Review Article

Kidney360

Left Atrial Appendage Closure: An Alternative to Anticoagulation for Stroke Prevention in Patients with Kidney Disease

Srikanth Vallurupalli,[1,2] *Tanya Sharma*,[1] *Subhi Al'Aref*,[1] *Subodh R. Devabhaktuni*,[1] *and Gaurav Dhar*[1,2]

Abstract

Anticoagulation to reduce thromboembolic stroke risk due to nonvalvular atrial fibrillation in ESKD is associated with increased bleeding. There is an existing debate in ESKD centers around the pros and cons of anticoagulation. We propose percutaneous left atrial appendage occlusion as a third alternative to balance thrombosis and bleeding risks in this high-risk population.

KIDNEY360 3: 396–402, 2022. doi: https://doi.org/10.34067/KID.0004082021

Introduction

> "There are three solutions to every problem: accept it, change it or leave it."
>
> —Unknown

Kidney disease and nonvalvular atrial fibrillation are increasing in incidence. These two epidemics share several similar risk factors: age, hypertension, and heart disease. The prevalence of nonvalvular atrial fibrillation is higher in people with ESKD compared with the general population (around 20% versus 1%–2%) (1). At the same time, CKD is highly prevalent in patients with atrial fibrillation (up to 40%–50%).

Embolic stroke is a dreaded complication of atrial fibrillation. CKD is an independent risk factor for stroke, and a drop in eGFR by 10 ml/min per 1.72 m^2 can lead to an increase in the risk of stroke by 7% (2). In patients with atrial fibrillation, the risk of stroke and systemic thromboembolism is about 49% higher in those with CKD and 83% higher in those requiring RRT compared with people with normal renal function (3). Anticoagulation with either vitamin K antagonists or nonvitamin K antagonist oral anticoagulants reduces the incidence of stroke. However, the presence of ESKD poses a significant dilemma in the management of atrial fibrillation. First, ESKD predisposes to both bleeding and thrombosis *via* various pathophysiologic mechanisms, which are described in detail elsewhere (4,5). Second, unlike patients without ESKD, oral anticoagulation options in patients with ESKD are limited, and the use of warfarin does not appear to reduce the risk of ischemic stroke significantly (6). Third, oral anticoagulant use in ESKD increases bleeding risk (7). Although apixaban is noted to be associated with lower bleeding outcomes than warfarin, retrospective studies comparing apixaban with no anticoagulation in patients on hemodialysis (HD) found the relative risk of a fatal hemorrhage or intracranial bleed was 2.74 times higher in those on apixaban (8,9). An analysis of Medicare beneficiaries from 2010 to 2015 reported an event rate of major bleeding of 19.7 and 22.9 per 100 patient years for the apixaban and warfarin, respectively (10). The risk of major bleeding in the general population with atrial fibrillation is 2% and 3% per year with apixaban and warfarin, respectively (11).

In this treatment conundrum, arguments to either accept the bleeding risk and continue anticoagulation ("accept it") or stop anticoagulation ("leave it") abound. Percutaneous occlusion of the left atrial appendage represents an alternative ("change it") to either of these strategies.

In this paper, we will discuss in greater detail the rationale of pursuing alternatives to oral anticoagulation in preventing thromboembolic events in patients with atrial fibrillation and CKD and review existing data on the safety and efficacy of left atrial appendage occlusion (LAAO) in this population.

Rationale for Nonpharmacologic Treatment of Atrial Fibrillation in ESKD

Patients with ESKD have a higher thromboembolic risk while also being at greater risk of bleeding. Elevated proinflammatory and prothrombotic factors and reduced levels of anticoagulant factors (activated protein C) lead to a prothrombotic state in ESKD (7). The bleeding risk on the other hand is driven by deficiencies in primary hemostatic pathways, namely, vasoconstriction, platelet function, and platelet interaction with the endothelium. Currently approved oral pharmacologic anticoagulation choices for a labeled indication for use in patients with ESKD in the United

[1]University of Arkansas for Medical Sciences, Little Rock, Arkansas
[2]Central Arkansas Veterans Healthcare System, Little Rock, Arkansas

Correspondence: Srikanth Vallurupalli, University of Arkansas for Medical Sciences, 4301 West Markham St, slot 532, Little Rock, AR 72205. Email: srivallurupalli@gmail.com

