoagulation; PPI, Proton pump inhibitor; VKA, Vitamin K antagonist.

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LAAC are often below the blood transfusion threshold. Whether severe anemia affects acute or one-year outcomes in patients undergoing LAAC is not known. We evaluated the procedural safety and one-year outcomes of LAAC in patients with and without severe anemia from the Left-Atrium-Appendage Occluder Register - Germany (LAARGE).

2. Methods

2.1. Registry structure and objectives

Clinical characteristics, periprocedural and one-year outcomes were compared between severely anemic and non-anemic patients in the LAARGE data set. LAARGE is a prospective, non-randomized multicentre real-world registry collecting data from patients treated with all commercially available LAAC devices. The non-profit organization “Stiftung Institut für Herzinfarktforschung“ (IHF, Ludwigshafen, Germany) is supervising the prospective, multicenter LAARGE registry. The registry was industry-independently funded by Stiftung IHF and driven by scientific interest of all participating sites. Recruitment began in July 2014 and ended in January 2016. All 38 participating centers were encouraged to enroll consecutive patients. Written informed consent was obtained from all patients. The study was carried out according to the declaration of Helsinki and approved by the ethics committee of the State Chamber of Medicine in Rhineland-Palatinate, Germany (837.173.14 (9412-F), 25.06.2014). The detailed data collection and privacy measures have been reported before [8].

2.2. Severe anemia definition and outcomes

The implantation procedure, device selection and antithrombotic/anticoagulant management were carried out according to local protocols. Implantation success was defined as stable position of the device according to the Munich consensus document [9]. Details of the procedure including sedation or anesthesia were captured. All in-hospital events were captured using the electronic case report forms (eCRF). The one-year follow-up was conducted by IHF via a standardized phone interview and reports from the implanting center. Severe anemia was defined as hemoglobin < 80 g/L. This value is often studied in clinical trials and recommended in society guidelines as a threshold for blood transfusion [10,11]. Patients were classified as anemic or non-anemic based on the last available hemoglobin value prior to the procedure.

2.3. Statistical analysis

Clinical parameters, scores, and comorbidities were compared between anemic and non-anemic patients. Categorical data are shown in relative percentages and absolute values. Normally distributed continuous data and risk scores are shown as means \pm standard deviation (SD), otherwise given as medians with interquartile ranges (25th and 75th percentiles). Statistical distributions were compared between both groups using either Mann-Whitney-Wilcoxon test or with a Chi-square test. Fisher's exact test was used for rates of in-hospital and follow-up complications. The one-year event-rates of death, composite outcome of death and stroke, and composite of death, stroke and systemic embolism were calculated by the Kaplan-Meier method. These outcomes were compared between age groups using the log-rank test. Hazard ratios (HR) and Odds ratios (OR) with 95% confidence intervals (CI) were estimated using Cox regression models. The HR of the composite outcome was adjusted for age, sex, and the significantly imbalanced conditions diabetes mellitus, chronic kidney failure, vascular disease, coronary artery disease and valvular heart disease. All statistical comparisons were two-sided, and P-values < 0.05 were considered statistically significant. Analyses were performed using the Statistical Analysis System (SAS, Version 9.4, SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Baseline characteristics

A total of 638 patients were included in the study. There were 142/638 (22.3%) severely anemic and 496/638 (77.7%) non-anemic patients. Anemic patients were slightly older (77.1 ± 7.9 years) than non-anemic patients (75.6 ± 7.9 years, $p = 0.014$) and had more comorbidities as illustrated by higher CHA2DS2-VASc (4.8 ± 1.6 vs 4.4 ± 1.5) and HAS-BLED (4.3 ± 1.0 vs 3.8 ± 1.1 , details see Table 1) scores. For instance, the anemic patients had a significantly higher proportion of coronary

Table 1

Clinical characteristics of the study population. OR: odds ratio; CI: confidence interval; BMI: body mass index; MI: myocardial infarction; PAD: peripheral artery disease; INR: international normalized ratio; LAAC: left atrial appendage closure; CVI: cerebrovascular incident; TIA: transient ischemic attack; OAC: oral anticoagulation; displayed are percentages and numbers or median and quartiles; P-values < 0.05 are considered significant, tested with either Pearson chi-squared test or Mann-Whitney-Wilcoxon test.

