How to Cite this article: Srikanth Vallurupalli, Tanya Sharma, Subhi Al'Aref, Subodh Devabhaktuni, and Gaurav Dhar, Left atrial appendage occlusion: an alternative to anticoagulation for stroke prevention in kidney disease, Kidney360, Publish Ahead of Print, 10.34067/KID.0004082021

Article Type: Review Article

Left atrial appendage occlusion: an alternative to anticoagulation for stroke prevention in kidney disease

DOI: 10.34067/KID.0004082021

Srikanth Vallurupalli, Tanya Sharma, Subhi Al'Aref, Subodh Devabhaktuni, and Gaurav Dhar

Key Points:
* 
* 
* 

Abstract:
Anticoagulation to reduce thromboembolic stroke risk due to nonvalvular atrial fibrillation in ESRD is associated with increased bleeding. Existing debate in ESRD 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.

Disclosures: S. Al'Aref reports the following: Research Funding: NIH 2R01 HL12766105, NIH 1R21EB030654; and Honoraria: Royalty fees from Elsevier. S. Devabhaktuni reports the following: Scientific Advisor or Membership: Editorial board: -Journal of Clinical Cardiology and Cardiovascular Therapy, - Cardiology Cases and Systematic Reviews, - International Journal of Cardiac Science and Research, - The Journal of Innovations in Cardiac Rhythm Management. G. Dhar reports the following: Consultancy Agreements: Abbott Vascular, Edwards Lifesciences, Medtronic and Boston Sci; Research Funding: Boston Sci; and Scientific Advisor or Membership: Boston Sci Advisory Board. The remaining authors have nothing to disclose.

Funding:

Author Contributions: Srikanth Vallurupalli: Conceptualization; Writing - original draft; Writing - review and editing Tanya Sharma: Conceptualization; Writing - original draft; Writing - review and editing Subhi Al'Aref: Writing - review and editing Subodh Devabhaktuni: Writing - review and editing Gaurav Dhar: Writing - review and editing

Data Sharing Statement:

Clinical Trials Registration:

Registration Number:

Registration Date:

The information on this cover page is based on the most recent submission data from the authors. It may vary from the final published article. Any fields remaining blank are not applicable for this manuscript.

Copyright 2021 by American Society of Nephrology.
Left atrial appendage closure: an alternative to anticoagulation for stroke prevention in patients with kidney disease

Srikanth Vallurupalli¹,², Tanya Sharma¹, Subhi Al Aref¹, Subodh R Devabhaktuni¹, Gaurav Dhar¹,²

University of Arkansas for Medical Sciences, Little Rock, AR
Central Arkansas Veterans Healthcare System, Little Rock, AR

Corresponding author:
Srikanth Vallurupalli MD
University of Arkansas for Medical Sciences
4301 West Markham St, slot 532
Little Rock, AR 72205
Email: srivallurupalli@gmail.com
Phone: 5016867882
Fax: 5016866439
Abstract
Anticoagulation to reduce thromboembolic stroke risk due to nonvalvular atrial fibrillation in ESRD is associated with increased bleeding. Existing debate in ESRD 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.

“There are three solutions to every problem: accept it, change it or leave it”- Unknown

Introduction:
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 non-valvular atrial fibrillation is higher in people with end-stage renal disease on dialysis (ESRD) compared to the general population (around 20% vs 1-2%). [1] At the same time, chronic kidney disease 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 drop in eGFR by 10 ml/min/1.72m2 can lead to an increase in risk of stroke by 7%. [2] In patients with atrial fibrillation, the risk of stroke and systemic thrombo-embolism is about 49% higher in those with CKD and 83% higher in those requiring renal replacement therapy when compared to people with normal renal function. [3] Anticoagulation with either vitamin K antagonists or non-vitamin K antagonist oral anticoagulants (NOACs) reduces the incidence of stroke. However, the presence of ESRD poses a significant dilemma in the management of atrial fibrillation. First, ESRD predisposes to both bleeding and thrombosis via various pathophysiological mechanisms which are described in detail elsewhere. [4,5] Second, unlike patients without ESRD, oral anticoagulation options in patients with ESRD are limited and use of warfarin does not appear to significantly reduce the risk of ischemic stroke. [6] Third, oral anticoagulant use in ESRD increases bleeding risk. [7] While apixaban is noted to be associated with lower bleeding outcomes than warfarin, retrospective studies comparing apixaban to no anticoagulation in patients on hemodialysis, found the relative risk of a fatal hemorrhage or intracranial bleed was seen to be 2.74 times higher in those on apixaban. [8,9] In 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 2.13% and 3.09% 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 chronic kidney disease and review existing data on the safety and efficacy of left atrial appendage occlusion in this population.

