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

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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.

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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 m² 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

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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 transcatheater 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 out-weighs 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 in the United States. Left: the WATCHMAN FLX (Boston Scientific, Marlborough, MA). Right: the Amplatzer Amulet (Abbott, Chicago, IL).

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).
left atrial appendage closure (LAAC) in patients with an eGFR of <60 ml/min per 1.72 m² (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 LAAC in ESKD.

**LAAC in Nonvalvular Atrial Fibrillation and CKD**

The vast majority of data on LAAC in patients with kidney disease come from a subpopulation review of retrospective registries of patients undergoing LAAC. 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 CHA2DS2-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 LAAC 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 m². 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 LAAC, including 299 patients with CKD, which reported similar implantation success and peri procedural 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/m², 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 m², 263 with an eGFR 60–90 ml/min per 1.72 m², and 216 with an eGFR >90 ml/min per 1.72 m². Patients with an eGFR <60 ml/min per 1.72 m² 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, >90 ml/min per 1.72 m², 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.

**LAAC in Patients with ESKD on Dialysis**

Current data on safety and efficacy of LAAC 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 LAAC. 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 LAAC. 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 | Participants with CKD | Hemodialysis Patients | Mean Age ±SD | Men, % | CHA2DS2-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                     | <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                    | <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                    | <60                    | 71                    | Not reported | Not reported | 77±0.7   | Not reported | 5.09±1.51          | 3.39±0.91                          | 97%                                | 11%                    | 365 days                | 0.77%           | 3%             |
| Della Rocca et al. (21)      | Multi center                     | <60                    | 104                   | Not reported | Not reported | Not reported | 46       | 4.9±1.8               | 3.7±0.9                           | 100%                                | 4%                     | 117.6 days              | 1.92%           | 4%             |
| Luani et al. (22)            | Single center                    | <45                    | 73                    | Not reported | Not reported | Not reported | 75.9±6.7 | 58                   | 4.5±1.42                     | 3.65±1.0                           | Not reported                                    | 3%                     | 310 PY                | 25 per 100 PY    | 4.1 per 100 PY |
| Singh et al. (23)            | Single center                    | <60                    | 31                    | Not reported | Not reported | Not reported | Not reported | 79.0±7              | 4.0±1.0                           | Not reported, but similar in both groups | 45 days            | Not reported, but similar in both groups |                      |                 |
| Fastner et al. (24)          | Multi center                     | <60                    | 299                   | Not reported | 77.8±7.5  | 54         | 4.9±1.5  | 4.3±1.0              | Not reported, but similar in both groups | 99%                                | 11%                    | 365 days                | 0.66%           | 1%             |
| Faroux et al. (25)           | Multi center                     | <45                    | 300                   | Not reported | 77.8±8.2  | 61         | 4.9±1.5  | 4.0±1.1              | Not reported, but similar in both groups | 12%                                | 730 days               | 0.7 per 100 PY          | 9.8 per 100 PY |
| **Studies in ESKD on hemodialysis** |                                  |                        |                       |              |        |             |          |                      |                                   |                        |                          |                 |                 |
| Genovesi et al. (26)         | Multi center                     | <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                    | <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                    | <15                    | 14                    | 14           | 69.21±11.38 | 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                    | <15                    | 6                     | 6            | 73.5±14  | 67         | 4.2±1.16 | 5.3±0.81             | 100%                                | 0%                     | 272                     | 0%              | 0%             |
| Manes et al. (30)*           | Single center                    | <15                    | 6                     | 6            | 72.6±5.5  | 67         | 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.

*The paper was originally in Italian and translated using third-party software.
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 (non-valvular 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 non-valvular 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 m² 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

### 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 m²) | ESKD on dialysis >90 days or eGFR <30 ml/min per 1.73 m² 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, LAAC 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.
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