States are either warfarin or apixaban. Warfarin use in this population is associated with significant risk of bleeding and some concern for decline in kidney function. The strict dietary precautions and need for International Normalized Ratio monitoring also reduce compliance and time spent in therapeutic range. The only nonvitamin K antagonist oral anticoagulant approved for use in ESKD is apixaban, and head-to-head comparisons between these drugs is lacking. Overall, the limitation of current pharmacologic therapies and the risk of bleeding poses a special challenge to treating physicians who have to choose between an imperfect treatment versus no treatment. This uncertainty is reflected in a large multinational physician survey published in 2020 where there was a significant heterogeneity in the use of anticoagulants by treating physicians in this population (12). In a 2019 meta-analysis, only 40% of 24,000 CKD patients >65 years of age with atrial fibrillation received anticoagulation (13). As noted in the United States Renal Data System database, in 2016, only 33% of HD, 32% of peritoneal dialysis (PD), and 33% of transplants patients with atrial fibrillation were prescribed warfarin, and 9% of HD, 9% of PD, and 18% of transplant patients received a direct oral anticoagulant (14).

In this setting, the use of percutaneous LAAO devices offers an attractive solution. Ninety percent of thrombi occur within the left atrial appendage in patients with nonvalvular atrial fibrillation (15). Percutaneous LAAO uses a venous transcatheter access with a trans-septal puncture to deploy a self-expanding device with a polymer membrane facing the atrial surface that implants into the left atrial appendage and excludes it from the rest of the atrium, thereby obliterating the site that acts as a nidus for thrombus formation. After an initial period of anticoagulation/dual antiplatelet therapy, adequate occlusion is confirmed after which the intensity of therapy can be reduced (often to low-dose aspirin), excluding the need for therapeutic anticoagulation. Although the procedure is invasive and has been associated with acute and long-term complications such as pericardial effusion, device embolization, device-related thrombus, and procedure-related stroke, the incidence of these complication is reasonably low and outweighs the benefits of stopping anticoagulation in patients at high risk of bleeding. In patients without ESKD and a high risk of bleeding, percutaneous LAAO has been proven to be noninferior to warfarin as part of a multicenter, randomized trial (NCT00129545) (16). The primary composite end point included stroke, cardiovascular death, and systemic embolism. The primary efficacy rate was 3 per 100 patient years in the intervention group versus 4.9 per 100 patient years in the warfarin-only group, with a relative risk of 0.62 (95% confidence interval, 0.35 to 1.25) and a >99.9% probability of noninferiority. Clinical trials comparing LAAO with DOACs are currently underway (NCT03642509).

Various percutaneously implantable LAAO devices have been studied and tested since their conception in the early 2000s. The WATCHMAN device (Boston Scientific, Marlborough, MA) and Amplatzer Amulet (Abbott, Chicago, IL) are currently approved by the Food and Drug Administration for those who require anticoagulation to reduce their risk of stroke and need an alternative to oral anticoagulation (Figure 1). Other devices being investigated or approved for use internationally include WaveCrest, Occlutech, LAmbre, Ultraseal, SealLA, and LeFort. With increased clinical experience with this type of LAAO, periprocedural safety and implantation success have significantly improved in contemporary practice compared with early randomized trial data. Between 2015 and 2017, the numbers of LAAO were noted to go up from 1195 to 11,165, with a significant decline in complications (from 26% in 2015 to 8% in 2017) and inpatient mortality (from 1% in 2015 to 0.1% in 2017) (17). However, the role of LAAO in ESKD has not been systematically investigated.

Figure 1. | The two left atrial appendage occlusion devices approved by the Food and Drug Administration in the United States. Left: the WATCHMAN FLX (Boston Scientific, Marlborough, MA). Right: the Amplatzer Amulet (Abbott, Chicago, IL).

We searched MedLine, EMBASE, Google scholar, and Ovid for relevant studies, including clinical trials, randomized controlled trials, and observational studies. The key medical subheadings (MeSH) "left atrial appendage closure" OR "left atrial appendage occlusion" AND "kidney disease" were used, yielding 41 results. The resulting studies along with their references and reviews and meta-analysis were manually screened to identify potential original studies. Our search retrieved 13 studies focused on

left atrial appendage closure (LAAC) in patients with an eGFR of <60 ml/min per 1.72 m^2 (18–30). Of these, five studies analyzed outcomes in patients with ESKD on dialysis (26–30). We also reviewed clinicaltrials.gov for ongoing studies of LAAO in ESKD.

