Catheter Ablation for Atrial Fibrillation in Patients with Chronic Kidney Disease and on Dialysis: A Meta-Analysis and Review

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Keywords  
Catheter ablation · Dialysis · Chronic kidney disease · Atrial fibrillation

Abstract  
Background: Atrial fibrillation (AF) is common in chronic kidney disease (CKD) patients and is difficult to treat with antiarrhythmics and anticoagulants due to abnormal metabolism and increased side effects. Catheter ablation, if successful, may be a safer alternative. This review aimed to analyse the effect of CKD or haemodialysis (HD) on recurrence of AF after catheter ablation.  
Methods: MEDLINE, Embase, and PubMed databases were searched until December 2020. Two authors abstracted the data independently. Relative risks were derived using random-effects meta-analysis.  
Results: Of the initially identified 782 studies, 6 and 4 observational studies investigating CKD and HD patients, respectively reported AF recurrence rates. During a mean (SD) follow-up of 25.5 (9.8) months, CKD patients demonstrated a higher risk of AF recurrence compared to patients without CKD (RR 1.50, 95% CI: 0.84–2.67, \( p < 0.01 \)). The heterogeneity analysis showed the studies were heterogeneous (\( I^2 = 90.1\%, 95\% \text{ CI: 77.5–95.6\%}, p < 0.01 \)). In a mean (SD) follow-up of 32.6 (26.8) months, HD patients may be at a higher risk of AF recurrence compared to healthy non-dialysis AF patients (RR 1.50, 95% CI: 0.84–2.67, \( p = 0.17 \)). Heterogeneity analysis showed the studies were heterogeneous (\( I^2 = 90.1\%, 95\% \text{ CI: 77.5–95.6\%}, p < 0.01 \)).  
Conclusion: Our meta-analysis suggests patients with CKD and on HD are more likely to have AF recurrences compared to AF patients who do not have CKD. However, more robust evidence from randomized controlled trials comparing catheter ablation to pharmaceutical rhythm therapy is urgently needed to guide therapy in this difficult to treat population.

Introduction  
Atrial fibrillation (AF) is the most common arrhythmia in chronic kidney disease (CKD) patients [1]. The prevalence of AF increases with decreasing estimated glomerular filtration rate (eGFR), while AF also increases the risk of CKD [2, 3]. The presence of AF in CKD patients is associated with increased cardiovascular events such as stroke, heart failure, and death [4, 5]. The prevalence of AF is even higher in end-stage kidney failure patients on
dialysis, estimated at 15–40%. This group of patients suffer an even higher adverse events rate due to comorbidity with AF [6, 7].

Currently, the management of AF in CKD patients is challenging. It involves pharmacological rate or rhythm control, along with oral anticoagulants for stroke prevention. There is a wide disparity in the approach to treating AF in this population due to limited evidence for these treatments in the CKD population [8]. These agents have major side effects that are more prevalent in CKD patients. Anticoagulation in CKD patients with AF is associated with a higher risk of bleeding compared to the general population [9]. Data from studies in dialysis patients suggest little or no benefit with anticoagulation. The direct oral anticoagulants (DOACs) are associated with lower risk of bleeding in early CKD patients compared with warfarin, but data from advanced CKD and dialysis patients are lacking [10]. Rhythm control with pharmacological agents requires careful selection and dose adjustment to avoid toxicity if used long term, and their long-term benefits are controversial [11].

In the general population, rate and rhythm control methods are similar in reducing all-cause mortality [12]. In a systematic review, Chatterjee et al. [13] demonstrated that patients receiving rhythm strategy had higher rehospitalization rates compared to those receiving rate control, while patients below 65 years old benefit from reduced all-cause mortality by being on a rhythm control strategy. However, there are very few studies of AF treatment strategies conducted in CKD patients. Williams et al. [14] showed no significant survival difference between CKD patients treated with rhythm or rate control using pharmaceutical agents. Ullal et al. [15] demonstrated no additional mortality risk when using amiodarone in CKD.