	Anemic patients(n = 142)	Non-anemic patients(n = 496)	P-value	OR (95%-CI)
Age, years	77.1 \pm 7.9	75.6 \pm 7.9	0.014	–
Female, %	39.4	38.7	0.88	–
BMI, kg/m ²	26.3 (24.5, 29.6)	26.9 (24.1, 30.1)	0.78	–
Cardiac history				
Coronary artery disease, %	54.2	43.3	0.022	1.55 (1.06–2.25)
History of MI, %	12.0	9.3	0.34	–
Valvular heart disease, %	27.5	18.8	0.024	1.64 (1.07–2.53)
Cardiomyopathy, %	7.0	7.1	1.00	–
Congestive heart failure, %	32.4	25.4	0.098	–
Hypertension, %	94.4	92.5	0.45	–
No structural heart disease, %	13.4	22.0	0.024	0.55 (0.32–0.93)
Extracardiac history				
Diabetes mellitus, %	45.8	30.6	< 0.001	1.91 (1.30–2.80)
Chronic kidney disease, %	52.8	33.5	< 0.001	2.23 (1.52–3.25)
Vascular disease (e. g. PAD), %	39.4	22.4	< 0.001	2.26 (1.52–3.36)
Labile INR, %	20.4	13.7	0.049	1.62 (1.00–2.61)
Chronic liver disease, %	12.7	8.9	0.18	–
Alcohol use disorder, %	3.5	4.1	0.76	–
Risk scores				
CHA2DS2-VASc Score	4.8 \pm 1.6	4.4 \pm 1.5	0.017	–
HAS-BLED Score	4.3 \pm 1.0	3.8 \pm 1.1	< 0.001	–
Indications for LAAC				
History of bleeding, %	94.4	75.2	< 0.001	5.52 (2.63–11.60)
– severe, %	44.4	38.1	0.18	–
– moderate, %	46.5	29.6	< 0.001	2.06 (1.41–3.02)
– mild, %	14.1	13.5	0.86	–
History of CVI, %	23.9	28.0	0.33	–
– History of stroke, %	16.9	22.8	0.13	–
– History of TIA, %	8.5	8.1	0.88	–
Contraindication to OAC, %	21.8	18.1	0.32	–
Poor adherence to OAC, %	3.5	5.6	0.31	–
Patient wish, %	16.2	27.8	0.005	0.50 (0.31–0.82)
Other indication, %	7.0	9.7	0.34	–

artery disease, valvular heart disease, prevalence of diabetes mellitus, chronic kidney failure, and vascular disease compared with the non-anemia cohort.

3.2. History of bleeding

Anemic patients had a higher prevalence of prior bleeding than non-anemic patients (94.4% vs 75.2%). In those with a history of major bleeding (Fig. 1; detailed in supplemental Table 1), anemic patients were more likely to have gastrointestinal bleeding and requiring transfusion but less likely to have had critical bleeding or hemodynamically relevant bleeding. They were also less likely to have intracranial bleeding and surgery for their bleeding. Contraindications to OAC (21.8% vs 18.1%), labile International normalized ratio (INR) or poor adherence to OAC were comparable (Table 1).

3.3. Procedural details

Procedural data is shown in Table 2. Implant success was high in both groups (99.3% vs 97.2%). In anemic patients significantly more procedures were carried out in general anaesthesia (25.4% vs 7.5%, $p < 0.001$). The distribution of LAAC devices was similar in both groups with Watchman (Boston Scientific, Marlborough, MA, USA) (47.9% vs 42.4%), Amplatzer Cardiac Plug (Abbott, Plymouth, MN, USA) (24.6% vs 28.7%), and Amplatzer Amulet (Abbott, Plymouth, MN, USA) (27.5% vs 25.1). Procedural duration was significantly shorter (median 54 min vs 60 min) in anemia patients with similar fluoroscopy duration (median 10 min vs 10 min) and dose area product. Device dislocation was rare in both groups (0.7% vs 1.6%, $p = 0.42$). Incidence of peridevice leaks were significantly higher in anemic patients (12.7% vs 3.0%), however no patient in either group had a peridevice leak > 5 mm.