Rationale for non-pharmacological treatment of atrial fibrillation in ESRD
Patients with ESRD have a higher thromboembolic risk while also being at a greater risk of bleeding. Elevated pro-inflammatory and pro-thrombotic factors as well as reduced levels of anticoagulant factors (activated protein C) lead to a pro-thrombotic state in ESRD. [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 pharmacological anticoagulation choices for a labeled indication for use in patients with ESRD in the United 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 INR monitoring also reduce compliance and time spent in therapeutic range. The only NOAC approved for use in ESRD is apixaban and head to head comparisons between these drugs is lacking. Overall, the limitation of current pharmacological 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 use of anticoagulants by treating physicians in this population. [12] In a 2019 meta-analysis, only 40% of 24,000 CKD patients over the age of 65 years with atrial fibrillation received anti-coagulation. [13] As noted in the United States Renal Data System (USRDS) database, in 2016, only 32.5% of HD, 31.5% of peritoneal dialysis (PD) and 32.6% of transplants patients with AF were prescribed warfarin and 9.4% of HD, 9.4% of PD and 17.8% of transplant patients received a direct oral anticoagulant. [14]

In this setting, the use of percutaneous left atrial appendage occlusion (LAAO) devices offers an attractive solution. 90% of thrombi occur within the left atrial appendage in patients with non-valvular atrial fibrillation. [15] Percutaneous LAAO uses a venous trans-catheter 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 which acts as a nidus for thrombus formation. Following an initial period of anticoagulation/dual antiplatelet therapy, adequate occlusion is confirmed following which intensity of therapy can be reduced (often to low dose aspirin), excluding the need for therapeutic anticoagulation. While the procedure is invasive and has been associated with acute as well as long term complications like 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 anti-coagulation in patients at high-risk of bleeding. In patients without ESRD 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 3.0 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 0.35-1.25] and a >99.9% probability of non-inferiority. Clinical trials comparing LAAO vs DOACs are currently underway (NCT03642509).

Various percutaneously implantable LAAO devices have been studied and tested since their conception in the early 2000s. Watchman device (Boston Scientific, Marlborough, MA) and Amplatzer Amulet (Abbott, Chicago, IL) are currently FDA approved 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, Ultrasense, SealLA and LeFort. With increased clinical experience with this type of LAAO, peri-procedural safety and implantation success have significantly improved in contemporary practice compared to early randomized trial data. Between 2015 to 2017 the numbers of LAAO were noted to go up from 1195 to 11,165 with a significant
decline in complications (26.4% in 2015 to 7.9% in 2017) as well as inpatient mortality (from 1.3% in 2015 to 0.1% in 2017). [17] However, the role of LAAO in ESRD has not been systematically investigated.

We searched MedLine, EMBASE, Google scholar and Ovid for relevant studies including clinical trials, randomized controlled trials, and observational studies. The following key medical sub-headings (MeSH) were used: left atrial appendage closure OR left atrial appendage occlusion AND kidney disease, which yielded 41 results. The resulting studies along with their references, as well as reviews and meta-analysis were manually screened to identify potential original studies. Our search retrieved thirteen studies focused on LAAC in patients with estimated glomerular filtration rate (eGFR) <60ml/min/1.72m². [18-30] Of these, five studies analyzed outcomes in patients with ESRD on dialysis. [26-30] We also reviewed clinicaltrials.gov for ongoing studies of left atrial appendage occlusion in ESRD.

