Effect of Glomerular Filtration Rates on Outcomes Following Percutaneous Left Atrial Appendage Closure

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Scarce data support the prescription of oral anticoagulation in patients with concomitant advanced chronic kidney disease (CKD) and atrial fibrillation, and left atrial appendage closure (LAAC) may provide a favorable risk-benefit ratio in this population. However, outcomes of LAAC in CKD patients are unknown. We aimed to investigate the impact of moderate-to-severe CKD on clinical outcomes following percutaneous LAAC. This was a multicenter study including 1094 patients who underwent LAAC. Moderate-to-severe CKD was defined as an eGFR<45 mL/min. Death, ischemic stroke, severe bleeding (≥BARC 3a) and serious adverse event (SAE; composite of death, stroke or severe bleeding) were recorded. A total of 300 patients (27.4%) had moderate-to-severe CKD. There were no differences between groups in periprocedural complications or device related thrombosis. At a median follow-up of 2 (1 to 3) years, patients with moderate-to-severe CKD did not present an increased risk of ischemic stroke (hazard ratio [HR]: 0.65; 95% confidence interval [CI]: 0.22 to 1.92; p = 0.435) but were at a higher risk of death (HR: 2.84; 95% CI: 2.22 to 3.64; p <0.001), severe bleeding (HR: 1.96; 95% CI: 1.36 to 2.81; p <0.001) and SAE (HR: 2.23; 95% CI: 1.80 to 2.77; p <0.001). By multivariable analysis, an eGFR<45 ml/min (HR: 1.92; 95% CI: 1.34 to 2.76; p <0.001) and previous bleeding (HR: 2.30; 95% CI: 1.27 to 4.17; p = 0.006) were associated with an increased risk of severe bleeding. In conclusion, patients with moderate-to-severe CKD who underwent LAAC had very high thrombotic and bleeding risks. Although the rates of device related thrombosis or ischemic stroke after-LAAC were not influenced by kidney dysfunction, patients with moderate-to-severe CKD remained at higher risk of severe bleeding events. **(Am J Cardiol 2021;145:77−84)**

Percutaneous left atrial appendage closure (LAAC) has emerged as an alternative treatment in patients with atrial fibrillation (AF) and contraindications for long-term OAC.[1,2] Chronic kidney disease (CKD) in AF patients has been associated with increased thrombotic and bleeding risks.[3,4] Current European guidelines do not provide specific recommendations regarding anticoagulation in patients with AF and eGFR<30 ml/min,[2] and the 2019 update of the American guidelines provided soft recommendation regarding the use of either warfarin or apixaban in patients with AF and end-stage CKD (with or without dialysis).[1] However, some authors have reported an increased risk of stroke associated with OAC in this population.[5,6] Although the optimal antithrombotic regimen following LAAC remains uncertain, a decrease in antithrombotic medications is generally achieved within the months following the procedure.[7] LAAC may therefore provide a favorable benefit-risk ratio (as compared with long-term OAC) in CKD patients with AF. However, to date no specific data is available regarding this high-risk subpopulation. Thus, the present study sought to investigate the impact of moderate-to-severe CKD on clinical outcomes (bleeding, ischemic events, death) following percutaneous LAAC.

Methods

This was a multicenter study including 1094 patients who underwent percutaneous LAAC in 8 centers. LAAC was performed as previously reported,[8] and the approach and device used were left at the discretion of the operators. Patients with failure to implant a device in the left atrial appendage were not included in the present analysis. Most

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procedures were performed under general anesthesia and trans-esophageal echocardiography (TEE) guidance. After-LAAC management consisted of short term (1 to 3 months) dual antiplatelet therapy or OAC. However, some patients at very high bleeding risk were treated with either single antiplatelet therapy or no antithrombotic medication, and the final decision was based on the clinical judgement of the physician responsible for the patient. TEE imaging during follow-up (within 3 months after-procedure) was left at physician discretion.

Baseline characteristics, CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack [TIA], vascular disease, age 65 to 74 years, female) and HAS-BLED (Hypertension, Abnormal renal and/or liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly [>65 years], Drugs and/or alcohol concomitantly) scores, antithrombotic medications, procedural details and outcomes, and follow-up results were collected. The eGFR was calculated on the basis of the CKD Epidemiology Collaboration equation[9]. Moderate-to-severe CKD was defined as an eGFR<45 ml/min/1.73m^2.[9] Thrombotic events were considered as either clinical ischemic stroke, TIA or peripheral embolism. Bleeding events were classified according to the Bleeding Academic Research Consortium (BARC) definition.[10] Serious adverse event (SAE) was defined as a combination of all-cause death, stroke or severe bleeding (≥ BARC 3a). Device-related thrombosis (DRT) was defined as a well-circumscribed echoreflective mass by trans-esophageal echocardiographic imaging on the left atrial side of the device.

