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Left atrial appendage occlusion in patients suffering from advanced chronic kidney disease (stage 4 and 5). Long-term follow-up

Sergio López-Tejero MD, PhD[1,2,3] | Pablo Antúnez-Muiños MD[1,2,3] | Pilar Fraile-Gómez MD, PhD[4] | Gilles Barreira-de Sousa MD[1,2,3] | Javier Rodríguez-Collado MD[1,2,3] | Jesús Herrero-Garibi MD, PhD[1,2,3] | Fabián Blanco-Fernández MD[1,2,3] | Alejandro Diego-Nieto MD, PhD[1,2,3] | Gonzalo C. Delgado-Lapeira MD[4] | M. Candelas Pérez del Villar-Moro MD, PhD[1,2,3] | Javier Martín-Moreiras MD, PhD[1,2,3] | Pedro L. Sánchez-Fernández MD, PhD[1,2,3] | Ignacio Cruz-González MD, PhD[1,2,3]

[1]Department of Cardiology, Complejo asistencial universitario de Salamanca (CAUSA), Salamanca, Spain

[2]Instituto de Investigación Biomédica de Salamanca (IBSAL), Salamanca, Spain

[3]Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBER-CV), Spain

[4]Department of Nephrology, Complejo asistencial universitario de Salamanca (CAUSA), Salamanca, Spain

Correspondence

Sergio López-Tejero, MD, PhD, Department of Cardiology, Complejo asistencial universitario de Salamanca (CAUSA), Paseo de la Transición Española s/n. CP: 37007. Salamanca, Spain.
Email: ser_slt@hotmail.com

Abstract

Introduction and Objectives: Advanced chronic kidney disease (A-CKD) combined with atrial fibrillation increases the risk of both thrombogenic and bleeding events. Left atrial appendage occlusion (LAAO) may be an alternative to oral anticoagulation to prevent thromboembolic events. We aimed to evaluate the outcomes of LAAO in patients with A-CKD.

Methods: Comparison at long-term follow-up of patients diagnosed with and without A-CKD (eGFR<30 mL/min/1.73 m^2) who underwent LAAO between 2009 and May 2022.

Results: Five hundred seventy-three patients were included. Eighty-one (14%) were diagnosed with A-CKD. There were no differences in sex, age, and cardiovascular risk factors, except for diabetes which was more frequent in patients with A-CKD. The control group had higher rates of stroke, both ischemic and hemorrhagic. There were no differences in the CHA_2DS_2-VASc score, although A-CKD patients had a higher bleeding risk according to the HASBLED scale. Global procedural success was 99.1%. At follow-up, there were no differences in stroke rate: at 1-year (HR: 1.22, IC-95%: 0.14–10.42, $p = 0.861$); at 5-years (HR: 0.60, IC-95%: 0.08–4.58, $p = 0.594$). Although bleeding events were higher in the A-CKD group, no differences were found in major bleeding (defined BARC ≥ 3) at 1-year (HR: 1.34, IC-95%: 0.63–2.88,

Abbreviations: A-CKD, advanced chronic kidney disease; AF, atrial fibrillation; BARC, Bleeding Academic Research Consortium; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulation; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; KDIGO, kidney disease improving global outcomes; LAAO, left atrial appendage occlusion; RRT, renal replacement therapy; SAPT, single antiplatelet therapy.

$p = 0.464$) or at 5-years follow-up (HR: 1.30, IC-95%: 0.69–2.48, $p = 0.434$). Mortality rate at 5 years was higher in the A-CKD patients (HR: 1.84, IC-95%: 1.18–2.87, $p = 0.012$).

Conclusions: LAAO is an effective and safe treatment in A-CKD patients to prevent ischemic events and bleeding. This strategy could be an alternative to oral anticoagulation in this high-risk group of patients.

KEYWORDS

atrial fibrillation, chronic kidney failure, high bleeding risk, high thrombogenic risk, left atrial appendage occlusion, stroke risk

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in adults, with an estimated prevalence of 2%–4%.[1] The prevalence is expected to increase 2-fold in the coming years due to increased life expectancy and increased screening for asymptomatic AF.[2] Stroke is the most disabling complication of AF, therefore, its prevention is the key goal of AF management.[3] Oral anticoagulation has become the standard treatment to prevent this potential complication and, most guidelines based the indication on a single clinical risk score (CHA_2DS_2-VASc).[4,5] However, this score has demonstrated modest performance in some conditions.[6]

One of the populations, that are underrepresented in oral anticoagulation trials and, therefore, in common scores, are patients suffering from chronic kidney disease (CKD), especially at an advanced stage. The KDIGO classification is the most accepted international classification CKD, and lower renal function is associated with renal complications, cardiovascular diseases, and death.[7] The global prevalence of CKD is 13.4%[8] and it has a bidirectional relationship with AF such that the presence of CKD increases the risk of incident AF while the presence of AF is associated with the development and progression of CKD.[9] In fact, it has been reported that AF prevalence increases in relation to renal dysfunction,[10] being 57% for those with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, and 32% for those with eGFR between 30 and 59 mL/min/1.73 m^2. In addition, CKD is also characterized by a prothrombotic state, becoming an independent risk factor for stroke.[11] It is interesting to highlight that bleeding risk is increased in this population too, there is a paradoxical rise in bleeding events in patients with CKD who have a high thromboembolic risk.[9] For every 10 mL/min/1.73 m^2 reduction of eGFR there is an associated 9% increase in hemorrhagic risk.[12] Thus, the standard anticoagulation therapy may have a potentially harmful role in this population. These aspects likely contributed to these patients with renal impairment, mainly <30 mL/min/1.73 m^2 of eGFR, being systematically excluded from trials. This type of population was not included in many of the pivotal oral anticoagulation trials such as the RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE-AF-TIMI 48. Direct oral anticoagulation (DOACs) prescriptions for these patients are mainly based on scarce observational experience.[13] In fact, it has been demonstrated that benefits from some therapies cannot be extrapolated from non-CKD to CKD cohorts, such as statins in CKD stage 5.[14] Recently, two trials have not reported positive results comparing apixaban versus warfarin for dialysis patients.[15,16]