**LAAO in non-valvular atrial fibrillation and CKD**

The vast majority of data on LAAO in patients with kidney disease comes from sub-population 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 significantly higher CHA2DS2-VASc and HAS-BLED score in every study. Table 1 summarizes the salient features of these studies. While some studies use eGFR to stratify outcomes, the number of patients with ESRD on dialysis is strikingly small.

Kefer et al compared outcomes between patients with and without CKD undergoing LAAO for non-valvular atrial fibrillation which was published in 2016. [18] The study was a part of a non-randomized multicenter registry (Amplatzer Cardiac Plug or ACP registry) which included a total of 1014 participants over 22 centers, of which 375 (36.9%) had eGFR < 60ml/min/1.72m². 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 (6.6% vs 5.3%, p=0.49). It also included 14 patients undergoing hemodialysis and 3 that had previously undergone renal transplantation. Due to the small number, no meaningful analysis of outcomes can be performed in this sub-group.

Another large study investigating outcomes in CKD patients was published as part of the multi-center Left-Atrium-Appendage occluder Register Germany (LAARGE). [24] It was a non-randomized prospective trial of 623 patients undergoing LAAO, including 299 patients with CKD which reported similar implantation success, peri-procedural major adverse cardiac events (MACE). However, primary efficacy end-point of absence of all-cause death and stroke during the one-year follow-up was lower in CKD patients (82% vs 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 LVEF ≤ 40%. All-cause mortality accounted for the difference, as there were no reported strokes in the CKD group and is explained by higher expected mortality in CKD patients. While incidence of severe non-fatal bleeding in follow-up period was low, it was observed only in the CKD group (1.4%). The study population comprised mostly of CKD stage 3 (n=239) with 45 and 15 patients representing CKD stage 4 and 5, respectively. The primary efficacy outcome did not differ significantly amongst the sub-groups.
While these studies compare outcomes in people with and without CKD undergoing LAAC, limited data exists 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 vs warfarin as a function of creatinine clearance. [31] They stratified 698 patients into three groups according to baseline eGFR. There were 219 patients with eGFR <60ml/min/1.72m2, 263 with eGFR 60-90ml/min/1.72m2, and 216 with eGFR >90ml/min/1.72m2. Patients with eGFR <60ml/min/1.72m2 were significantly older, had higher CHADS2 scores, and had higher incidence of anemia and prior cerebral thrombo-embolic events. No difference was seen in the composite outcome of stroke, systemic embolism, and CV death as well as each individual component (HR 0.51, 0.84, and 1.23 for composite outcome in eGFR <60, 60-90 and >90ml/min/1.72m2, respectively with p=0.43)

Besides the limitations of non-randomization and observational nature of the studies, the lack of representation of patients on renal replacement therapy due to small numbers is a pervasive across studies done on patients with CKD. Faroux et al’s paper was the only one amongst these studies to include 47 patients on hemodialysis. [25] They reported rates of device related thrombosis were not influenced by kidney dysfunction. Patients with moderate-severe CKD (defined as eGFR<45 ml/kg/min) had similar ischemic stroke risk at follow-up but higher risk of severe bleeding and all cause death.

**LAAO in patients with ESRD on dialysis**

Current data on safety and efficacy of LAACO in patients on renal replacement therapy is limited to 5 small studies (total of 84 patients). The data from the trials is 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 non-blinded, multi-institutional, prospective cohort study with initial enrollment of 55 patients with ESRD on renal replacement therapy (hemodialysis or peritoneal dialysis) undergoing LAACO. The current paper is the first part of a two-phase design and focuses on procedural success and peri-procedural 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 peri-procedural events including access site bleeding, none of which required an intervention or transfusion. Phase-two of the study will follow patients up for two years with the composite primary end-point of death, major thrombo-embolic events and major bleeding.