Qualitative variables were expressed as number (percentage) and continuous variables as mean±SD. Categorical variables were compared using the chi-square or Fisher exact test as appropriate. Numerical variables were compared using the Student t test or Mann-Whitney U nonparametric test according to their distribution (assessed by the Kolmogorov-Smirnov test). Event rates for the study outcomes were calculated according to the eGFR. Survival curves for time-to-event variables were performed with the use of Kaplan-Meier estimates and compared using log-rank tests. The factors associated with severe bleeding occurrence were determined using a univariable Cox regression model. The proportional hazards assumption was tested by plotting log-minus-log survival. Variables with p ≤0.10 by univariable analysis were entered into a multivariable Cox regression with stepwise selection (backward elimination). A p <0.05 was considered significant for all statistical tests. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina) and Prism version 8.1.2 (GraphPad Software, San Diego, Californa).

Results

The main baseline characteristics of the study population are shown in Table 1. The mean patient's age was 75.9± 8.4 years, with 38.8% of women. Mean CHA_2DS_2-VASc and HAS-BLED scores were 4.5±1.5 and 3.6±1.1, respectively. A total of 324 patients (29.6%) had a prior ischemic stroke. Most patients (80.9%) experienced a previous bleeding, of whom 380 (34.7%) had multiple bleeding episodes. A total of 300 patients (27.4%) had an eGFR<45ml/min, including 47 patients with hemodialysis. Patients with moderate-to-severe CKD were older (77.8±8.2 vs. 75.1± 8.4 years, p <0.001) and had higher CHA_2DS_2-VASc (4.9±1.5 vs. 4.4±1.5, p <0.001) and HAS-BLED (4.0± 1.1 vs. 3.5±1.0, p <0.001) scores. The rate of patients with previous bleeding did not significantly differ according to the presence of moderate-to-severe CKD (p = 0.690), but patients with moderate-to-severe CKD had more frequently multiple episodes of prior bleeding (40.0% vs 32.8%, p = 0.025). A higher rate of previous gastro-intestinal bleeding (51.0% vs 37.0%, p <0.001) and a lower rate of previous intracranial bleeding (18.0% vs 33.5%, p <0.001) were observed in patients with moderate-to-severe CKD.

Most LAAC procedures were performed under general anesthesia (79.9%) and with TEE guidance (88.7%). Procedural characteristics and outcomes of LAAC procedures are presented in Table 2. About half of implanted devices were Amplazter Amulet (Abbott, Chicago, Illinois) (54.2%). Overall, rates of periprocedural death, cardiac tamponade, stroke and device embolization were all < 1%. A total of 45 patients (4.1%) and 36 patients (3.3%) presented a vascular complication and a severe bleeding (≥BARC 3a), respectively. Rates of periprocedural death (p = 0.355), cardiac tamponade (p = 1.000), stroke (p = 1.000), vascular complication (p = 0.822) and severe bleeding (p = 0.235) did not differ according to the presence of moderate-to-severe CKD. A total of 6 periprocedural deaths occurred, related to cardiac tamponade in 2 cases and to ischemic stroke, intracranial bleeding, mesenteric ischemia and unexplained sudden death in the 4 remaining cases. At discharge, 477 patients (43.9%) were on dual antiplatelet therapy and 290 (26.6%) received OAC, without differences according to baseline moderate-to-severe CKD (p = 0.764).