Left atrial appendage occlusion (LAAO) has emerged as a nonpharmacological alternative to prevent thromboembolic events in nonvalvular AF patients.[17,18] Around 90% of left atrial thrombi are located in the left atrium appendage,[19,20] this is even higher in CKD patients, due to its influence on the prothrombotic state.[21] LAAO has become an attractive option in those patients who cannot receive oral anticoagulation, with excellent reported results in the global population.[22,23] However, no study or registry has been focused on LAAO in advanced chronic kidney disease (A-CKD) patients defined as <30 mL/min/1.73 m^2, with the exception of those studies designed for end-stage renal disease requiring renal replacement therapy (RRT).[24,25]

The aim of this study was to assess the efficacy and safety of LAAO in A-CKD patients. To the best of our knowledge, this is the largest unicentric cohort reported in this specific population.

2 | METHODS

This retrospective study included consecutive patients who underwent LAAO from December 2009 to May 2022 in a single center. Patients diagnosed with A-CKD (defined as eGFR <30 mL/min/1.73 m^2 or patients undergoing hemodialysis) were identified, and they were compared with those without A-CKD according to the previous definition. Follow-up was retrospectively performed by reviewing clinical records from the hospital database. All clinical data, in-hospital, and follow-up outcomes were prespecified in the online database used by the center, complying with the Law on Data Protection requirements, and were accessible only to participating operators and registry coordinators. This study was done following the Declaration of Helsinki. It was approved by the local ethics committee.

TABLE 1 Clinical characteristics at baseline of overall population and groups.

	Global cohort *n* = 573	Control group *n* = 492 (86%)	A-CKD group *n* = 81 (14%)	*p*
Clinical characteristics				
Sex, female	226 (39.4)	195 (39.6)	31 (38.2)	0.800
Age	78.6 ± 8.2	78.6 ± 7.81	78.2 ± 10.3	0.658
Hypertension	478 (83.4)	405 (83.1)	73 (90.1)	0.257
Dyslipidemia	291 (51.2)	244 (50.1)	47 (58)	0.187
Diabetes mellitus	210 (37)	168 (34.5)	42 (51.9)	0.003*
Smoker	55 (9.7)	47 (9.7)	8 (9.9)	0.958
Alcohol consumption	27 (4.8)	22 (4.5)	5 (6.3)	0.734
Prior stroke	186 (32.8)	171 (35.2)	15 (18.5)	0.003*
Prior hemorrhagic stroke	111 (19.5)	108 (22.2)	3 (3.7)	<0.001*
Prior TIA	38 (6.7)	35 (7.2)	3 (3.7)	0.245
Prior systemic embolization	56 (9.9)	49 (10.1)	7 (8.6)	0.684
Peripheral artery disease	81 (14.3)	65 (13.4)	16 (19.8)	0.129
Prior coronary artery disease	136 (24)	115 (23.7)	21 (25.9)	0.616
Prior PCI	91 (16)	77 (15.8)	14 (17.3)	0.744
Prior CABG	30 (5.3)	26 (5.3)	4 (4.9)	0.881
Prior heart failure	193 (34)	157 (32.2)	36 (44.4)	0.032*
Prior cancer	123 (25.6)	106 (26.2)	21 (25.9)	0.922
Previous bleeding	473 (83.3)	408 (83.8)	65 (80.2)	0.430
Labile INR	60 (10.6)	41 (8.5)	19 (23.8)	<0.001*
CHA_2DS_2-VASc	4.66 ± 1.39	4.66 ± 1.38	4.65 ± 1.48	0.987
HASBLED	3.57 ± 0.95	3.53 ± 0.93	3.83 ± 1.00	0.010*
Cr levels	1.45 ± 1.32	1.05 ± 0.33	3.92 ± 2.14	<0.001*
eGRF - CKDEPI	59.4 ± 26.6	66.4 ± 21.6	16.8 ± 8.22	<0.001*
LVEF (%)	58.4 ± 9.79	58.7 ± 9.65	56.8 ± 10.5	0.110
Type of AF				0.608
Paroxysmal	171 (30.8)	144 (30.3)	27 (33.8)	
Persistent	65 (11.7)	54 (11.4)	11 (13.8)	
Permanent	319 (57.5)	277 (58.3)	42 (52.5)	

Abbreviations: CABG, coronary artery bypass graft; GI, gastro-intestinal; INR, international normalized ratio; LVEF, left ventricle ejection fraction; PCI, percutaneous coronary intervention; TIA, transit ischemic attack.

*Statistically significance.

2.1 | Study endpoints

The primary endpoint was to assess the efficacy of LAAO and to compare stroke rates between both groups at follow-up. Secondary endpoints included the comparison of bleeding rate and mortality rates between both groups and to define predictors of both events. Total bleeding, significant bleeding during hospitalization (defined as bleeding which leads to blood transfusion), and major bleeding during follow-up (defined as BARC ≥ 3) were recorded.