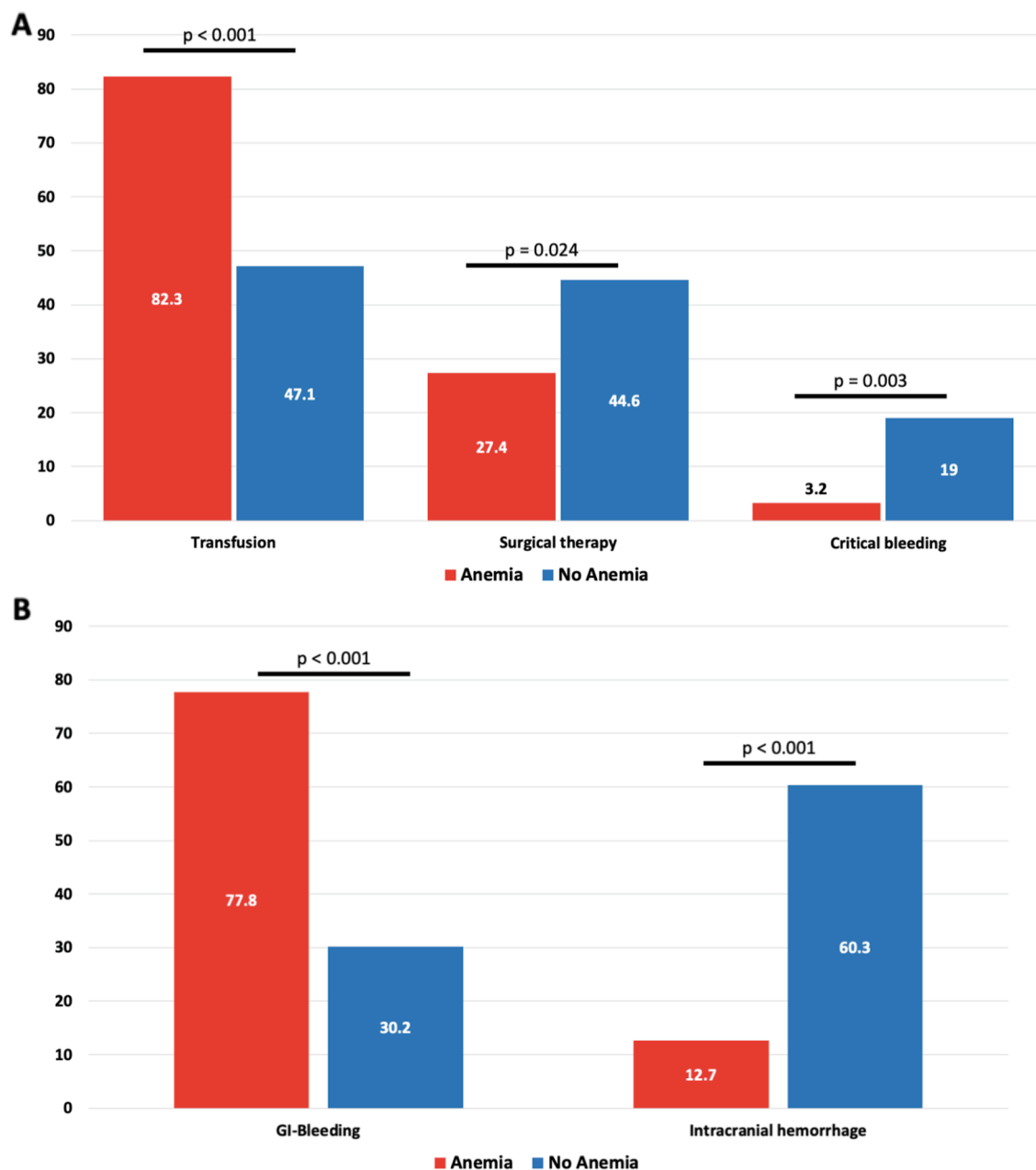


Fig. 1. Patients presenting with major bleeding as indication for interventional closure. GI: gastrointestinal; displayed in the bars are percentages; P-values < 0.05 are considered significant, tested with either Pearson chi-squared test or Mann-Whitney-Wilcoxon test.