Amongst other studies on dialysis population, Torres-Saura et al reported two deaths (one sudden death and another related to sepsis). [29] The study included 6 patients on hemodialysis who underwent LAACO. All patients underwent successful implantation and were discharged at 24 hours. The median follow-up was 272 days with trans-esophageal echocardiograms at three, six and twelve months, with no device related thromb. While they reported no thrombo-embolic events or major bleeding during the follow up period, the authors note that amongst the two deaths in the series, a link or contribution of thrombo-embolic events to the sudden cardiac death cannot be excluded. The authors also report that the the participants all had high comorbidity scores and those of the deceased subjects were found to be the highest (Charlson comorbidity index 13 and 9, respectively). Similarly, Manes et al also described two deaths secondary to non-device related causes in their single-center experience with six patients on dialysis undergoing LAACO. [30]
Limitations of LAAO in eliminating thromboembolism risk in ESRD
While 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). ESRD is associated with an increased risk of thrombosis in both venous and arterial beds. Thus, a residual risk of thrombo-embolism is to be expected. The ideal approach to completely eliminate this risk would be a treatment modality that can reduce the thrombosis risk across multiple vascular beds with an acceptable risk of bleeding. Thus, while we advocate for more studies in the area of LAAO, efforts to understand underlying mechanisms of thrombosis in ESRD 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 3). Two of these, which were randomized (Left atrial appendage occlusion vs. usual care in patients with atrial fibrillation and severe chronic kidney disease (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 eGFR <15ml/min/1.72m2 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 towards studying this problem. For example, the current version of the 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 to those without kidney disease. While kidney disease databases such as the US renal data system (USRDS) can provide long term follow-up data, peri-procedural safety is unlikely to be addressed in a meaningful manner. Overall, a coalition of cardiologists and nephrologists is needed to study this condition.

Conclusion
While available data is scant, percutaneous LAAO offers an alternative to reduce risk of thromboembolic stroke in patients with kidney disease and non-valvular atrial fibrillation. Existing studies show comparable implantation success and peri-procedural safety in patients with CKD as well as those with ESRD on hemodialysis. While enough evidence does not exist to produce evidence-based guidelines for this population, the ACC/AHA 2019 update of the 2014 guidelines on management of atrial fibrillation recommend 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 ESRD as compared to 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 following: Research Funding: NIH 2R01 HL12766105, NIH 1R21EB030654; and Honoraria: Royalty fees from Elsevier. S. Devabhaktuni reports the following: Scientific Advisor or Membership: Editorial board: -Journal of Clinical Cardiology and Cardiovascular Therapy, - Cardiology Cases and Systematic Reviews, - International Journal of Cardiac Science and Research, - The Journal of Innovations in Cardiac Rhythm Management. G. Dhar reports the following: Consultancy Agreements: Abbott Vascular, Edwards Lifesciences, Medtronic and Boston Sci; Research Funding: Boston Sci; and Scientific Advisor or Membership: Boston Sci Advisory Board. The remaining authors have nothing to disclose.

Funding:
None

Author Contributions:
Srikanth Vallurupalli: Conceptualization; Writing - original draft; Writing - review and editing. Tanya Sharma: Conceptualization; Writing - original draft; Writing - review and editing. Subhi Al'Aref: Writing - review and editing. Subodh Devabhaktuni: Writing - review and editing Gaurav Dhar: Writing - review and editing.
References:


Table 1: (Attached separately) Studies comparing safety and efficacy of left atrial appendage occlusion for non-valvular atrial fibrillation in patients with kidney disease

<table>
<thead>
<tr>
<th>PY: Patient Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARC: Bleeding Academic Research Consortium score</td>
</tr>
<tr>
<td>DAPT: Dual anti-platelet therapy with acetylsalicylic acid and clopidogrel</td>
</tr>
</tbody>
</table>