The median follow-up was 2 (IQR= 1 to 3) years after-LAAC. A total of 746 patients (68.2%) underwent a TEE at a median of 72 (IQR: 48 to 156) days following LAAC. DRT was identified in 35 (4.7%) patients, with no differences between groups (moderate-to-severe CKD: 4.0%, no moderate-to-severe CKD: 4.9%, p = 0.608). Rates of late events according to the presence of moderate-to-severe CKD and estimates from Cox regression analyses are presented in Table 3. Patients with moderate-to-severe CKD presented a higher risk of death (hazard ratio [HR]: 2.84; 95% confidence interval [CI]: 2.22 to 3.64; p <0.001), all bleeding (HR: 1.60; 95% CI: 1.20 to 2.12; p = 0.001), severe bleeding (HR: 1.96; 95% CI: 1.36 to 2.81; p <0.001) and SAE (HR: 2.23; 95% CI: 1.80 to 2.77; p <0.001) (Figure 1). Conversely, the risk of ischemic stroke (p = 0.435) (Figure 1), TIA (p = 0.617), peripheral embolism (p = 0.491) or hemorrhagic stroke (p = 0.435) did not differ between groups. Most (83.7%) severe bleeding events observed in the subpopulation of patients with moderate-to-severe CKD were BARC 3a type (Figure 2). There were no differences between groups in antithrombotic medication at the time of the severe bleeding or ischemic stroke event (Table 4). Severe bleeding occurred more frequently in patients receiving a Watchman device than those receiving an Amplatzer device (15.7% vs 10.4%, p = 0.025), but no significant difference regarding the risk of stroke was

Table 1
Baseline characteristics according to the estimated glomerular filtration rate

Variable	All patients (N=1094)	Glomerular Filtration Rate (ml/min)		p-value
		<45 (N=300)	≥45 (N=794)	
Age (years)	75.9±8.4	77.8±8.2	75.1±8.4	<0.001
BMI (kg/m^2)	27.5±4.8	26.7±4.3	27.8±5.0	0.002
Women	424 (38.8%)	116 (38.7%)	308 (38.8%)	0.970
Atrial fibrillation type				0.397
Paroxysmal	380 (34.7%)	103 (34.3%)	277 (34.9%)	
Persistent	84 (7.7%)	18 (6.0%)	66 (8.3%)	
Permanent	630 (57.6%)	179 (59.7%)	451 (56.8%)	
Hypertension	952 (87.0%)	283 (94.3%)	669 (84.3%)	<0.001
Diabetes mellitus	379 (34.6%)	134 (44.7%)	245 (30.9%)	<0.001
LVEF (%)	56.2±10.2	54.8±11.7	56.7±9.6	0.023
Congestive heart failure	296 (27.1%)	118 (39.3%)	178 (22.4%)	<0.001
eGFR (ml/min)	62.8±28.8	30.6±11.5	75.0±23.5	<0.001
Dialysis	47 (4.3%)	47 (15.7%)	0	<0.001
Previous CAD	362 (33.1%)	124 (41.3%)	238 (30.0%)	<0.001
Previous PAD	234 (21.4%)	83 (27.5%)	151 (19.0%)	0.002
Previous TIA	74 (6.8%)	20 (6.7%)	54 (6.8%)	0.937
Previous ischemic stroke	324 (29.6%)	75 (25.0%)	249 (31.4%)	0.040
Previous bleeding	885 (80.9%)	245 (81.7%)	640 (80.6%)	0.690
Gastro-intestinal	447 (40.9%)	153 (51.0%)	294 (37.0%)	<0.001
Intracranial	320 (29.3%)	54 (18.0%)	266 (33.5%)	<0.001
≥2 previous	380 (34.7%)	120 (40.0%)	260 (32.7%)	0.025
Liver disease	83 (7.6%)	21 (7.0%)	62 (7.8%)	0.652
Labile INRs	107 (9.8%)	31 (10.3%)	76 (9.6%)	0.705
Alcohol abuse	55 (5.0%)	18 (6.0%)	37 (4.7%)	0.366
CHA_2DS_2-VASc score (categorical)				<0.001
1	28 (2.6%)	3 (1.0%)	25 (3.2%)	
2	74 (6.8%)	7 (2.3%)	67 (8.4%)	
3	179 (16.4%)	39 (13.0%)	140 (17.6%)	
4	255 (23.3%)	71 (23.7%)	184 (23.2%)	
5	267 (24.4%)	86 (28.8%)	181 (22.7%)	
6	181 (16.5%)	44 (14.6%)	137 (17.3%)	
7	88 (8.0%)	36 (12.0%)	52 (6.6%)	
8	21 (1.9%)	13 (4.3%)	8 (1.0%)	
9	1 (0.1%)	1 (0.3%)	0	
CHA_2DS_2-VASc score (continuous)	4.5±1.5	4.9±1.5	4.4±1.5	<0.001
HAS-BLED score (categorical)				<0.001
0	1 (0.1%)	0	1 (0.1%)	
1	28 (2.6%)	2 (0.7%)	26 (3.3%)	
2	122 (11.2%)	25 (8.3%)	97 (12.2%)	
3	350 (32.0%)	76 (25.3%)	274 (34.5%)	
4	380 (34.6%)	104 (34.6%)	276 (34.8%)	
5	176 (16.1%)	71 (23.7%)	105 (13.2%)	
6	34 (3.1%)	20 (6.7%)	14 (1.8%)	
7	3 (0.3%)	2 (0.7%)	1 (0.1%)	
HAS-BLED score (continuous)	3.6±1.1	4.0±1.1	3.5±1.0	<0.001
Antithrombotic medication				0.152
None	215 (19.7%)	48 (16.0%)	167 (21.0%)	
SAPT	214 (19.5%)	62 (20.7%)	152 (19.1%)	
DAPT	45 (4.1%)	17 (5.7%)	28 (3.5%)	
OAC	504 (46.1%)	136 (45.3%)	368 (46.4%)	
OAC+AP	116 (10.6%)	37 (12.3%)	79 (10.0%)	