Table 2

Procedural data of left atrial appendage closure in anemic patients and non-anemic patients. OR: odds ratio; CI: confidence interval; LAAC: left atrial appendage closure; CVI: cerebrovascular insult; OAC: oral anticoagulation; TIA: transient ischemic attack; INR: international normalized ratio; displayed are percentages and numbers; P-values < 0.05 are considered significant, tested with Fisher's exact test.

	Anemic patients(n = 142)	Non-anemic patients(n = 496)	P-value	OR (95%-CI)
Implant success, %	99.3	97.2	0.14	–
Anesthesia				
Conscious sedation, %	74.6	86.9	< 0.001	0.45 (0.28–0.70)
General anesthesia, %	25.4	7.5	< 0.001	4.20 (2.54–6.97)
LAAC device				
Watchman, %	47.9	42.4	0.25	–
Amplatzer Cardiac Plug, %	24.6	28.7	0.34	–
Amplatzer Amulet, %	27.5	25.1	0.56	–
Other device, %	0.0	3.8	0.018	–
Periprocedural data				
Sheath retractions	1.7 ± 1.4	1.6 ± 1.1	0.48	–
Duration, min	54 (40, 70)	60 (44, 82)	0.007	–
Fluoroscopy duration, min	10 (6, 14)	10 (7, 15)	0.11	–
Dose area product, cGy*cm ²	2024 (1100, 4187)	2055 (680, 4196)	0.25	–
Device dislodgement, %	0.7 (1/142)	1.6 (8/496)	0.42	–
– Catheter-based retrieval	1/1	8/8	–	–
– Surgical retrieval	0/1	0/8	–	–
Peridevice leak, %	12.7 (18/142)	3.0 (14/496)	< 0.001	4.75 (2.30–9.82)
– < 3 mm	13/18	11/14	–	–
– 3–5 mm	5/18	3/14	–	–
– > 5 mm	0/18	0/14	–	–

3.4. In-hospital complications and safety

In **Table 3**, a detailed overview of in-hospital complications is given. The composite outcome (MACCE) of death, myocardial infarction (MI) or stroke was statistically similar between both groups (0% vs 0.6%, $p = 1.0$). Other severe complications were significantly lower in severely anemic patients compared with non-anemic patients. The combined outcome of MACCE and other severe complications was significantly lower in the severely anemic patients (0.7% vs 5.6%, $p = 0.01$, OR 0.12 (95%-CI 0.02–0.88)). There was no difference statistically between both groups in moderate complications. In the combined analysis of severe and moderate complications, incidence was numerically higher in non-anemic patients. No difference was observed in minor complications.

3.5. One-year outcomes

The one-year follow-up is detailed in **Table 4** and corresponding Kaplan-Meier curves given in **Fig. 2**. Follow-up was documented in 97.2 % of anemic vs 97.8 % of non-anemic patients with a median follow-up of 382 days and 377 days, respectively. There was no difference in the rates of stroke, TIA or any bleeding. In the sub-analysis, severe bleeding was significantly higher in the non-anemic patients. Mortality was not significantly different between both groups but associated with an increased hazard ratio (16.0% vs 10.3%, HR 1.61 (95%-CI: 0.97–2.67)). Affirmatively, the composite outcomes of death/stroke (16.0% vs 11.1%, HR 1.49 (95%-CI: 0.90–2.44) and death/stroke/systemic embolism (16.0% vs 11.4%, HR 1.46 (95%-CI: 0.89–2.39) were numerically higher in anemia patients. Precisely, in the one-year follow-up, death or stroke or systemic embolism occurred in 22/142 anemic

Table 3

In-hospital safety data after the procedure. OR: odds ratio; CI: confidence interval; MACCE: Major Adverse Cardiovascular and Cerebrovascular Event; AV: arteriovenous; TIA: transient ischemic attack; CPR: cardiopulmonary resuscitation; displayed are percentages and numbers; P-values < 0.05 are considered significant, tested with Fisher's exact test.