2.2 | Statistical analysis

Categorial variables are presented as frequencies, and comparisons between groups were performed using the chi-square. Continuous

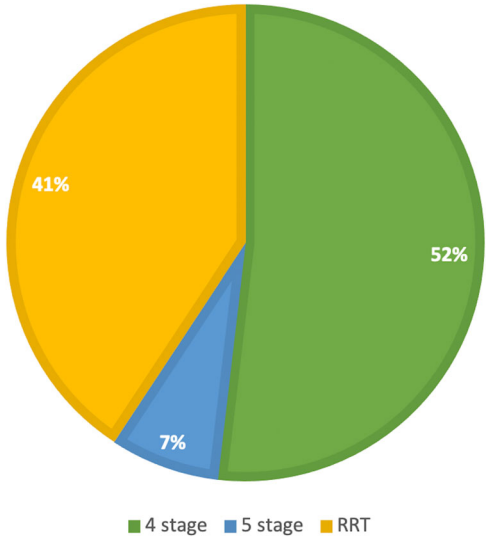

FIGURE 1 A-CKD patients according to the KDIGO stage. [Color figure can be viewed at wileyonlinelibrary.com]

variables are expressed as mean (±standard deviation). Between-group comparisons were performed using the *t*-test or Mann-Whitney U test according to the distribution of the variables. Cox multivariable regression analysis was performed to identify the independent predictors for major bleeding and mortality in the A-CKD cohort. The multivariable model was built by backward stepwise (likelihood ratio) selection. For the univariate analysis, all variables considered potential clinical predictors for events were analyzed. The variables included for the multivariable model were those with $p \leq 0.10$ in the univariate analysis. For major bleeding in the global cohort prior hemorrhagic stroke, prior heart failure, and baseline hemoglobin were included in the model. On the other hand, hypertension, FA type, prior stroke, CHA2DS2Vasc, and HASBLED, were the ones included for mortality multivariate analysis. Respecting the A-CKD cohort, for bleeding, few variates were significant with $p \leq 0.10$: prior heart failure, labile INR, ASA treatment, and, baseline platelets. Similar results were found for mortality, variables included were: hypertension, AF type, prior stroke, CHA2DS2Vasc, and HASBLED. Verification of the proportional hazard assumption was performed. In addition, the incidence of ischemic and bleeding complications was recorded inside the hospital and in the long-term follow-up and was analyzed independently. We analyzed time to 1- and 5-year mortality by Kaplan-Meier event-free survival curves and comparison was performed using the log-rank test. All tests were two-sided at the 0.05 significance level. Categorical analysis and group comparisons were performed using Jamovi. Kaplan-Meier curves for survival analysis and Cox multivariable regression were performed using Stata.

3 | RESULTS

From December 2009 to May 2022, a total of 573 patients who underwent LAAO were included. Eighty-one patients (14%) had A-CKD.

3.1 | Baseline characteristics of the study population

Table 1 includes the main baseline characteristics of the population. There were no differences in sex (female control group 39.6% vs. A-CKD 38.2%, $p = 0.800$), age (78.6 ± 7.81 vs. 78.2 ± 10.3, $p = 0.658$), hypertension (83.1% vs. 90.2%, $p = 0.257$) or dyslipidemia (50.1% vs. 58%, $p = 0.187$) between both groups. There were differences in the history of diabetes mellitus (control group 34.5% vs. A-CKD 51.2%, $p = 0.003$), heart failure (32.2% vs. 44.4%, $p = 0.032$), and labile INR (8.5% vs. 23.8%, $p < 0.001$). There were no differences in the CHA_2DS_2-VASc score (4.66 ± 1.38 vs. 4.65 ± 1.48, $p = 0.987$) although A-CKD patients had a higher bleeding risk according to the HAS-BLED score (3.53 ± 0.93 vs. 3.83 ± 1.00, $p = 0.010$). Despite these facts, previous bleeding was similar between both groups (83.8% vs. 80.2%, $p = 0.430$) but the control group had suffered more prior strokes (32.8% vs. 18.5%, $p = 0.003$) and hemorrhagic strokes (22.2% vs. 3.7%, $p < 0.001$).

A-CKD patients had a mean creatinine level of 3.92 ± 2.14 mg/dL with an eGRF by CKD-EPI of 16.8 ± 8.22 mL/min/1.73 m2. According to the KDIGO classification, half of the patients (42, 51.85%) were at the 4 stage, while 6 (7.41%) were at the 5 stage and, 33 patients (40.74%) were receiving RRT (Figure 1).

3.2 | Procedural characteristics and in-hospital results

The procedural and in-hospital evolution characteristics are summarized in Table 2. The main indication for LAAO in the overall population was prior bleeding (80.6%) followed by stroke/embolism despite OAC (7.6%). The most common device used was Amulet (Abbot Medical) (42.1%) followed by Watchman (33.9%) (Boston-Scientific).

Global procedural success was 99.1%, achieving 100% in the A-CKD group ($p = 0.974$). LAAO intervention was guided by transesophageal echocardiogram (TEE) in 94.9% of the cases, of which 65.1% were micro-TEE, with no differences between both groups. Overall, the rate of acute procedural complications was 1.9% (11 patients), without significant differences between the groups, mainly led by cardiac tamponade (5 patients). There were only one stroke and one device embolization at the beginning of the learning curve. No death during the procedure was recorded.

There were two strokes (0.4%) during in-hospital evolution, none of them in the A-CKD group. Significant bleeding (defined as bleeding that needs bleeding transfusion) was registered in 1.4% of the control group versus 4.9% of A-CKD ($p = 0.105$). During hospitalization four patients died (0.7%): one cardiac shock, one intracranial bleeding and one gastrointestinal bleeding which were the reason leading LAAO, and one severe respiratory disease. There were no differences between groups (0.6% vs. 1.2%, $p = 0.538$).