In the general population, catheter ablation has been shown to be equal to anti-arrhythmic drug therapy in reducing rates of mortality, disabling strokes, serious bleeding, and cardiac arrest in a randomized control trial [16]. This is contrary to results from observational studies showing catheter ablation to be superior in reducing strokes and mortality [17]. Recently, a cohort study showed AF catheter ablation significantly reduces the risk of both ischaemic strokes and intracranial haemorrhages compared to medical therapy, regardless of whether sinus rhythm was maintained [18].

Previous meta-analyses have suggested that catheter ablation is viable in CKD and haemodialysis (HD) patients [19, 20]; however, as there has been some new studies on this topic [21, 22], a new meta-analysis is necessary. This systematic review analyses the up-to-date evidence on the risk ratio of AF recurrence after a single catheter ablation procedure in CKD and dialysis patients compared to non-CKD patients. In addition, it will explore the pathophysiology of AF in CKD patients as an understanding of this bidirectional relationship may highlight further avenues for treating AF in CKD.

**Methods**

This study was performed according to the guidelines of the Meta-analysis of Observational Studies in Epidemiology Group (MOOSE) [23]. The MOOSE checklist for meta-analysis of observational studies can be found in online supplementary Table S1 (see www.karger.com/doi/10.1159/000525388 for all online suppl. material).

**Study Selection**

Prospective or retrospective observational studies were selected with the aim to analyse the risk of recurrence of AF after catheter ablation in CKD and dialysis patients. Titles and abstracts were evaluated against the following inclusion criteria: (1) sample size >10 patients; (2) renal function evaluated at baseline; (3) follow-up >12 months; and (4) contains CKD stage 3–5 patients or patients on dialysis.

**Data Search**

Ovid MEDLINE, Embase, and PubMed databases were searched with the following search terms: (atrial fibrillation) AND (chronic kidney disease OR renal failure OR renal function OR dialysis) AND (ablation) for journal articles of any language until December 2020. This was supplemented by hand-searching through reference lists for additional relevant studies that fit the inclusion criteria.

Two blind investigators (I.C. and Y.K.) independently performed data extraction using a data extraction form to determine eligibility for inclusion. Risk of bias of individual studies was assessed using the National Institute of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [24].

**Definitions**

Since the definition of CKD varied amongst the studies found, we defined patients with an eGFR prior to catheter ablation <60 mL/min/1.73 m² (using MDRD or CKD-EPI equations) as CKD patients.

**Statistical Analysis**

To assess the relative risk of AF recurrence post-ablation, we calculated the relative risk of individual studies and combined them using random-effects meta-analysis. Relative risk was used as AF recurrence and was common in patients after catheter ablation. Heterogeneity was measured using the I² statistic. Statistical significance was defined at p value <0.05. Publication bias was evaluated using a funnel plot despite the small number of studies enrolled. All analyses were performed in RStudio using R and the package meta v4.13-0.
Results