Abbrevations: AP= antiplatelet; BMI= body mass index; CAD= coronary artery disease; DAPT= dual antiplatelet therapy; eGFR= estimated glomerular filtration rate; LVEF= left ventricle ejection fraction; INR= international normalized ratio; OAC= oral anticoagulant; PAD= peripheral artery disease; SAPT= single antiplatelet therapy; TIA= transient ischemic attack.

observed (2.8% vs 2.2%, p = 0.587). About half of severe bleeding episodes occurred within 3 months following LAAC procedure (46% of them of gastrointestinal origin), without differences according to the presence of baseline moderate-to-severe CKD (p = 0.279) (Figure 3). By multivariable analysis, moderate-to-severe CKD (adjusted HR: 1.92; 95% CI: 1.34 to 2.76; p <0.001) and a previous bleeding (adjusted HR: 2.30; 95% CI: 1.27 to 4.17; p = 0.006)

Table 2
Procedural characteristics and complications according to the estimated glomerular filtration rate

Variable	All patients (N=1094)	Glomerular Filtration Rate (ml/min)		p-value
		<45 (N=300)	≥45 (N=794)	
General anesthesia	874 (79.9%)	222 (74.0%)	652 (82.1%)	0.003
Trans-esophageal echocardiography	970 (88.7%)	257 (85.7%)	713 (89.8%)	0.055
Contrast volume (mL)	123.9±85.5	107.6±76.3	129.8±88.0	<0.001
Fluoroscopy time (min)	17.7±11.2	18.8±14.3	17.3±9.6	0.195
Device implanted				0.792
Amplatzer Cardiac Plug	176 (16.1%)	43 (14.3%)	133 (16.8%)	
Amplatzer Amulet	593 (54.2%)	168 (56.0%)	425 (53.5%)	
Watchman	249 (22.8%)	68 (22.7%)	181 (22.8%)	
Other*	76 (6.9%)	21 (7.0%)	55 (6.9%)	
Procedural complications				
Death	6 (0.5%)	3 (1.0%)	3 (0.4%)	0.355
Pericardial effusion with cardiac tamponnade	9 (0.8%)	2 (0.7%)	7 (0.9%)	1.000
Stroke	4 (0.4%)	1 (0.3%)	3 (0.4%)	1.000
TIA	8 (0.7%)	2 (0.7%)	6 (0.8%)	0.878
Device embolization	3 (0.3%)	1 (0.3%)	2 (0.3%)	1.000
Vascular complication	45 (4.1%)	13 (4.3%)	32 (4.0%)	0.822
Severe bleeding (≥ BARC 3a)	36 (3.3%)	13 (4.3%)	23 (2.9%)	0.235
Discharge (N=1088)				
Length of stay, days	2.3±3.9	2.9±4.9	2.1±3.5	0.008
Antithrombotic medication				0.764
None	22 (2.0%)	7 (2.4%)	15 (1.9%)	
SAPT	299 (27.5%)	82 (27.6%)	217 (27.4%)	
DAPT	477 (43.9%)	134 (45.1%)	343 (43.4%)	
OAC	231 (21.2%)	62 (20.9%)	169 (21.4%)	
OAC+AP	59 (5.4%)	12 (4.0%)	47 (5.9%)	

Abbreviations: AP= antiplatelet; DAPT= dual antiplatelet therapy; eGFR= estimated glomerular filtration rate; OAC= oral anticoagulant; SAPT= single antiplatelet therapy

* Lambre (Lifetech Scientific, Shenzhen, China) and Ultraseal (Cardia, Eagan, Minnesota)

were associated with an increased risk of severe bleeding (Table 5). In patients with hemodialysis (N = 47), death, ischemic stroke and severe bleeding rates were 29.6 (95% CI: 18.3 to 45.2) per 100 person-year (PY), 1.4 (95% CI: 0.04 to 7.8) per 100 PY and 15.3 (95% CI: 7.0 to 29.0) per 100 PY, respectively.