TABLE 2 Procedural and in-hospital outcomes of the overall population and groups.

	Global cohort *n* = 573	Control group *n* = 492 (86%)	A-CKD group *n* = 81 (14%)	*p*
Indication for LAAO				<0.001*
Prior bleeding	458 (80.6)	398 (81.7)	60 (74.1)	
Stroke/embolism with OAC	43 (7.6)	43 (8.8)	0	
High risk without prior bleeding	38 (6.7)	29 (6.0)	9 (11.1)	
Labile INR	4 (0.7)	1 (0.2)	3 (3.7)	
A-CKD	8 (1.4)	0	8 (9.9)	
Other reasons	17 (3.0)	16 (3.3)	1 (1.4)	
Procedural success	563 (99.1)	482 (99)	81 (100)	0.974
Device				0.018*
ACP	40 (7.0)	39 (7.9)	1 (1.2)	
Amulet	241 (42.1)	215 (43.8)	26 (32.1)	
Watchman	194 (33.9)	155 (31.6)	39 (48.1)	
Lambre	78 (13.6)	65 (13.2)	13 (16.0)	
Others	19 (3.3)	17 (3.4)	2 (2.5)	
Main procedural characteristics				
General anesthesia	224 (39.6)	198 (40.9)	26 (32.1)	0.134
TEE[a]	539 (94.9)	462 (94.9)	77 (95.1)	0.941
Micro-TEE	310 (65.1)	261 (64.9)	49 (66.2)	0.830
ICE	27 (6.6)	23 (6.7)	4 (6.2)	0.865
Contrast volumen used	148 ± 92.1	152 ± 94.9	123 ± 64.8	0.020*
Procedural complications	11 (1.9)	9 (1.8)	2 (2.5)	0.699
Cardiac tamponade	5 (0.87)	4 (0.81)	1 (1.23)	
Stroke	1 (0.17)	1 (0.2)	0	
Device embolization	1 (0.17)	1 (0.2)	0	
Vascular complication	2 (0.35)	1 (0.2)	1 (1.23)	
Death	0	0	0	
In-hospital complications				
In-hospital stroke	2 (0.4)	2 (0.4)	0	0.563
In-hospital TIA	3 (0.5)	3 (0.6)	0	0.479
In-hospital relevant bleeding	11 (1.9)	7 (1.4)	4 (4.9)	0.105
In-hospital death	4 (0.7)	3 (0.6)	1 (1.2)	0.538

Abbreviations: A-CKD, advanced chronic kidney disease; ICE, intracardiac echocardiography; INR, international normalized ratio; LAAO, left atrial appendage occlusion; OAC, oral anticoagulation; TIA, transit ischemic attack; TTEE, transesophagueal echocardiography.

[a]TEE is referred to procedures guided by both standard TEE probe and micro-TEE probe.

*Statistically significance.

3.3 | Follow-up outcomes

The median follow-up was 682 days (IQR 25–75: 382–1206) (Table 3). In the overall population, the incidence of stroke during follow-up was 2.7%. There were no differences in the primary endpoint (stroke rate) during follow-up (2.9% vs. 1.2%, $p = 0.481$), at 1-year follow-up (HR: 1.22, IC-95%: 0.14–10.42, $p = 0.8606$) and 5 years follow-up (HR: 0.60, IC-95%: 0.08–4.58, $p = 0.5940$) (Figure 2). The annual rate estimated for stroke was 0.57 × 100 patients/year in the overall population and 0.25 × 100 patients/year in the A-CKD group.

Most of the patients received single antiplatelet therapy at follow-up (Table 4), differences were only found regarding

TABLE 3 Follow-up outcomes of the overall population and groups.

	Global cohort *n* = 573	Control group n = 492 (86%)	A-CKD group *n* = 81 (14%)	*p*
Median follow up, days [IQR]	682 [382–1206]	746 [403–1308]	426 [316–845]	0.0003*
FU stroke	13 (2.3)	12 (2.5)	1 (1.2)	0.481
FU TIA	3 (0.5)	2 (0.4)	1 (1.2)	0.353
FU systemic embolism	1 (0.2)	0	1 (1.2)	0.015*
FU bleeding	129 (23.1)	106 (22.2)	23 (28.4)	0.219
FU major bleeding	79 (13.9)	68 (13.9)	11 (13.6)	0.932
FU Rehospitalization	303 (54.4)	248 (52.1)	55 (67.9)	0.008*
1-year FU death	83 (14.4)	62 (12.6)	21 (25.9)	0.002*
5-year FU death	189 (32.9)	145 (29.4)	44 (51.3)	<0.001*

Abbreviations: DOAC, direct oral anticoagulation; TIA, transit ischemic attack.
*Statistically significance.

anticoagulation treatment. The total bleeding rate during follow-up was 23.1%. There were no differences at 1-year follow-up (HR: 1.72, IC-95%: 0.99–2.98, $p = 0.0668$), but at 5 years follow-up there was more total bleeding in the A-CKD group (HR: 1.82, IC-95%: 1.17–2.81, $p = 0.0119$) (Figure 3). However, these differences disappeared if only major bleeding (defined according to BARC classification ≥3) was analyzed: 1-year follow-up HR 1.34, IC-95%: 0.63–2.88, $p = 0.464$; 5-year follow-up HR 1.30, IC-95%: 0.69–2.48, $p = 0.434$ (Figure 4). The total bleeding annual rate was 4.49 × 100 patients/year and it was higher in the A-CKD group (5.64), than in the control group (4.29). Nevertheless, major bleeding had an annual rate of 2.75 × 100 patients/year, and it was higher in the control population 2.75 × 100 patients/year than in the A-CKD group: 2.72.