LAAO in Nonvalvular Atrial Fibrillation and CKD

The vast majority of data on LAAO in patients with kidney disease come from a subpopulation review of retrospective registries of patients undergoing LAAO. Across studies, it was observed that patients with CKD were older and had more comorbidities, especially diabetes, coronary artery disease, and congestive heart failure. Unsurprisingly, CKD patients had a significantly higher CHA_2DS_2-VASc and HAS-BLED score in every study. Table 1 summarizes the salient features of these studies. Whereas some studies use eGFR to stratify outcomes, the number of patients with ESKD on dialysis is strikingly small.

Kefer *et al*. compared outcomes between patients with and without CKD undergoing LAAO for nonvalvular atrial fibrillation, which was published in 2016 (18). The study was a part of a nonrandomized multicenter registry (Amplatzer Cardiac Plug or ACP registry), which included a total of 1014 participants over 22 centers, of whom 375 (37%) had an eGFR <60 ml/min per 1.72 m^2. The outcomes, stratified by stage of CKD (n for stage 3a=76, stage 3b=19, stage 4=61, and stage 5=19), showed no significant difference in thrombotic or bleeding risks. The total complications were not significantly different between those with and without CKD (7% versus 5%; P=0.49). It also included 14 patients undergoing HD and three who had previously undergone renal transplantation. Due to the small number, no meaningful analysis of outcomes could be performed in this subgroup.

Another large study investigating outcomes in CKD patients was published as part of the multicenter Left-Atrium-Appendage occluder Register Germany (LAARGE) (24). It was a nonrandomized prospective trial of 623 patients undergoing LAAO, including 299 patients with CKD, which reported similar implantation success and periprocedural major adverse cardiac events. However, the primary efficacy end point of absence of all-cause death and stroke during the 1-year follow-up was lower in CKD patients (82% versus 93%; P<0.001) after adjusting for age, sex, body mass index >25 kg/m^2, arterial hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, and left ventricular ejection fraction ≤40%. All-cause mortality accounted for the difference because there were no reported strokes in the CKD group and is explained by higher expected mortality in CKD patients. Although the incidence of severe nonfatal bleeding in the follow-up period was low, it was observed only in the CKD group (1%). The study population consisted mostly of CKD stage 3 (n=239), with 45 and 15 patients representing CKD stages 4 and 5, respectively. The primary efficacy outcome did not differ significantly among the subgroups.

Although these studies compare outcomes in people with and without CKD undergoing LAAC, limited data exist on the comparison of LAAC with oral anticoagulants. Valderbano *et al*. presented a *post hoc* analysis from the PROTECT-AF trial to analyze the efficacy of LAAC versus warfarin as a function of creatinine clearance (31). They stratified 698 patients into three groups according to baseline eGFR. There were 219 patients with an eGFR <60 ml/min per 1.72 m^2, 263 with an eGFR 60–90 ml/min per 1.72 m^2, and 216 with an eGFR >90 ml/min per 1.72 m^2. Patients with an eGFR <60 ml/min per 1.72 m^2 were significantly older, had higher CHADS2 scores, and had a higher incidence of anemia and prior cerebral thromboembolic events. No difference was seen in the composite outcome of stroke, systemic embolism, and CV death and each individual component (hazard ratios of 0.51, 0.84, and 1.23 for composite outcome in eGFR <60, 60–90, and >90 ml/min per 1.72 m^2, respectively; P=0.43)

Besides the limitations of nonrandomization and observational nature of the studies, the lack of representation of patients on RRT due to small numbers is a pervasive across studies done on patients with CKD. Faroux *et al*.'s paper was the only one among these studies to include 47 patients on HD (25). Their reported rates of device-related thrombosis were not influenced by kidney dysfunction. Patients with moderate-to-severe CKD (defined as eGFR <45 ml/kg per minute) had similar ischemic stroke risk at follow-up but a higher risk of severe bleeding and all-cause death.

LAAO in Patients with ESKD on Dialysis

Current data on safety and efficacy of LAAO in patients on RRT is limited to five small studies (total of 84 patients). The data from the trials are summarized in the second part of Table 1. Reported implantation success was 100% across different device types.

The 2018 paper by Genovesi *et al*. has the largest number of patients to date (26). It is a nonblinded, multi-institutional, prospective cohort study with initial enrollment of 55 patients with ESKD on RRT (HD or PD) undergoing LAAO. The current paper is the first part of a two-phase design and focuses on procedural success and periprocedural complications with follow-up for up to 30 days. They report a 100% implantation success and no deaths within the 30-day follow-up period. There were no major adverse events, including thromboembolic events or major bleeding. Only three patients had periprocedural events, including access site bleeding, none of which required an intervention or transfusion. Phase 2 of the study will follow patients up for two years with the composite primary end point of death, major thromboembolic events, and major bleeding.