A total of 209 patients (19.1%) had no prior episode of bleeding (eGFR≥45 ml/min: 154 [73.7%]; eGFR<45 ml/min: 55 [26.3%]). Rates of late outcomes according to the baseline moderate-to-severe CKD are presented in Supplementary Table 1. In the subpopulation of patients without prior bleeding, the risk of death and SAE were higher in patients with moderate-to-severe CKD (p <0.001), but the risk of all bleeding (HR: 0.91; 95% CI: 0.30 to 2.73; p = 0.863) and severe bleeding (HR= 0.77; 95% CI: 0.16 to 3.63; p = 0.742) did not differ between groups.

Discussion

Some studies have reported an increased risk of stroke in AF patients with CKD.[5,6] Despite the high thrombotic risk observed in CKD patients,[11] specific data regarding the efficacy of LAAC in this population were lacking. The present study failed to identify any increase in the thrombotic risk (DRT, ischemic stroke, TIA or peripheral embolism) associated with CKD, and provided reassuring information regarding the efficacy of LAAC in such patients. In fact, the rate of ischemic stroke observed in our study (1.0 per 100 PY; 1.4 per 100 PY in hemodialysis patients) seems to compare favorably with the rate observed in advanced CKD patients receiving OAC (4.1 to 11.7 per 100 PY).[3,12,13] CKD is known to be associated with increased all-cause mortality, independent of other known risk factors.[14,15] The pathophysiological characteristics of CKD such as oxidative stress, long-term inflammation and vascular calcification likely explain the high morbidity and mortality seen in these patients.[15]

The prescription of OAC in AF patients with CKD raises several issues. In patients with severe CKD receiving vitamin K antagonists, the time percentage with an INR within the target range is lower than in patients with mild or no CKD.[16] and this has indeed been associated with an increased risk of bleeding, stroke and death.[17] Concerning direct OACs, patients with moderate-to-severe CKD have been largely excluded from trials, and concern remains about drug accumulation in patients with severe CKD. In fact, the net-benefit of OAC has never been prospectively assessed in a randomized trial in patients with moderate-to-severe CKD, leading to the absence of robust recommendations regarding the use of this therapy in this population.

Percutaneous LAAC allows a decrease in antithrombotic medication[7] and has been shown to be effective for stroke prevention in all-comer AF patients.[18,19] Thus, LAAC may reduce the thrombotic risk while avoiding the issue of long-term OAC. However, in the present study patients with moderate-to-severe CKD presented an increased risk of both all bleeding and severe bleeding events following LAAC. Interestingly, patients with eGFR<45 ml/min had a