In the A-CKD group, we found a more frequent all-cause mortality, remained with an almost significant mortality rate of 1 year (HR: 1.79, IC-95%: 1.03–3.12, $p = 0.0506$), which is statistically significant at 5 years (HR: 1.84, IC-95%: 1.18–2.87, $p = 0.0121$) (Figure 5). The annual rate for mortality was 10.8% in A-CKD patients versus 6.2% in the control ones. During the follow-up, more than half of the patients had rehospitalization (54.4%). The rate of this event was more often in the A-CKD population at 1 year (HR: 1.87, IC-95%: 1.28–2.72, $p = 0.0021$), achieving the double at 5 years (HR: 2.05, IC-95%: 1.51–2.78, $p < 0.001$).

Finally, we performed a multivariable analysis to identify potential predictors of major bleeding and death (Table 5) in the A-CKD cohort. HAS-BLED was the only independent predictor of mortality. Respecting major bleeding, prior heart failure was the only independent risk factor identified.

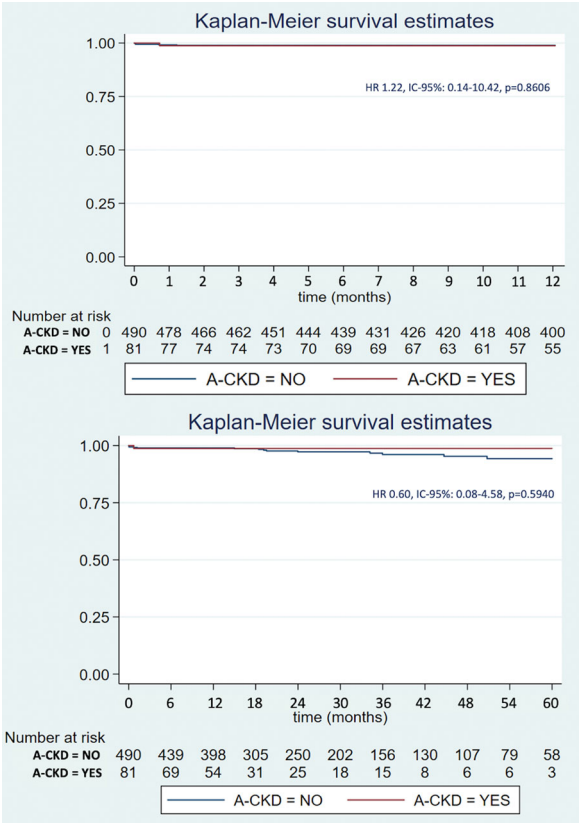

FIGURE 2 Survival curves reflecting 1-year (A) and 5-years (B) survival free of stroke according to the presence of A-CKD. *Blue: control group. Red: A-CKD group*. [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

The primary findings of our study are: (a) LAAO has a high success rate and is a safe procedure both in A-CKD patients and patients with nonsevere renal impairment with no differences between both groups; (b) LAAO is an effective treatment for stroke prevention, even in the high-risk population of A-CKD patients; (c) Bleeding events were lower than expected based on bleeding scores, in this high-risk cohort; (d) Mortality at long-term follow-up were higher in A-CKD patients.

TABLE 4 Treatment reassessment.

Discharge	Control	A-CKD	*p* value
No treatment	5 (1%)	2 (2.5%)	0.275
SAPT	150 (30,5%)	23 (27.8%)	0.652
DAPT	217 (44,5%)	46 (57.5%)	0.040*
DOAC + SAPT	9 (1,5%)	0	0.218
DOAC	71 (14%)	1 (1.25%)	0.001*
Warfarin	5 (1%)	2 (2.5%)	0.275
LMWH	39 (8%)	7 (8.8%)	0.838
6 m	**Control**	**A-CKD**	***p* value**
No treatment	46 (9.7%)	13 (16.3%)	0.079
SAPT	297 (62.5%)	44 (55%)	0.201
DAPT	55 (11.5%)	17 (21.3%)	0.017*
DOAC + SAPT	34 (7%)	2 (2.5%)	0.118
DOAC	39 (8%)	1 (1.25%)	0.026*
Warfarin	5 (1%)	2 (2.5%)	0.283
LMWH	3 (0.5%)	1 (1.25%)	0.552

Abbreviations: DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulants; LMWH, low molecular weight heparin; SAPT, single antiplatelet therapy.

*Statistically significance.