Among other studies on dialysis population, Torres-Saura *et al*. reported two deaths (one sudden death and another related to sepsis) (29). The study included six patients on HD who underwent LAAO. All patients underwent successful implantation and were discharged at 24 hours. The median follow-up was 272 days, with transesophageal echocardiograms at 3, 6, and 12 months, with no device-related thrombi. Although they reported no thromboembolic events or major bleeding during the follow-up period, the authors note that among the two deaths in the series, a link or contribution of thromboembolic events to the sudden cardiac death cannot be excluded. The authors also report that the participants all had high comorbidity scores, and those of the deceased subjects were found to be the highest (Charlson comorbidity index values of 13 and

Table 1. Studies comparing the safety and efficacy of left atrial appendage occlusion for nonvalvular atrial fibrillation in patients with kidney disease

Study	Multi Center versus Single Center	Design	GFR	Participants with CKD	Hemodialysis Patients	Mean age±SD	Men, %	CHA_2DS_2-VASc	HAS-BLED	Implantation Success	Periprocedural Major Complications	Average Duration of Follow-Up	Thrombo-Embolic Events	Major Bleeding
Studies in chronic kidney disease														
Kefer *et al.* (18)	Multi center	Prospective, nonrandomized	<60	375	14	77.9±7.3	55	4.9±1.5	3.4±1.3	99%	6%	498 days	2%	2%
Xue *et al.* (19)	Single center	Retrospective, *post hoc* analysis	<60	151	Not reported	77.0±7.2	61	4.3±1.5	4.0±1.0	99%	3%	637 days	2%	7%
So *et al.* (20)	Single center	Retrospective	<60	71	Not reported	Not reported	Not reported	5.09±1.51	3.39±0.91	97%	11%	365 days	0.77%	3%
Dela Rocca *et al.* (21)	Multi center	Prospective, nonrandomized	<60	104	Not reported	77±7	46	4.9±1.8	3.7±0.9	100%	4%	117.6 days	1.92%	4%
Luani *et al.* (22)	Single center	Prospective, nonrandomized	<45	73	Not reported	75.9±6.7	58	4.50±1.42	3.65±1.0	Not reported	3%	310 PY	2.5 per 100 PY	4.1 per 100 PY
Singh *et al.* (23)	Single center	Retrospective	<60	31	Not reported	79.0±7	Not reported	Not reported	4.0±1.0	Not reported, but similar in both groups	Not reported, but similar in both groups	45 days	Not reported, but similar in both groups	Not reported, but similar in both groups
Fastner *et al.* (24)	Multi center	Prospective, nonrandomized	<60	299	Not reported	77.8±7.5	54	4.9±1.5	4.3±1.0	99%	11%	365 days	0.66%	1%
Faroux *et al.* (25)	Multi center	Prospective, nonrandomized	<45	300	47	77.8±8.2	61	4.9±1.5	4.0±1.1	Not reported	12%	730 days	0.7 per 100 PY	9.8 per 100 PY
Studies in ESKD on hemodialysis														
Genovesi *et al.* (26)	Multi center	Prospective nonrandomized	<15	50	50	71.8±9.6	76	4.0±1.5	4.4±0.9	100%	0%	30	0%	0%
Xipell *et al.* (27)	Single center	Retrospective nonrandomized	<15	8	8	67.5±7.2	75	4.75±1.16	4.62±0.91	100%	0%	427	0%	0%
Cruz-Gonzalez *et al.* (28)	Single center	Retrospective nonrandomized	<15	14	14	69.21±11.58	71	4.5±1.45	5.0±0.96	100%	0%	585	0%	28.5 (n=4; two BARC 2 events and two BARC 3a events)
Torres-Saura *et al.* (29)	Single center	Prospective nonrandomized	<15	6	6	73.5±14	67	4.2±1.16	5.3±0.81	100%	0%	272	0%	0%
Manes *et al.* (30)[a]	Single center	Prospective nonrandomized	<15	6	6	72.6±5.5	Not noted	4.16±2.13	5.8±0.98	100%	0%	420	0%	Not measured

PY, patient years; BARC, Bleeding Academic Research Consortium score; DAPT, dual antiplatelet therapy with acetylsalicylic acid and clopidogrel.
[a]The paper was originally in Italian and translated using third-party software.