Table 3
Event rate and association estimates from Cox regression analyses

	All patients (N=1094)	Glomerular Filtration Rate (ml/min)		Unadjusted Hazard ratio (95% CI)	p-value
		<45 (N=300)	≥45 (N=794)		
Death					
No. of PY	2365	544	1821	2.84 (2.22-3.64)	<0.001
No. of Events	261	120	141		
Event Rate per 100 PY (95% CI)	11.0 (9.7-12.5)	22.1 (18.3-26.4)	7.7 (6.5-9.1)		
Ischemic stroke					
No. of PY	2329	541	1788	0.65 (0.22-1.92)	0.435
No. of Events	24	4	20		
Event Rate per 100 PY (95% CI)	1.0 (0.7-1.5)	0.7 (0.2-1.9)	1.1 (0.6-1.7)		
TIA					
No. of PY	2329	539	1790	0.75 (0.25-2.28)	0.617
No. of Events	19	4	15		
Event Rate per 100 PY (95% CI)	0.8 (0.5-1.3)	0.7 (0.2-1.9)	0.8 (0.5-1.4)		
Peripheral embolism					
No. of PY	2359	544	1815	2.65 (0.17-42.31)	0.491
No. of Events	2	1	1		
Event Rate per 100 PY (95% CI)	0.08 (0.01-0.3)	0.2 (0.005-1.0)	0.05 (0.002-0.3)		
All bleeding					
No. of PY	2036	452	1584	1.60 (1.20-2.12)	0.001
No. of Events	217	74	143		
Event Rate per 100 PY (95% CI)	10.7 (9.3-12.2)	16.4 (12.9-20.1)	9.0 (7.6-10.6)		
Severe bleeding (≥ BARC 3a)					
No. of PY	2190	500	1690	1.96 (1.36-2.81)	<0.001
No. of Events	125	49	76		
Event Rate per 100 PY (95% CI)	5.7 (4.8-6.8)	9.8 (7.3-13.0)	4.5 (3.5-5.6)		
Hemorrhagic stroke					
No. of PY	2360	544	1816	0.43 (0.05-3.52)	0.435
No. of Events	9	1	8		
Event Rate per 100 PY (95% CI)	0.4 (0.2-0.7)	0.2 (0.005-1.0)	0.4 (0.2-0.9)		
All stroke					
No. of PY	2319	541	1778	0.59 (0.23-1.53)	0.278
No. of Events	33	5	28		
Event Rate per 100 PY (95% CI)	1.4 (1.0-2.0)	0.9 (0.3-2.2)	1.6 (1.0-2.3)		
SAE (Death, stroke or severe bleeding)					
No. of PY	2155	498	1657	2.23 (1.80-2.77)	<0.001
No. of Events	346	142	204		
Event Rate per 100 PY (95% CI)	16.1 (14.1-17.8)	28.5 (24.0-33.6)	12.3 (10.7-14.1)		

Abbreviations= CI= confidence interval; eGFR= estimated glomerular filtration rate; PY= person-year; SAE= serious adverse event; TIA= transient ischemic attack

higher proportion of prior gastrointestinal bleeding (51%) and a lower proportion of prior intracranial bleeding (18%) compared with patients with eGFR≥45 ml/min (rates of approximately 30% for each site of previous bleeding). In fact, the risk of gastrointestinal bleeding increases as eGFR decreases, independent of other factors including antithrombotic therapy.[20] In addition, CKD is associated with an increased risk of recurrent bleeding in patients with obscure gastrointestinal bleeding.[21] Therefore, LAAC followed by an antithrombotic medication de-escalation is unlikely to fully correct the gastrointestinal bleeding diathesis in patients with moderate-to-severe CKD, especially in those with prior bleeding. In contrast, in the subpopulation of patients without prior bleeding, moderate-to-severe CKD was no longer associated with an increased risk of severe bleeding. Future studies are needed to better characterize the positive impact of antithrombotic medication de-escalation following LAAC in patients with CKD. Among approximately 9,000 patients with end-stage kidney disease and AF receiving either warfarin or apixaban (without LAAC), Siontis et al[12] reported rates of death, ischemic stroke and major bleeding of 24.7 per 100 PY, 11.9 per 100 PY and 22.3 per 100 PY, respectively. In the present study, the subpopulation of patients with hemodialysis exhibited similar mortality rate but lower ischemic stroke and severe bleeding rates. Despite the remaining higher risk of severe bleeding observed in patients with moderate-to-severe CKD (as compared with patients with milder or no CKD), LAAC might be associated with a decrease in the risk of bleeding as compared with long-term OAC in this high-risk population. A randomized clinical trial of OAC vs. LAAC in patients with CKD will be required to confirm this assumption.

The optimal antithrombotic therapy following LAAC remains unclear and has to take into account both the risk of DRT and bleeding. To date, antiplatelet therapy after-LAAC has been widely used, as most treated patients are contra-indicated to OAC therapy[7]. In the present study, 71% of patients received antiplatelet therapy at discharge,