	Anemic patients(n = 142)	Non-anemic patients (n = 496)	P-value	OR (95%-CI)
MACCE (Death, MI, Stroke), %	0.0	0.6	1.00	–
– Death, %	0.0	0.4	1.00	–
– MI, %	0.0	0.2	1.00	–
– Stroke, %	0.0	0.2	1.00	–
Other severe complications, %	0.7	5.0	0.016	0.13 (0.02–0.99)
– Severe bleeding, %	0.0	1.4	0.36	–
– AV-Fistula/Aneurysmal hematoma, %	0.0	1.2	0.35	–
– Pericardial effusion – surgical treatment, %	0.7	0.2	0.40	–
– Pericardial effusion – interventional treatment, %	0.0	2.6	0.083	–
– Hemo-/Pneumothorax – surgical treatment, %	0.0	0.0	–	–
– Device dislodgment – surgical treatment, %	0.0	0.0	–	–
– Device dislodgment – interventional treatment, %	0.0	0.4	1.00	–
MACCE + other severe complication, %	0.7	5.6	0.010	0.12 (0.02–0.88)
Moderate complications, %	7.7	10.3	0.42	0.73 (0.37–1.45)
– TIA, %	0.0	0.0	–	–
– Non-fatal CPR, %	0.0	0.6	1.00	–
– Moderate bleeding, %	0.7	2.2	0.48	–
– Access site infection, %	0.0	0.2	1.00	–
– Groin hematoma, %	2.8	2.8	1.00	–
– Pericardial effusion – conservative treatment, %	2.1	1.6	0.72	–
– Hemo-/Pneumothorax – interventional treatment, %	0.0	0.4	1.00	–
– Hemo-/Pneumothorax – conservative treatment, %	0.0	0.0	–	–
– Device embolisation – at index procedure, %	0.7	1.2	1.00	–
Minor complications, %	2.1	2.8	0.78	0.74 (0.21–2.62)
Overall complications (severe & moderate), %	8.5	13.7	0.11	0.58 (0.31–1.11)

patients, and in 54/496 non-anemic patients with an adjusted hazard ratio of 1.04 (95%-CI 0.62–1.73, $p = 0.89$).

3.6. Antithrombotic therapy

In **Table 5**, an overview of anti-thrombotic therapy before and after the procedure, as well as in the one-year follow-up is shown. Patients with anemia had similar antiplatelet therapies than non-anemic patients but were more often on combination therapy with anticoagulant and antiplatelet (15.5 vs 6.9, $p = 0.001$). After the procedure, proton-pump inhibitor (PPI) therapy was more often given to anemic patients at discharge (65.5% vs 41.7%, $p < 0.001$) and during one-year follow-up (52.4 % vs 38.3 %, $p = 0.009$), while non-steroidal anti-inflammatory drugs (NSAID) were less often given to anemic patients (2.8% vs 8.3%, $p = 0.024$) at discharge.

Table 4

One-year follow-up safety data. HR: hazard ratio; CI: confidence interval; FU: follow up; TIA: transient ischemic attack; MI: myocardial infarction; SE: systemic embolism; displayed are percentages and numbers; P-values < 0.05 are considered significant, tested with either Fisher's exact test or Mann-Whitney-Wilcoxon test.

	Anemic patients(n = 138)	Non-anemic patients(n = 483)	P-value	HR (95%-CI)
FU documented, %	97.2	97.8	0.68	–
Procedure -> FU-Contact [Days]	382 (368, 414)	377 (367, 405)	0.15	–
Device	1.4 (2)	2.6 (13)	0.54	–
dislodgement, %				
– Surgical treatment	1/2	2/13	0.37	–
– Interventional treatment	1/2	9/13	1.00	–
– Conservative treatment	0/2	2/13	1.00	–
Groin complications, %	2.8 (4)	3.4 (17)	1.00	–
– Surgical treatment	0/4	3/17	1.00	–
– Blood transfusion	0/4	0/17	–	–
– Conservative treatment	4/4	14/17	1.00	–
Pericardial effusion, %	3.5 (5)	4.9 (23)	0.65	–
– Surgical treatment	1/5	41/23	0.33	–
– Interventional treatment	0/5	14/23	0.041	–
– Conservative treatment	4/5	8/23	0.13	–
Rehospitalisation, %	45.9	36.1	0.076	–
Stroke, %	00.0	1.2	0.35	–
TIA, %	0.7	0.2	0.40	–
MI, %	0.0	1.2	0.35	–
Bleeding (severe or moderate), %	6.3	7.3	0.85	–
Severe bleeding, %	0.0	2.8	0.048	–
Moderate bleeding, %	6.3	4.5	0.38	–
Composite outcomes[†]				
Death, %	16.0	10.3	0.060	1.61 (0.97–2.67)
Death/Stroke, %	16.0	11.1	0.12	1.49 (0.90–2.44)
Death/Stroke/SE, %	16.0	11.4	0.14	1.46 (0.89–2.39)

[†] Kaplan-Meier estimates at 1 year after the index procedure, comparisons by log-rank test and hazard ratios.