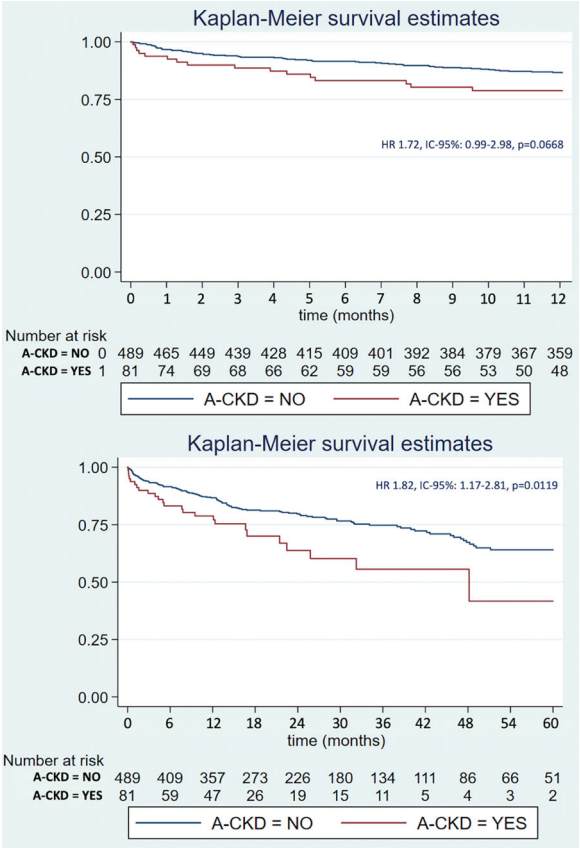

FIGURE 3 Survival curves reflecting 1-year (A) and 5-years (B) survival free of global bleeding according to the presence of A-CKD. *Blue: control group. Red: A-CKD group*. [Color figure can be viewed at wileyonlinelibrary.com]

The main objective of our study was to analyze LAAO in A-CKD patients, these patients have been systematically excluded from the pivotal trials for DOACS. Therefore, robust data on the benefits and risks in patients with A-CKD are lacking.[13] It is known that the proportion of time in the INR target range is lower in this A-CKD cohort,[26] and it increases the risk of stroke, bleeding, and death.[27] Another important aspect of anticoagulation in this population is anticoagulant-related nephropathy, which is thought to be secondary to glomerular hemorrhage and renal tubular obstruction as a consequence of excessive anticoagulation,[28] which may be lower with DOACs. For these reasons, there is a disagreement between guidelines concerning anticoagulation prescription in stage-4 or greater CKD. AHA/ACC/HRS guidelines suggest DOACs in stage 4 CKD and provide a soft recommendation for stage 5, whereas KDIGO suggests they may be considered in stage 4 and concludes there is not enough evidence for stage 5 CKD.[5,29]

LAAO results in patients with renal impairment have previously been reported, for example, Faroux et al. in patients with eGRF <45 mL/min/1.73 m^2[30] or Ahuja et al. in patients under RRT.[31] However, LAAO results in the A-CKD cohort, following our definition, are limited. Even national registries of LAAO, such as the German LAARGE registry, only included 60 patients with A-CKD.[22] The first experiences concerning LAAO reported a procedural success of 91% in the PROTECT-AF,[17] increasing to 95.1% in the PREVAIL Trial.[18] Most recent studies, such as the PRAGUE-17 have shown a 96.8% success rate[32] or 98.3% in the NCDR registry.[33] Our procedural success is even higher (99.1%), with 100% procedural success in A-CKD patients. Furthermore, the procedural complication rate was 1.9% which is similar to the rate of major complications reported in the EWOLUTION trial,[34] although vascular complications were not included. Pericardial effusion requiring intervention in the A-CKD group was 1.2% which is similar to the one reported in the NCDR registry (1.39%).[33] Therefore, even in these high-risk patients, the procedural success and complication rates are similar or better than the reported rates in non-A-CKD patients.

The primary endpoint was the cornerstone of our findings, we reported in the global population a lower stroke rate at follow-up compared with other studies. Our annual stroke rate was lower (0.57%) than the rate reported in Prague-17 at 4 years (2.1%)[35] or in the EWOLUTION (1.1%) registry.[34] In addition, in the A-CKD group, the stroke rate was only 0.25% despite its potentially higher risk for thrombus generation.[11] Ahuja et al. study showed a higher rate of 1.7% (including TIA) during a short follow-up (90 days),[31] and so do other cohorts with a prothrombotic state, such as amyloidosis[36] or in the experience from an older Spanish population.[37] It is interesting that the annual rate was lower than expected according to CHA_2DS_2-VASc (for a 4.5 score on the scale it should be around 6%),[38] which implies a relative reduction risk of 90.5% for the global population and 95.5% for A-CKD patients (Figure 6).

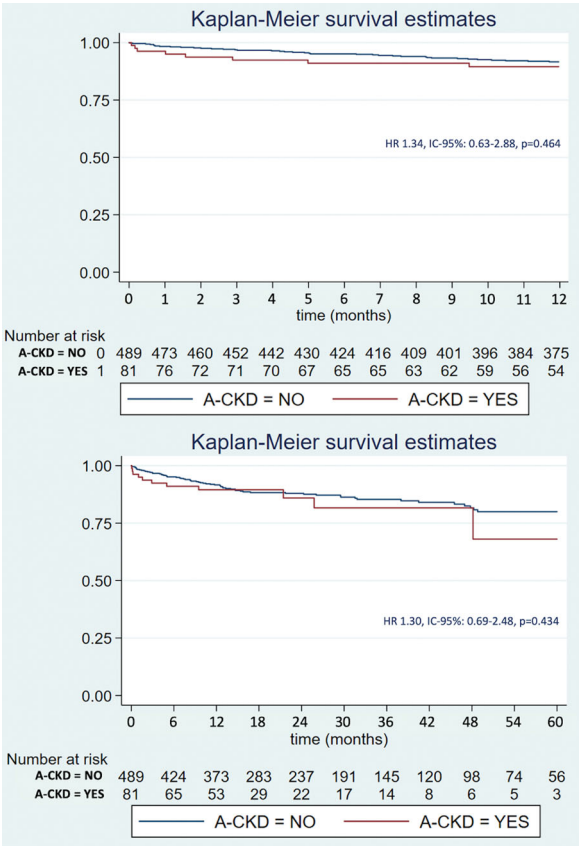

FIGURE 4 Survival curves reflecting 1-year (A) and 5-years (B) survival free of major bleeding according to the presence of A-CKD. *Blue: control group. Red: A-CKD group*. [Color figure can be viewed at wileyonlinelibrary.com]