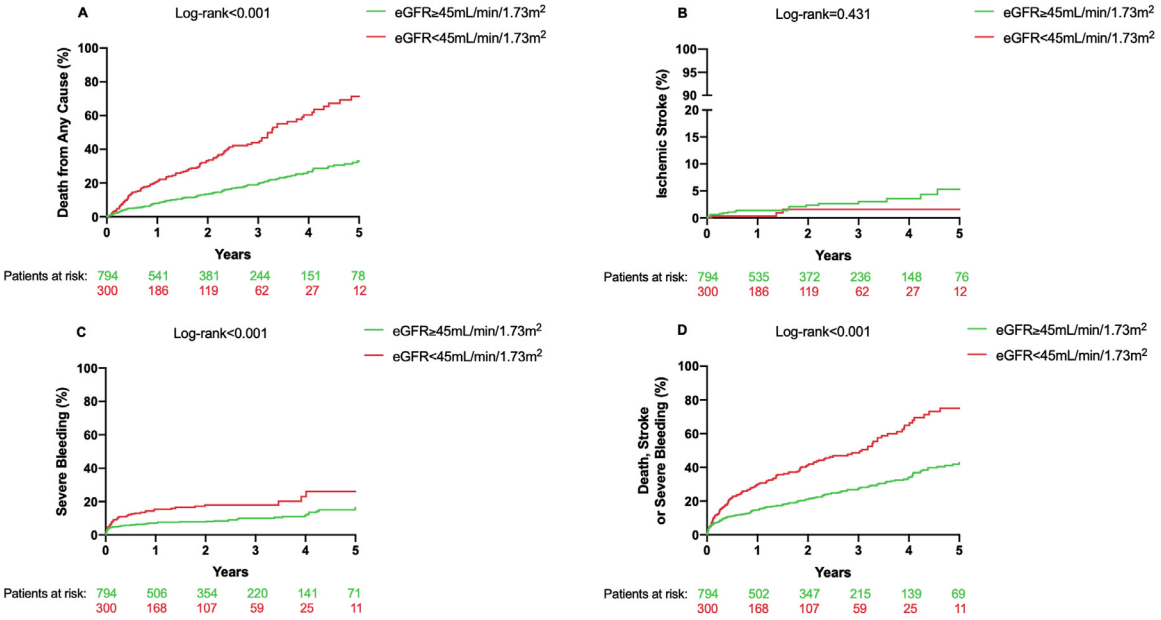

Figure 1. Time-to-event curves for death from any cause, ischemic stroke, severe bleeding and serious adverse event after left atrial appendage closure according to the estimated glomerular filtration rate

A= Death from any cause; *B*= *C*= Ischemic stroke *C*= Severe bleeding; *D*= Serious adverse event (death, stroke and severe bleeding). eGFR= estimated glomerular filtration rate.

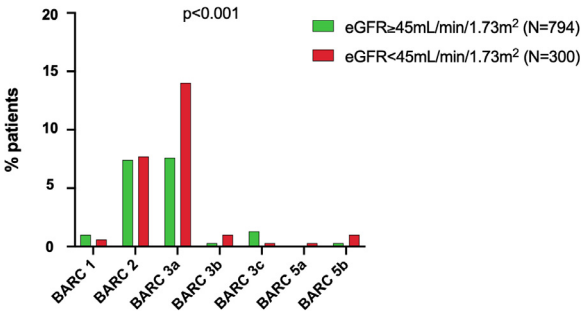

Figure 2. Bleeding severity according to the estimated glomerular filtration rate.BARC= Bleeding Academic Research Consortium; eGFR= estimated glomerular filtration rate

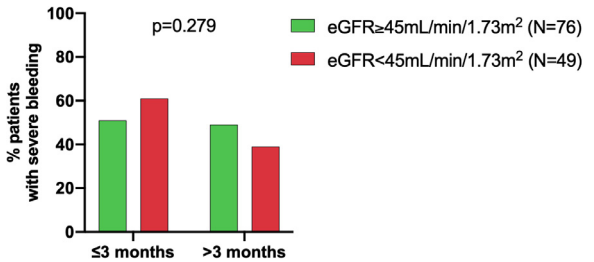

Figure 3. Timing of the severe bleeding according to the estimated glomerular filtration rate.eGFR= estimated glomerular filtration rate

2% didn't receive any antithrombotic medication, and 27% received OAC. Under these regimens, the DRT rate was approximately 4%, that is consistent with the 0.9% to 7.2% rates of DRT reported in the literature.[7] On the other hand, the multivariable analysis failed to find any impact of antithrombotic medication at discharge on the risk of severe bleeding. However, among the 125 patients who presented a severe bleeding, 40 patients (32%) were receiving dual antiplatelet therapy and 8 patients (5%) were on OAC at the severe bleeding event, without differences according to eGFR values. In addition, about half of the severe bleeding events occurred within 3 months after-LAAC. These findings suggest that a more aggressive antithrombotic therapy de-escalation (with single antiplatelet therapy or even no antithrombotic therapy immediately after-procedure in

Table 4
Antithrombotic medication at the time of the severe bleeding (≥ BARC 3a) and ischemic stroke event