Table 2. Salient features of proposed trials on left atrial appendage closure (LAAC) in patients with ESKD and on dialysis

Study	WatchAFIB	STOP HARM	WATCH-HD
Type	Open, randomized, controlled, multi center	Open, randomized, controlled, single center	Observational, prospective
Focus population	CKD 4–5 (eGFR <30 ml/min per 1.73 m^2)	ESKD on dialysis >90 days or eGFR <30 ml/min per 1.73 m^2 for >90 days	ESKD on hemodialysis
Intervention	LAAC versus VKA	LAAC versus OAC	LAAC
Primary outcome	Frequency of episodes of moderate or major bleeding	Time from randomization to the first occurrence of major bleeding	Composite of all-cause mortality, stroke, and bleeding
Follow-up	24 months	5 years	24 months
Anticipated enrollment	300	23	150
Actual enrollment	14	0	Unavailable
Anticipated completion date	June 2017	December 2021	March 2021
Status	Terminated	Terminated	Recruiting

A search on ClinicalTrials.gov with the keywords "left atrial appendage closure/occlusion" and "chronic renal disease" yielded the above results. WatchAFIB, LAAO versus usual care in patients with atrial fibrillation and severe CKD; STOP HARM, Strategy TO Prevent Hemorrhage associated with Anticoagulation in Renal disease Management trial; WATCH-HD, Left Atrial Appendage Occlusion With WATCHMAN Device in Patients With Non-valvular Atrial Fibrillation and End-stage Chronic Kidney Disease on Hemodialysis; VKA, vitamin K antagonist; OAC, oral anticoagulants.

9, respectively). Similarly, Manes *et al*. also described two deaths secondary to nondevice-related causes in their single-center experience with six patients on dialysis undergoing LAAO (30).

Limitations of LAAO in Eliminating Thromboembolism Risk in ESKD

Although these studies show LAAO reduces the risk of thrombus formation, it is limited to a single cardiac structure (LAA) and reduces embolic risk from a single disease (nonvalvular atrial fibrillation). ESKD is associated with an increased risk of thrombosis in both venous and arterial beds. Thus, a residual risk of thromboembolism is to be expected. The ideal approach to eliminate this risk completely would be a treatment modality that can reduce the thrombosis risk across multiple vascular beds with an acceptable risk of bleeding. Thus, although we advocate for more studies in the area of LAAO, efforts to understand underlying mechanisms of thrombosis in ESKD remain crucial in hopes that such an effective therapeutic option can be developed.

Clinical Trials and Future Directions

In recent times, there are three clinical trials envisaged to study the efficacy of LAAO in patients with CKD and nonvalvular atrial fibrillation (Table 2). Two of these, which were randomized (LAAO versus usual care in patients with atrial fibrillation and severe CKD [WatchAFIB] and the Strategy TO Prevent Hemorrhage associated with Anticoagulation in Renal disease Management [STOP HARM] trial), had to be prematurely terminated due to poor enrollment. Left Atrial Appendage Occlusion With WATCHMAN Device in Patients With Non-valvular Atrial Fibrillation and End-stage Chronic Kidney Disease on Hemodialysis (WATCH-HD) is currently recruiting and is estimated to complete this year (NCT03446794). It is an observational prospective registry that aims to enroll 150 participants with an eGFR <15 ml/min per 1.72 m^2 on dialysis. This would be the largest study on dialysis patients yet and would add valuable knowledge to current clinical practice.

Prior experience has shown that randomized trials in this area are hard to recruit to. Contemporary LAAC databases are not geared toward studying this problem. For example, the current version of the American College of Cardiology (ACC) LAAO registry does not collect data on eGFR or dialysis use at patient entry, thus losing a valuable opportunity to study the safety and efficacy compared with those without kidney disease. Although kidney disease databases such as the United States Renal Data System can provide long-term follow-up data, periprocedural safety is unlikely to be addressed in a meaningful manner. Overall, a coalition of cardiologists and nephrologists is needed to study this condition.