* The paper was originally in Italian and translated using a third-party software.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>GFR</th>
<th>Participants with CKD</th>
<th>Hemodialysis patients</th>
<th>Mean age ± SD</th>
<th>Male (%)</th>
<th>CHADS2VASc</th>
<th>HAS-BLED</th>
<th>Implantation success</th>
<th>Peri-procedural major complications</th>
<th>Average duration of follow up</th>
<th>Thromboembolic events</th>
<th>Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies in chronic kidney disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kefer et al</td>
<td>Multi-center, non-randomized</td>
<td>&lt;60</td>
<td>375</td>
<td>14</td>
<td>77.9 ± 7.3</td>
<td>54.6</td>
<td>4.9 ± 1.5</td>
<td>3.4 ± 1.3</td>
<td>99%</td>
<td>6.10%</td>
<td>498 days</td>
<td>2.30%</td>
<td>2.10%</td>
</tr>
<tr>
<td>Xue et al</td>
<td>Single-center, post-hoc analysis</td>
<td>&lt;60</td>
<td>151</td>
<td>Not reported</td>
<td>77.0 +/- 7.2</td>
<td>60.9</td>
<td>4.3 +/- 1.5</td>
<td>4.0 +/- 1.0</td>
<td>98.70%</td>
<td>3.30%</td>
<td>637 days</td>
<td>2%</td>
<td>6.60%</td>
</tr>
<tr>
<td>Chak Yu So et al</td>
<td>Single-center</td>
<td>&lt;60</td>
<td>71</td>
<td>Not reported</td>
<td>77±7</td>
<td>46.1</td>
<td>4.9±1.8</td>
<td>3.7±0.9</td>
<td>100%</td>
<td>3.80%</td>
<td>117.6 days</td>
<td>1.92%</td>
<td>3.80%</td>
</tr>
<tr>
<td>Dela Rocca et al</td>
<td>Multi-center, non-randomized</td>
<td>&lt;60</td>
<td>104</td>
<td>Not reported</td>
<td>77.8 ± 7.5</td>
<td>54.2</td>
<td>4.9 ± 1.5</td>
<td>4.3 ± 1.0</td>
<td>100%</td>
<td>3.80%</td>
<td>310 PY</td>
<td>2.5 per 100 PY</td>
<td>4.1 per 100 PY</td>
</tr>
<tr>
<td>Luani et al</td>
<td>Single-center, non-randomized</td>
<td>&lt;45</td>
<td>73</td>
<td>Not reported</td>
<td>75.9 ± 6.7</td>
<td>57.5</td>
<td>4.50 ± 1.42</td>
<td>3.65 ± 1.0</td>
<td>100%</td>
<td>2.70%</td>
<td>730 days</td>
<td>0.7 per 100 PY</td>
<td>9.8 per 100 PY</td>
</tr>
<tr>
<td>Singh et al</td>
<td>Retrospective</td>
<td>&lt;60</td>
<td>31</td>
<td>Not reported</td>
<td>79.0 ± 7</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported, but similar in both groups</td>
<td>Not reported, but similar in both groups</td>
<td>45 days</td>
<td>Not reported, but similar in both groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fastner et al</td>
<td>Multi-center, non-randomized</td>
<td>&lt;60</td>
<td>299</td>
<td>Not reported</td>
<td>77.8 ± 7.5</td>
<td>54.2</td>
<td>4.9 ± 1.5</td>
<td>4.3 ± 1.0</td>
<td>97.90%</td>
<td>10.70%</td>
<td>365 days</td>
<td>0.66%</td>
<td>1.40%</td>
</tr>
<tr>
<td>Faroux et al</td>
<td>Multi-center, non-randomized</td>
<td>&lt;45</td>
<td>300</td>
<td>47</td>
<td>77.8/-8.2</td>
<td>61.3</td>
<td>4.9/-1.5</td>
<td>4.0/-1.1</td>
<td>Not reported, but similar in both groups</td>
<td>Not reported, but similar in both groups</td>
<td>730 days</td>
<td>0.7 per 100 PY</td>
<td>9.8 per 100 PY</td>
</tr>
<tr>
<td><strong>Studies in end stage renal disease on hemodialysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genovesi et al</td>
<td>Multi-center, non-randomized</td>
<td>&lt;15</td>
<td>50</td>
<td>50</td>
<td>71.8 +/-9.6</td>
<td>76</td>
<td>4.0 +/-1.5</td>
<td>4.4 +/-0.9</td>
<td>100%</td>
<td>0</td>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Xipell et al</td>
<td>Single-center, non-randomized</td>
<td>&lt;15</td>
<td>8</td>
<td>8</td>
<td>67.5/-7.2</td>
<td>75</td>
<td>4.75/1.16</td>
<td>4.62/0.91</td>
<td>100%</td>
<td>0</td>
<td>427</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cruz-Gonzalez et al</td>
<td>Retrospective, non-randomized</td>
<td>&lt;15</td>
<td>14</td>
<td>14</td>
<td>69.21/11.5</td>
<td>71.4</td>
<td>4.5/1.45</td>
<td>5.0/0.96</td>
<td>100%</td>
<td>0</td>
<td>585</td>
<td>0</td>
<td>28.5 (n=4; 2 BARC 2 events and 2 BARC 3a events)</td>
</tr>
<tr>
<td>Torres Saura et al</td>
<td>Single-center, non-randomized</td>
<td>&lt;15</td>
<td>6</td>
<td>6</td>
<td>73.5/-14</td>
<td>66.6</td>
<td>4.2/-1.16</td>
<td>5.3/-0.81</td>
<td>100%</td>
<td>0</td>
<td>272</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Manes et al</td>
<td>Single-center, non-randomized</td>
<td>&lt;15</td>
<td>6</td>
<td>6</td>
<td>72.6/-5.5</td>
<td>Not noted</td>
<td>4.16/-2.13</td>
<td>5.8/-0.98</td>
<td>100%</td>
<td>0</td>
<td>420</td>
<td>0</td>
<td>Not measured</td>
</tr>
</tbody>
</table>
Table 2: Salient features of proposed trials on left atrial appendage closure (LAAC) in patients with end-stage renal disease (ESRD) and on dialysis. A search on ClinicalTrials.gov with the key-words [left atrial appendage closure/occlusion] and [chronic renal disease] yielded the above results.