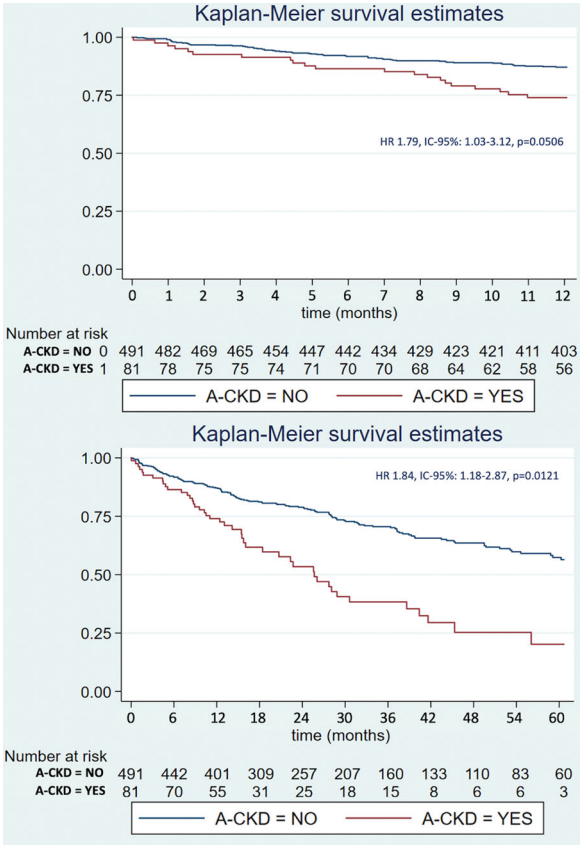

FIGURE 5 Survival curves reflecting 1-year (A) and 5-years (B) according to the presence of A-CKD. *Blue: control group. Red: A-CKD group*. [Color figure can be viewed at wileyonlinelibrary.com]

Regarding bleeding, there were no differences in major bleeding (BARC ≥ 3) between the two groups at follow-up. The annual rate was 2.75%, similar to the EWOLUTION global cohort (2.3%)[34] and Prague-17 (3,4%).[35] Nevertheless, it is lower than the one reported in the AMULET IDE trial (>11.5% independently of the devices used)[39] and the study from Tarantini et al. (4.8–7.8%),[40] although these last studies had a higher risk for bleeding assessed by HASBLED. Moreover, in the A-CKD group, the major bleeding rate was 2.72% without differences compared to the global group, this bleeding rate is similar to the ones reported by Kefer et al. (2.1%)[23] and it is inferior to the 9.8% reported by Faroux et al.[30] The annual major bleeding rate was inferior to the one estimated based on HASBLED score (estimation >6.3% and 7%, 3.57 for overall population and 3.83 for A-CKD).[41] Therefore, the relative risk reduction was 56% for the whole cohort, having more benefits in the A-CKD cohort: a relative risk reduction of 61% (Figure 7). It is interesting that HASBLED was not an independent predictor of major bleeding for A-CKD patients in our cohort. Only prior heart failure acted as a predicted factor of major bleeding. The 6-months follow-up treatment revealed that more than two-thirds of patients underwent SAPT or no treatment, with no ischemic implications, so this factor may influence the bleeding results.

It is remarkable the outcomes exposed: low stroke rate, low percentage of procedure complications and bleeding rate are similar to the reported literature. We highlight that these results along with the lack of evidence for OAC in A-CDK patients, and the weak support of guidelines recommendations described above, could justify this technique taking on a central role in the management of AF in such a comorbid cohort such as A-CKD.

Finally, A-CKD patients had double the mortality compared to the non-A-CKD group at long follow-up. Faroux et al. reported similar differences in mortality between these populations (HR: 2.84).[30] Benini-Tapia et al. also identified an important difference in survival between groups.[42] A meta-analysis conducted by Zhang, found almost the same ratio (HR: 2.0) as our results.[43] It is remarkable that HASBLED was identified as an independent predictor of death in the A-CKD cohort. These findings should be taken into account when LAAO is considered in these patients.

5 | LIMITATIONS

This is an observational and retrospective registry with the inherent limitations of this study type. The conduct of the intervention was not influenced by the study protocol and was based on the operators'

TABLE 5 Multivariable analysis for the A-CKD population. Mortality.