4. Discussion

4.1. Main findings

Severe anemia below the blood transfusion threshold is present in a quarter of patients undergoing LAAC. A history of gastrointestinal bleeding is common. Despite older age and more comorbidity, peri-procedural complications after LAAC are rare and one-year outcomes are rather comparable to non-anemic patients receiving LAAC. The optimal stroke prevention therapy in high-risk anemic patients with AF requires further study in controlled clinical trials such as CLOSURE-AF or NCT04298723.

4.2. Prognostic value of anemia

Anemia has been shown to be an independent predictor of all-cause mortality and cardiovascular death in community-based settings as well as cardiology inpatient cohorts [12,13]. In patients undergoing transcatheter aortic valve implantation (TAVI), pre-procedural anemia has been shown to be associated with increased mid-term mortality and acute kidney injury [14]. In 3378 AF patients in Japan, anemia was

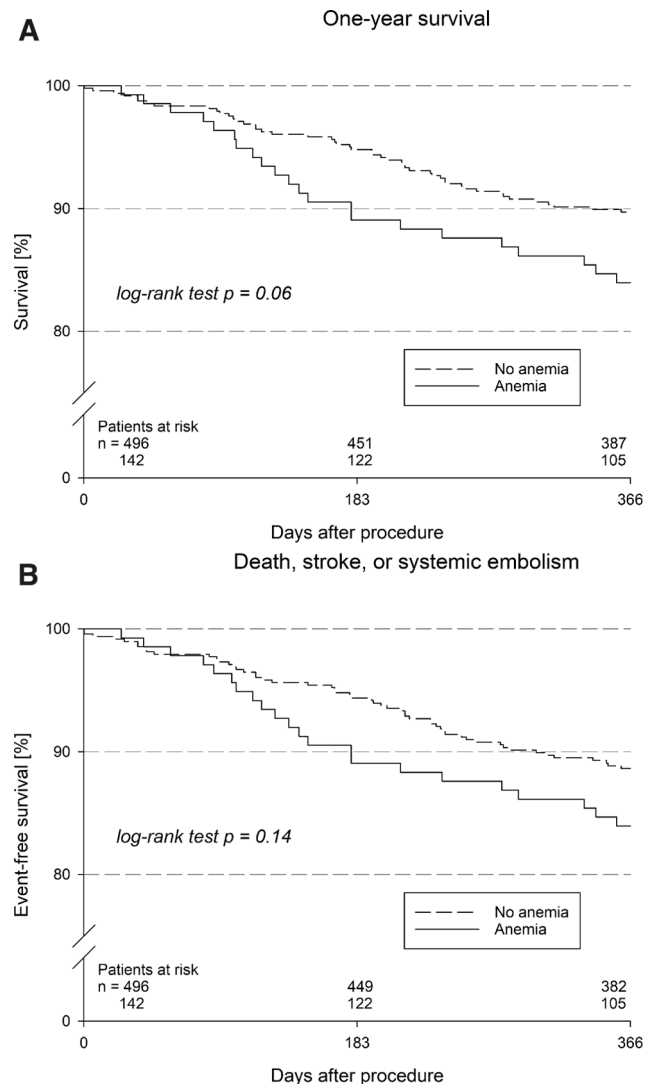


Fig. 2. One-year outcomes of death (A) and MACCE (death, stroke, systemic embolism) (B) in patients with and without severe anemia. P-values < 0.05 are considered significant, tested with either Pearson chi-squared test or Mann-Whitney-Wilcoxon test.