Conclusion

Although available data are scant, percutaneous LAAO offers an alternative to reduce risk of thromboembolic stroke in patients with kidney disease and nonvalvular atrial fibrillation. Existing studies show comparable implantation success and periprocedural safety in patients with CKD and those with ESKD on HD. Although enough evidence does not exist to produce evidence-based guidelines for this population, the ACC/American Heart Association 2019 update of the 2014 Guideline for the Management of Patients with Atrial Fibrillation proposes LAAO as a class IIb recommendation in patients at an increased risk of stroke who have contraindications to long-term anticoagulation in the general population (32). Given a similar safety profile in patients with ESKD compared with the general population, LAAO may be considered after a risk-benefit discussion, especially those at risk for severe or recurrent bleeding and poor drug tolerance or adherence. Growing interest and continued investigation of utility of

LAAO in this challenging yet large population with atrial fibrillation offers promise at meeting an enduring clinical conundrum.

Disclosures

S. Al'Aref reports the research funding (NIH 2R01 HL12766105 and NIH 1R21EB030654), and honoraria in the form of royalty fees from Elsevier. S.R. Devabhaktuni reports being on the editorial board for the *Journal of Clinical Cardiology and Cardiovascular Therapy*, *Cardiology Cases and Systematic Reviews*, *International Journal of Cardiac Science and Research*, and *The Journal of Innovations in Cardiac Rhythm Management*. G. Dhar reports consultancy agreements with Abbott Vascular, Boston Sci, Edwards Lifesciences, and Medtronic; research funding from Boston Sci; and is a member of Boston Sci Advisory Board. The remaining authors have nothing to disclose.

Funding

None.

Author Contributions

T. Sharma and S. Vallurupalli conceptualized the study and wrote the original draft of the manuscript, and all authors reviewed and edited the manuscript.