782 records were identified by the primary literature search. Ninety-six records were identified as duplicates and excluded. A further 660 were identified as reviews, case reports, or unrelated to current analysis. Twenty-six remaining original publications were evaluated in detail, and 17 were excluded as they did not fulfil the inclusion criteria (Fig. 1). Among those 17, nine studies were excluded as they did not report AF recurrence according to CKD stages [25–33]. Two studies were excluded as they reported their AF recurrence along the eGFR cut-off of 68 mL/min/1.74 mm² [34, 35], and a further four studies were excluded as they had no baseline characteristics of patients with eGFR above or below 60 mL/min/1.74 mm² [36–39]. One study was excluded as their follow-up period was less than 1 year [40]. Lastly, an additional study was excluded as their study protocol included renal sympathetic nerve denervation in addition to catheter ablation for AF [41]. Nine studies were found to fulfil our inclusion criteria [21, 42–48]. Five of the studies were conducted in CKD populations [21, 42–44, 48] (Table 1), while the four others focused on HD patients [22, 45–47] (Table 2). The baseline characteristics of CKD and non-CKD patients are presented in Table 3, while HD and non-HD patients are reported on Table 4. Most of the studies were conducted in Japan [22, 42, 44–47] and tended to be retrospective, analysing data from existing databases or AF ablation registries [21, 22, 42, 44, 47, 48]. Most studies found selected patients with drug-refractory paroxysmal AF, except Navaravong et al. [48], Naruse et al. [44], and Takamiya et al. [22]. Navaravong did not specify the type of AF patients within their inclusion criteria, while Naruse specified paroxysmal or permanent AF patients with a history of drug treatment failure. Takamiya selected patients with paroxysmal AF; however, did not specify whether they failed anti-arrhythmic drug therapy. Takamiya reported their follow-up period as median (IQR); this was converted to mean (SD) to allow it to be comparable to the other studies [49]. The follow-up period ranged from 12.0 to 31.9 months for studies regarding CKD patients, while it ranged from 22.8 to 47.2 months for studies investigating HD patients. The methods used for measuring eGFR varied: 3 studies used the MDRD formula adjusted for Japanese people, 1 study used Cockcroft-Gault formula, and 1 study used the unadjusted MDRD formula. Tokuda was the only study where a proportion of patients (81.3%) with AF recurrence had undergone a repeat ablation procedure [42], while all other studies investigating CKD patients were single-ablation studies [21, 43, 44, 48]. Sairaku and Takamiya did not examine multiple ablations for patients with AF recurrence, while Takigawa et al. [46] and Hayashi et al. [45] both analysed the outcomes of multiple ablations for HD and non-HD patients. The quality assessment of studies involving CKD and HD patients are in online supplementary Tables S2 and S3, respectively.

In studies investigating CKD patients, the recurrence rates generally increased as follow-up time increased. Navaravong et al. [48] found that CKD stage 1 patients had
Table 1. Baseline characteristics of all patients in studies involving CKD patients undergoing catheter ablation

| Investigators | Chao | Deng | Naruse | Navaravong | Tokuda |
|---------------|------|------|--------|------------|--------|
| Location      | Taiwan | China | Japan | USA | Japan |
| Study design  | Prospective cohort | Retrospective cohort | Retrospective cohort | Retrospective cohort | Retrospective cohort |
| Year          | 2011 | 2019 | 2011 | 2015 | 2011 |
| Participants, n | 232 | 1,407 | 77.3 | 100 | 224 |
| Mean follow-up, months | 25.4±13.3 | 20.7±8.8 | 31.9±7.6 | 12 | 37.4±24.4 |
| Mean age, years | 53.4 | 57.3±11.5 | 59.2 | 57.5 | 55.3 |
| Paroxysmal AF, % | 100 | 77.3 | 3.2±1.2 | NA | 100 |
| Mean number of anti-arrhythmic drugs used | NA | NA | 5.8±5.4 (paroxysmal AF), 2.8±4.5 (persistent AF) | NA | 4.4±3.9 |
| Duration of AF, years | 4.1±3.9 | NA | 6.3±5.4 (paroxysmal AF), 8.6±4.5 (persistent AF) | NA | 1.8±0.8 |
| Male, % | 86 | 68.1 | 81 | 63.7 | 83.4 |
| BMI, kg/m² | 24.9±3.2 | 24.5±3.3 | 24.5±3.4 | NA | 24.1±2.5 |
| HTN, % | 35 | 36.1 | 57.9 | 60.7 | 25 |
| Diabetes, % | 6.3 | 10.2 | 8.6 | 16.3 | NA |
| LA diameter, mean, mm | 38.2±6.0 | 36.9±5.3 | NA | NA | 38.0±5.3 |
| LVEF, % | 59.9±8.0 | 64.7±6.1 | 64.1±10.1 | 57.6±10.2 | 67.0±6.6 |
| CAD, % | 15.5 | 7.5 | NA | 16.8 | NA |
| CHF, % | 5.0 | NA | NA | 9.0 | 13.8 |

AF, atrial fibrillation; BMI, body mass index; HTN, hypertension; LA, left atrial; LVEF, left ventricular ejection fraction; CAD, coronary artery disease; CHF, chronic heart failure. * Navaravong reported a 44.0% of persistent AF patients within their study population. † Naruse reported left atrial volume (mL) 65.6±27.2 within their study population. ‡ Naruse and Tokuda reported 10.4% and 15.1% of structural heart disease within their study population.