associated with increased cardiovascular events [15]. The most recent ESC guidelines on AF recommend considering LAAC in patients with contraindication to OAC, especially in those with a history of bleeding [2]. This, of course, contrasts with the available data from randomized controlled trials which mandated ability to receive OAC in their inclusion criteria [5]. Therefore, it is critical to assess the real-life influence of bleeding and anemia in this vulnerable population. This study, for the very first time, systematically investigates the influence of severe anemia. However, we did find that severe anemia is associated with higher comorbidity and its impact on mortality is attenuated after adjusting. Comparing the different studies is difficult because of the investigated population (community-based vs. inpatient cohort) and the varying definitions of anemia. For instance, Culleton et al. defined anemia as hemoglobin < 110 g/L while Seiffert et al. used the World Health Organization definition from 1968 (in men < 130 g/L and in women < 120 g/L) [12,14,16]. In this study, we used the threshold for blood transfusion as recommended in guidelines and widely used in blood transfusion studies to identify patients at risk [10,11]. As our population is rather small, effects of preprocedural anemia in LAAC must be evaluated in bigger trials. Until such data is available, we believe that it is reassuring that this high-risk population shows no immediate safety signals

Table 5

Antithrombotic therapy before, at discharge and one year after the procedure. OR: odds ratio; CI: confidence interval; DAPT: dual antiplatelet therapy; SAPT: single antiplatelet therapy; PPI: proton pump inhibitor; NSAID: non-steroidal anti-inflammatory drugs; displayed are percentages and numbers; P-values < 0.05 are considered significant, tested with either Pearson chi-squared test or Mann-Whitney-Wilcoxon test.

	Anemic patients	Non-anemic patients	P-value	OR (95%-CI)
Therapy at admission	n = 142	n = 496		
– Anticoagulation, %	46.5	50.0	0.46	–
– DAPT, %	7.7	7.1	0.78	–
– SAPT, %	17.6	15.3	0.51	–
– Double antithrombotic therapy, %	15.5	6.9	0.001	2.49 (1.41–4.42)
– Triple antithrombotic therapy, %	1.4	3.4	0.21	–
– No antithrombotic therapy, %	11.3	17.3	0.082	–
Therapy at discharge	n = 142	n = 494		
– Anticoagulation, %	0.7	3.4	0.083	–
– DAPT, %	87.3	83.4	0.26	–
– SAPT, %	1.4	3.2	0.25	–
– Double antithrombotic therapy, %	7.0	6.9	0.95	–
– Triple antithrombotic therapy, %	3.5	2.2	0.39	–
– No antithrombotic therapy, %	0.0	0.6	–	–
– PPI, %	65.5	41.7	< 0.001	2.66 (1.80–3.92)
– NSAID, %	2.8	8.3	0.024	0.32 (0.11–0.91)
Therapy at one-year follow-up	n = 105	n = 402		
– Anticoagulation, %	3.8	5.0	0.62	–
– DAPT, %	8.6	6.0	0.34	–
– SAPT, %	78.1	75.4	0.56	–
– Double antithrombotic therapy, %	1.9	1.2	0.61	–
– Triple antithrombotic therapy, %	0.0	0.5	0.47	–
– No antithrombotic therapy, %	7.6	11.9	0.21	–
– PPI, %	52.4	38.3	0.009	1.77 (1.15–2.73)
– NSAID, %	1.9	6.0	0.093	–

for LAAC. Therefore, the procedure should be conducted under the necessary safety measurements even if the patient presents with severe anemia.

4.3. Clinical characteristics and periprocedural events

Implant success was high in both groups (99.3% vs 97.2%) and was not impeded by preprocedural anemia. The LAARGE population represents a high-risk population compared to other observational data sets, and the anemic patients represent a particularly high-risk subgroup as illustrated by high HAS-BLED Score (anemic patients in LAARGE 4.3 ± 1.0 , non-anemic patients 3.8 ± 1.1 , higher than in the US NCDR LAAC registry (mean score 3.0 ± 1.1) and the European EWOLUTION registry (mean score 2.3 ± 1.2) [6,17]. The location of bleeding was also different between anemic and non-anemic patients: Anemic patients with previous major bleeding often had a history of gastrointestinal bleeding or bleeding requiring transfusion, suggesting that chronic blood loss contributed to anemia. Another contributing factor to preprocedural anemia could be combination antithrombotic therapy which is associated with bleeding [18]. Postprocedural antithrombotic regimen in our study was not different between anemic and non-anemic