References

1. Reinecke H, Engelbertz C, Schäbitz WR: Preventing stroke in patients with chronic kidney disease and atrial fibrillation: Benefit and risks of old and new oral anticoagulants. *Stroke* 44: 2935–2941, 2013 https://doi.org/10.1161/STROKEAHA.113.001701
2. Masson P, Webster AC, Hong M, Turner R, Lindley RI, Craig JC: Chronic kidney disease and the risk of stroke: A systematic review and meta-analysis. *Nephrol Dial Transplant* 30: 1162–1169, 2015 https://doi.org/10.1093/ndt/gfv009
3. Olesen JB, Lip GY, Kamper AL, Hommel K, Køber L, Lane DA, Lindhardsen J, Gislason GH, Torp-Pedersen C: Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med* 367: 625–635, 2012 https://doi.org/10.1056/NEJMoa1105594
4. Bonde AN, Lip GY, Kamper AL, Hansen PR, Lamberts M, Hommel K, Hansen ML, Gislason GH, Torp-Pedersen C, Olesen JB: Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: A nationwide observational cohort study. *J Am Coll Cardiol* 64: 2471–2482, 2014 https://doi.org/10.1016/j.jacc.2014.09.051
5. van Zyl M, Abdullah HM, Noseworthy PA, Siontis KC: Stroke prophylaxis in patients with atrial fibrillation and end-stage renal disease. *J Clin Med* 9: 123, 2020 https://doi.org/10.3390/jcm9010123
6. Shah M, Avgil Tsadok M, Jackevicius CA, Essebag V, Eisenberg MJ, Rahme E, Humphries KH, Tu JV, Behlouli H, Guo H, Pilote L: Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. *Circulation* 129: 1196–1203, 2014 https://doi.org/10.1161/CIRCULATIONAHA.113.004777
7. Van Der Meersch H, De Bacquer D, De Vriese AS: Vitamin K antagonists for stroke prevention in hemodialysis patients with atrial fibrillation: A systematic review and meta-analysis. *Am Heart J* 184: 37–46, 2017 https://doi.org/10.1016/j.ahj.2016.09.016
8. Mavrakanas TA, Garlo K, Charytan DM: Apixaban versus no anticoagulation in patients undergoing long-term dialysis with incident atrial fibrillation. *Clin J Am Soc Nephrol* 15: 1146–1154, 2020 https://doi.org/10.2215/CJN.11650919
9. Chokesuwattanaskul R, Thongprayoon C, Tanawuttiwat T, Kaewput W, Pachariyanon P, Cheungpasitporn W: Safety and efficacy of apixaban versus warfarin in patients with end-stage renal disease: Meta-analysis [published correction appears in *Pacing Clin Electrophysiol* 41: 879, 2018 10.1111/pace.13431]. *Pacing Clin Electrophysiol* 41: 627–634, 2018 https://doi.org/10.1111/pace.13331
10. Siontis KC, Zhang X, Eckard A, Bhave N, Schaubel DE, He K, Tilea A, Stack AG, Balkrishnan R, Yao X, Noseworthy PA, Shah ND, Saran R, Nallamothu BK: Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. *Circulation* 138: 1519–1529, 2018 https://doi.org/10.1161/CIRCULATIONAHA.118.035418
11. Hylek EM, Held C, Alexander JH, Lopes RD, De Caterina R, Wojdyla DM, Huber K, Jansky P, Steg PG, Hanna M, Thomas L, Wallentin L, Granger CB: Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, characteristics, and clinical outcomes. *J Am Coll Cardiol* 63: 2141–2147, 2014 https://doi.org/10.1016/j.jacc.2014.02.549
12. Potpara TS, Ferro C, Lip GYH, Dan GA, Lenarczyk R, Mallamaci F, Ortiz A, Sarafidis P, Ekart R, Dagres N: Management of atrial fibrillation in patients with chronic kidney disease in clinical practice: A joint European Heart Rhythm Association (EHRA) and European Renal Association/European Dialysis and Transplantation Association (ERA/EDTA) physician-based survey. *Europace* 22: 496–505, 2020 https://doi.org/10.1093/europace/euz358
13. He W, Zhang H, Zhu W, Xue Z: Effect of anticoagulation therapy in older patients with chronic kidney disease and atrial fibrillation: A meta-analysis. *Medicine (Baltimore)* 98: e17628, 2019 https://doi.org/10.1097/MD.0000000000017628
14. United States Renal Data System: 2018 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States, 2018. Available at: https://www.usrds.org/annual-data-report. Accessed September 24, 2021
15. Blackshear JL, Odell JA: Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* 61: 755–759, 1996 https://doi.org/10.1016/0003-4975(95)00887-X
16. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P; PROTECT AF Investigators: Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: A randomised non-inferiority trial. *Lancet* 374: 534–542, 2009 https://doi.org/10.1016/S0140-6736(09)61343-X
17. Munir MB, Khan MZ, Darden D, Pasupula DK, Balla S, Han FT, Reeves R, Hsu JC: Contemporary procedural trends of WATCHMAN percutaneous left atrial appendage occlusion in the United States. *J Cardiovasc Electrophysiol* 32: 83–92, 2021 https://doi.org/10.1111/jce.14804
18. Kefer J, Tzikas A, Freixa X, Shakir S, Gafoor S, Nielsen-Kudsk JE, Berti S, Santoro G, Aminian A, Landmesser U, Nietlispach F, Ibrahim R, Danna PL, Benit E, Budts W, Stammen F, De Potter T, Tichelbäcker T, Gloekler S, Kanagaratnam P, Costa M, Cruz-Gonzalez I, Sievert H, Schillinger W, Park JW, Meier B, Omran H: Impact of chronic kidney disease on left atrial appendage occlusion for stroke prevention in patients with atrial fibrillation. *Int J Cardiol* 207: 335–340, 2016 https://doi.org/10.1016/j.ijcard.2016.01.003
19. Xue X, Jiang L, Duenninger E, Muenzel M, Guan S, Fazakas A, Cheng F, Illnitzky J, Keil T, Yu J: Impact of chronic kidney disease on WATCHMAN implantation: Experience with 300 consecutive left atrial appendage closures at a single center. *Heart Vessels* 33: 1068–1075, 2018 https://doi.org/10.1007/s00380-018-1157-x
20. So C, Cheung GSH, Chan CKY, Kam KKH, Chan AKY, Au SWS, Chan SKC, Lam YY, Lee AP-W, Yan BPY: Effect of chronic kidney disease on legft atrial appendage occlusion outcome: A single-centre retrospective. *J Am Coll Cardiol* 71: A302, 2018 https://10.1016/S0735-1097(18)30843-X
21. Della Rocca DG, Gasperetti A, Fassini G, Mohanty S, Trivedi C, Natale VN, Horton R, Gianni C, Al-Ahmad A, Burkhardt JD, Choudhury FA, Moheeth MA, Gallinghouse J, Hranitzky P, Sanchez JE, Mohanty P, Di Biase L, Tondo C, Natale A: Safety and