VKA: Vitamin K antagonist
OAC: Oral anti-coagulants
eGFR: Estimated GFR

<table>
<thead>
<tr>
<th>Study</th>
<th>WatchAFIB</th>
<th>STOP-HARM</th>
<th>WATCH-HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Open, randomized, controlled, multicenter</td>
<td>Open, randomized, controlled, single-center</td>
<td>Observational, prospective</td>
</tr>
<tr>
<td>Focus population</td>
<td>CKD 4 -5 (eGFR &lt; 30 ml/min)</td>
<td>ESRD on dialysis &gt;90 days or eGFR &lt;30 ml/min/1.73m2 for &gt;90 days</td>
<td>ESRD on hemodialysis</td>
</tr>
<tr>
<td>Intervention</td>
<td>LAAC vs VKA</td>
<td>LAAC vs OAC</td>
<td>LAAC</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>&gt;= episode of moderate or major bleeding</td>
<td>Time from randomization to the first occurrence of major bleeding</td>
<td>Composite of all-cause mortality, stroke and bleeding</td>
</tr>
<tr>
<td>Follow up</td>
<td>24 months</td>
<td>5 years</td>
<td>24 months</td>
</tr>
<tr>
<td>Anticipated enrollment</td>
<td>300</td>
<td>23</td>
<td>150</td>
</tr>
<tr>
<td>Actual enrollment</td>
<td>14</td>
<td>0</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Anticipated completion date</td>
<td>June 2017</td>
<td>December 2021</td>
<td>March 2021</td>
</tr>
<tr>
<td>Status</td>
<td>Terminated</td>
<td>Terminated</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>

Figure 1: The two FDA approved left atrial appendage occlusion devices in the United States. On the left is the WATCHMAN FLX (Boston Scientific, Marlborough, MA, USA) and on the right, the Amplatzer Amulet (Abbott, Chicago, IL, USA).