patients, mainly consisting of DAPT (87.3% vs 83.4%) at a higher rate than in the EWOLUTION (60%) and Amulet Observational Study data sets (57.7%) [19,20]. Prevention of gastrointestinal bleeding using proton pump inhibitors was more commonly used in anemic patients discharged with more PPI (65.5% vs 41.7%) and less NSAID (2.8% vs 8.3%), suggesting increased awareness due to pre-existing anemia. Intracranial bleeding as a major bleeding, in contrast, a condition where a small amount of blood in the brain causes severe clinical consequences, was less common in anemic patients than in their non-anemic patients. Chronic kidney disease was found in 1/2 of the population in LAARGE, more often than in NCDR (13.6%), EWOLUTION (15.8%) or the global Amulet Observational study (14.3%) [17,19,21]. In-hospital complications were lower in anemic patients than in non-anemic patients despite higher comorbidities and age. There is certainly the possibility of a chance finding. However, anemic patients were also more likely to receive general anesthesia during the procedure and have more minor peridevice leak. This may suggest that the operators were more aware of the frailty of anemic patients during the implant procedure. Minor peridevice leak has not been shown to be prognostically relevant and treatment options usually limited [22].

As the indication for general anesthesia was left to the operating center, it is not possible to identify which factor may have led to not utilize conscious sedation as its standart in Germany. The anemic patients present with more comorbidities such as chronic kidney disease or peripheral vascular disease that are detrimental for interventional procedures.

The difference in the in-hospital data are major bleedings and pericardial effusion in the non-anemic patients. Due to the small number of events, we see no statistically significant differences which should therefore be seen with caution. The dual antiplatelet therapy was conducted after the procedure for 6–12 weeks and then followed by single antiplatelet therapy. Since this is standard of care in Germany [23], it is not surprising that we cannot report differences in antithrombotic therapy directly after the procedure.

4.4. One-year complications

Mortality was comparable in our study (anemic patients 16.0%, patients 10.3%) to other data sets: 8.4% in EWOLUTION; 16.8% in a German single-center cohort respectively [16,17]. The mitigation of the observed effects in the composite endpoint after adjusting for comorbidities suggest that mortality is mainly driven by said comorbidities. A recent analysis of the Amulet Observational shows that mortality is correlated with higher CHA₂DS₂-VAsc and HAS-BLED scores. Mortality was shown to be substantially higher if patients had a CHA₂DS₂-VAsc > 3 or even > 6 with 14.4% and 21.2% [18]. Major bleeding at one-year follow were low in LAARGE and not different between anemic and non-anemic patients. Other LAAC closure studies with high risk populations for bleeding report major bleeding rates of 10.7% or 8% respectively [16,17]. There may have been some reporting bias as each center was responsible for documenting in-hospital events.

5. Limitations

Due to the observational study design, associations of anemia with other risk factors do not allow causal interpretation of the results. Exact implantation techniques and peri- and postprocedural management were left to each participating center. The operators experience with implanting devices is not documented. This may also be a strength due to real world conditions. Centers would also report adverse events which may lead to a reporting bias. Additionally, enrollment of consecutive patients was encouraged but not mandated. There is also a need for caution in interpreting and comparing HAS-BLED and bleeding rates. Some studies may be more liberal in the definition for the HAS-BLED. Additionally, anemia itself is part of the HAS-BLED which gives anemic patients a higher HAS-BLED and “more at risk” for bleeding by

definition. Additionally, our study size is certainly underpowered to give definite evidence for mortality and adverse events. Differences such as bleeding must be reported in bigger trials to adequately answer the influence of procedural techniques and concomitant antithrombotic therapy. Also, we cannot be sure on the temporal evolution of anemia in the patients as this may have been only a temporary occurrence and not a chronic one.

Larger analyses are needed and therefore our data must be interpreted with caution.

6. Conclusion

Patients with pre-existing severe anemia before LAAC are more likely to have a history of bleeding and chronic kidney disease. Major bleeding and severe anemia is associated with chronic gastrointestinal bleeding whereas major bleeding and no severe anemia is associated with intracranial haemorrhage. Severe anemia is associated with a higher degree of double antithrombotic therapy which was stopped after the procedure. Preprocedural severe anemia does not seem to impede safety of the procedure. However, one-year mortality is higher in severely anemic patients, mainly driven by co-morbidities.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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