clinical effectiveness of left atrial appendage occlusion in patients with chronic kidney disease. *Circulation* 138: A12696, 2018 https://www.ahajournals.org/doi/10.1161/circ.138.suppl_1.12696
22. Luani B, Genz C, Herold J, Mitrasch A, Mitusch J, Wiemer M, Schmeißer A, Braun-Dullaeus RC, Rauwolf T: Cerebrovascular events, bleeding complications and device related thrombi in atrial fibrillation patients with chronic kidney disease and left atrial appendage closure with the WATCHMAN™ device. *BMC Cardiovasc Disord* 19: 112, 2019 https://doi.org/10.1186/s12872-019-1097-0
23. Singh S, Okoh AK, Mehta H, Sandhu M, Singh V, Rajmeet M, Dobesh D, Cohen M, Waxman S: Left atrial appendage closure in patients with end-stage chronic kidney disease: Experience with 156 consecutive cases at a single center. *Circulation* 140: A16612, 2019 https://www.ahajournals.org/doi/10.1161/circ.140.suppl_1.16612
24. Fastner C, Brachmann J, Lewalter T, Zeymer U, Sievert H, Borggrefe M, Nienaber CA, Weiß C, Pleger ST, Ince H, Maier J, Achenbach S, Sigusch HH, Hochadel M, Schneider S, Senges J, Akin I: Left atrial appendage closure in patients with chronic kidney disease: Results from the German multicentre LAARGE registry. *Clin Res Cardiol* 110: 12–20, 2021 https://doi.org/10.1007/s00392-020-01638-5
25. Faroux L, Cruz-González I, Arzamendi D, Freixa X, Nombela-Franco L, Peral V, Caneiro-Queija B, Mangieri A, Trejo-Velasco B, Asmarats L, Regueiro A, McInerney A, Mas-Lladó C, Estevez-Loureiro R, Laricchia A, O'Hara G, Rodés-Cabau J: Effect of glomerular filtration rates on outcomes following percutaneous left atrial appendage closure. *Am J Cardiol* 145: 77–84, 2021 https://doi.org/10.1016/j.amjcard.2020.12.081
26. Genovesi S, Slaviero G, Porcu L, Casu G, Bertoli S, Sagone A, Pieruzzi F, Rovaris G, Buskermolen M, Danna P, Montoli A, Oreglia J, Contaldo G, Mazzone P: Implant success and safety of left atrial appendage occlusion in end stage renal disease patients: Peri-procedural outcomes from an Italian dialysis population. *Int J Cardiol* 262: 38–42, 2018 https://doi.org/10.1016/j.ijcard.2018.03.083
27. Xipell M, Flores-Umanzor E, Ojeda R, Arias M, Cepas-Guillén PL, Regueiro A, Freixa X, Cases A, Maduell F: Percutaneous left atrial appendage closure, a safe alternative to anticoagulation for patients with nonvalvular atrial fibrillation and end-stage renal disease on hemodialysis: A single center experience. *Artif Organs* 44: 513–521, 2020 https://doi.org/10.1111/aor.13603
28. Cruz-González I, Trejo-Velasco B, Fraile MP, Barreiro-Pérez M, González-Ferreiro R, Luis Sánchez P: Left atrial appendage occlusion in hemodialysis patients: Initial experience. *Rev Esp Cardiol (Engl Ed)* 72: 792–793, 2019 https://doi.org/10.1016/j.rec.2018.12.007
29. Torres-Saura F, Romero-Vazquiánez M, Pérez-Berbel P, Cotilla-de la Rosa E, Diez-Ojea B, Arroyo Ucar E: New approach to the prevention of stroke in patients with non-valvular fibrillation in hemodialysis: Percutaneous closure of left atrial appendage. *Arch Cardiol Mex* 90: 102–105, 2020 https://doi.org/10.24875/ACME.M20000089
30. Manes M, Radin E, Pellù V, Parodi E, Caputo D, Gabrielli D, Molino A, Paternoster G, Pelloni E, Pisano F: [Monocentric experience of left atrial appendage occlusion among patients with advanced chronic kidney disease and non-valvular atrial fibrillation]. *G Ital Nefrol* 37: 2020–vol1, 2020
31. Valderranbano M, Price M, Reddy V, Buchbinder M, Holmes D, Sievert H, Turi Z, Gordon N, Mullin C, Sick PB, Best P: Do patients with CKD benefit from Left Atrial Appendage Closure (LAAC) with WATCHMAN? Insights from PROTECT AF. *J Am Coll Cardiol* 68: B251, 2016 https://doi.org/10.1016/j.jacc.2016.09.756
32. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW: 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. *Circulation* 140: e125–e151, 2019 https://doi.org/10.1161/CIR.0000000000000665

Received: June 22, 2021 **Accepted:** December 6, 2021