	Severe bleeding (≥ BARC 3a) (N=125)			Ischemic stroke (N=24)		
	eGFR<45 ml/min (N=49)	eGFR≥45 ml/min (N=76)	p-value	eGFR<45 ml/min (N=4)	eGFR≥45 ml/min (N=20)	p-value
None	9 (18.4%)	15 (19.7%)	0.932	2 (50.0%)	4 (20.0%)	0.835
SAPT	22 (44.8%)	31 (40.8%)		2 (50.0%)	7 (35.0%)	
DAPT	16 (32.7%)	24 (31.6%)		0	5 (25.0%)	
OAC	2 (4.1%)	4 (5.3%)		0	2 (10.0%)	
OAC+AP	0	2 (2.6%)		0	2 (10.0%)	

Abbreviations: AP= antiplatelet; DAPT= dual antiplatelet therapy; eGFR= estimated glomerular filtration rate; OAC= oral anticoagulant; SAPT= single antiplatelet therapy

Table 5
Univariable and multivariable predictors of severe bleeding (≥ BARC 3a) after left atrial appendage closure

	Univariable model		Multivariable model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.03 (1.00-1.05)	0.036	-	-
Female gender	1.01 (0.71-1.44)	0.963	-	-
Hypertension	1.26 (0.71-2.24)	0.432	-	-
Diabetes mellitus	1.08 (0.75-1.56)	0.671	-	-
eGFR<45 ml/min	1.96 (1.36-2.81)	<0.001	1.92 (1.34-2.76)	<0.001
Liver disease	1.22 (0.64-2.33)	0.550	-	-
Previous ischemic stroke	0.91 (0.61-1.35)	0.636	-	-
Previous PAD	1.07 (0.69-1.65)	0.767	-	-
Previous CAD	1.19 (0.82-1.17)	0.359	-	-
Previous bleeding	2.35 (1.30-4.26)	0.005	2.30 (1.27-4.17)	0.006
No antithrombotic or SAPT at discharge	1.06 (0.71-1.58)	0.768	-	-

Abbreviations= CI= confidence interval; eGFR= estimated glomerular filtration rate; HR= hazard ratio; SAPT= single antiplatelet therapy.

extreme bleeding risk patients) may be required to reduce the bleeding risk in CKD patients undergoing LAAC.

Study limitations. The low rate of ischemic events may explain the absence of impact of eGFR on thrombotic risk (low statistical power). Consequently, no multivariable modeling was performed for ischemic events. A significant proportion of patients (31.8%) had no imaging examination for evaluating the presence of DRT, and this may have biased the results regarding the incidence of this event.

In conclusion, the rate of periprocedural complications as well as the risk of DRT or ischemic stroke during follow-up were not influenced by the presence of renal dysfunction, further reinforcing the role of LAAC as an alternative therapy in this high-risk group of patients. However, patients with moderate-to-severe CKD remained at higher risk of severe bleeding, with approximately 50% of the severe bleeding episodes occurring within 3 months after-LAAC. These findings highlight the urgent need for studies determining the most appropriate antithrombotic treatment (likely with reduced antithrombotic regimes or a more rapid antithrombotic therapy de-escalation) in such patients.

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Credit Author Statement

Laurent Faroux: Methodology, Formal Analysis, Investigation, Writing − Original Draft; Ignacio Cruz-González: Investigation, Writing − Review & Editing; Dabit Arzamendi: Investigation, Writing − Review & Editing; Xavier Freixa: Investigation, Writing − Review & Editing; Luis Nombela-Franco: Investigation, Writing − Review & Editing; Vicente Peral: Investigation, Writing − Review & Editing; Berenice Caneiro-Queija: Investigation, Writing − Review & Editing; Antonio Mangieri: Investigation, Writing − Review & Editing; Blanca Trejo-Velasco: Investigation, Writing − Review & Editing; Lluis Asmarats: Investigation, Writing − Review & Editing; Ander Regueiro: Investigation, Writing − Review & Editing; Angela McInerney: Investigation, Writing − Review & Editing; Caterina Mas-Lladó: Investigation, Writing − Review & Editing; Rodrigo Estevez-Loureiro: Investigation, Writing − Review & Editing; Alessandra Laricchia: Investigation, Writing − Review & Editing; Gilles O'Hara: Investigation, Writing − Review & Editing; Josep Rodés-Cabau: Conceptualization, Methodology, Investigation, Writing − Review & Editing, Supervision

Declaration of Interests

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 study.

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Supplementary materials

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