Major bleeding			
Univariate analysis	***p* value**	***p* value for multivariable analysis**	**IC 95%**
Age	0.4001		
Gender	0.8883		
Diabetes	0.3970		
Dyslipidemia	0.8020		
Alcohol	0.5304		
AF type	0.7365		
Prior stroke	0.4410		
Prior hemorrhagic stroke	0.0293*	0.132	
Prior heart failure	0.0410*	0.044*	2.29 (0.57–4.53)
Prior vascular disease	0.3022		
Prior coronary disease	0.9341		
Prior myocardial infarct	0.8381		
Prior LV disfunction	0.9244		
LVEF	0.6781		
A-CKD according KDIGO	0.5433		
Prior cancer	0.9729		
CHA_2DS_2-VASc	0.2087		
HASBLED	0.7626		
Baseline Hemoglobin	0.0874*	0.135	
Baseline platelets	0.4784		
Prior bleeding	0.3022		
Prior relevant bleeding	0.5150		
Prior intracranial bleeding	0.1948		
Prior GI bleeding	0.4475		
Labile INR	0.3093		
Prior ASA treatment	0.4084		
Prior ADP inhibitor treatment	0.8234		
Prior warfarin treatment	0.3067		
Prior other anticoagulation	0.9510		
ASA treatment at discharge	0.3976		
ADP treatment at discharge	0.3434		
DAPT treatment at discharge	0.8910		
Heparin treatment at discharge	0.9568		
Global mortality			
Age	0.2691		
Gender	0.5939		
Hypertension	0.0759*	0.272	
Diabetes	0.7160		
Dyslipidemia	0.8103		
Smoking	0.2044		
Alcohol	0.8590		
AF type	0.0496*	0.098	
Prior stroke	0.0948*	0.478	
Prior TIA	0.4559		
Prior systemic embolization	0.3326		
Prior heart failure	0.2715		
Prior vascular disease	0.8626		
Prior coronary disease	0.7161		
Prior myocardial infarct	0.2323		
Prior LV disfunction	0.2044		
LVEF	0.1735		
A-CKD stage according KDIGO	0.4678		
Prior cancer	0.9729		
Prior liver disease	0.7713		
CHA_2DS_2-VASc	0.0191*	0.513	
HASBLED	<0.0001*	0.003*	1.09 (0.38–1.80)

(Continues)

TABLE 5 (Continued)

Major bleeding			
Univariate analysis	***p* value**	***p* value for multivariable analysis**	**IC 95%**
Baseline Hemoglobin	0.3388		
Baseline platelets	0.1330		
Prior bleeding	0.1314		
Prior relevant bleeding	0.4744		
Prior intracranial bleeding	0.1194		
Prior GI bleeding	0.7742		
Labile INR	0.2439		
Prior ASA treatment	0.3445		
Prior ADP inhibitor treatment	0.1194		
Prior DAPT treatment	0.5840		
Prior warfarin treatment	0.7452		
Prior other anticoagulation	0.5105		
ASA treatment at discharge	0.7789		
ADP treatment at discharge	0.1426		
DAPT treatment at discharge	0.2941		
DOAC treatment at discharge	0.9143		

Abbreviations: A-CKD, advanced chronic kidney disease; ADP, adenosine diphosphate receptor inhibitor; ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; INR, international normalized ratio; LVEF, left ventricular ejection fraction; TIA, transit ischemic attack.

*Statistically significance.

discretion as well as the relevant recommendations, which respected the observational character of the registry. In Spain, Health Care is mainly driven by the Public System, therefore, patients are usually attending public hospitals, where all visits are recorded; so, we could review hospital and family doctor consultations. Despite this accurate correlation between patients' care assistance and the research performed, there were some losses at follow-up, which may influence the results. Although this study included the largest cohort of patients with A-CKD for one single center, this cohort is relatively small compared with the no-CKD and therefore may limit the interpretation of findings.

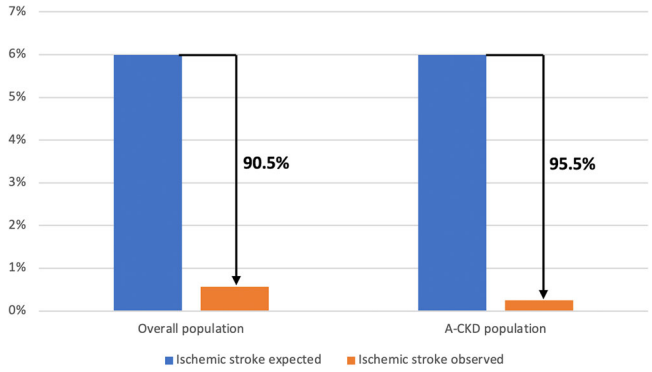

FIGURE 6 Ischemic stroke rate estimated from CHA_2DS_2-VASc score and ischemic stroke rate observed in our study. Relative risk reduction. [Color figure can be viewed at wileyonlinelibrary.com]

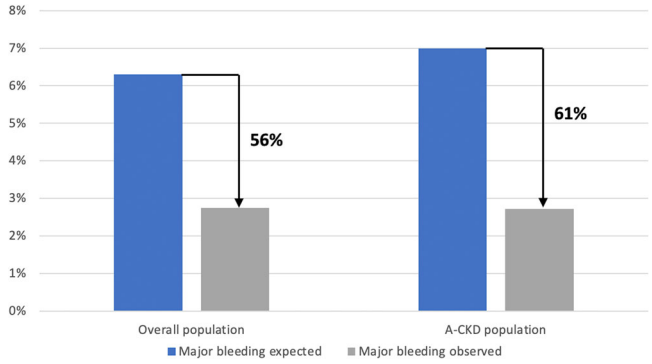

FIGURE 7 Major bleeding rate expected from HASBLED score and major bleeding rate observed in our study. Relative risk reduction. [Color figure can be viewed at wileyonlinelibrary.com]

6 | CONCLUSION

LAAO is an effective and safe procedure for patients with A-CKD and nonvalvular AF to prevent ischemic events and bleeding. Pivotal trials involving DOACs largely excluded the A-CKD population, LAAO may be an alternative to OAC to prevent thromboembolic events in this ischemic and bleeding high-risk populations.

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CONFLICT OF INTEREST STATEMENT

Dr. Cruz-González is proctor for Boston Scientific, Omega, Abbott and LifeTech.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Sergio López-Tejero http://orcid.org/0000-0002-6462-4061
Pablo Antúnez-Muiños http://orcid.org/0000-0003-0573-4321
Jesús Herrero-Garibi http://orcid.org/0000-0002-1547-460X

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