Table 2. Baseline characteristics of all patients in studies involving HD patients undergoing catheter ablation

| Investigators | Hayashi | Saiaraku | Takamiya | Takigawa |
|---------------|---------|----------|----------|----------|
| Location      | Japan | Japan | Japan | Japan |
| Study design  | Prospective cohort | Retrospective cohort | Retrospective cohort | Prospective cohort |
| Year          | 2014 | 2012 | 2020 | 2014 |
| Participants, n | 127 | 90 | 88 | 1,364 |
| Mean follow-up, months | 22.8 (HD), 34.5 (non-HD) | 29.3±7.8 | 22.3 (14.3–77.4) (CB-HD group), 47.2 (35.4–52.0) (RF-HD group), 26.7 (20.1–31.8) (CB-non-HD group) | 29.2±21.4 |
| Mean age, years | 59.2±9.8 | 64±10 | 64.3±10.0 | 61±10 |
| Paroxysmal AF, % | 77.2 | 100 | 100 | 100 |
| Duration of AF, years | NA | 4.5±4.5 | NA | 5.0±5.4 |
| Male, % | 78.0 | 56.7 | 58.0 | 76.8 |
| BMI, kg/m² | NA | 22.5±3.5 | 22.6±4.0 | 23.5±3.0 |
| Mean number of anti-arrhythmic drugs used | 1.53±0.78 | 1.7±1.2 | NA | 1.8±1.4 |
| HTN, % | 53.5 | 45.6 | 56.8 | 44.3 |
| Diabetes mellitus, % | 12.6 | 7.8 | NA | 10.6 |
| LA diameter, mean, mm | 40±7 | 38±5 | 37.0±7.7 | 37.7±5.1 |
| Structural heart disease, % | 0.0 | 13.3 | 0 | 17.0 |
| LVEF, % | 65.9±8.5 | 63.7 | 64.6±10.9 | 66.1±7.3 |
| CHADS2 score | 0.78±0.87 | NA | NA | 0.8±1.0 |

AF, atrial fibrillation; BMI, body mass index; LA, left atrial; LVEF, left ventricular ejection fraction. * Hayashi reported median follow-up times after first catheter ablation procedure. † Hayashi excluded patients with structural heart disease from the study.

an AF recurrence rate of 21.2% with 1-year follow-up. Naruse et al. [44] found 25% of CKD stage 1 patients to have AF recurrences with a mean follow-up period of 31.9 months. Recurrence rates also increased as patient kidney function decreased. Deng et al. [21] found AF recurrence rates post-ablation for CKD stage 1, 2, 3A, and 3B to be 11.5%, 39.3%, 72%, and 93.3%, respectively. This trend was also demonstrated by Tokuda (eGFR >60: 6.7%,
### Table 3. Baseline characteristics of CKD and control group in studies of catheter ablation in CKD patients

| Investigator | Chao | Deng | Naruse | Navaravong | Tokuda | Total | p value |
|--------------|------|------|--------|------------|--------|-------|---------|
| Group        | CKD  | Non-CKD | CKD  | Non-CKD | CKD  | Non-CKD | CKD  | Non-CKD | CKD  | Non-CKD | CKD vs. non-CKD |
| Participants, n | 36   | 196   | 115   | 1,292 | 54   | 167   | 76   | 316   | 29   | 195   | 310       |
| Mean age, years | 62.4±10.3 | 51.8±11.1 | 65.1±8.9 | 56.7±11.2 | 64.4±11.9 | 57.6±9.9 | 68.8±9.6 | 63.9±12.3 | NA   | NA   | 65.6±10.1 | 57.4±11.7 | <0.01 |
| Paroxysmal AF, % | 100  | 100   | 60.9   | 77.8  | 56.9  | 59.3  | NA   | NA   | NA   | NA   | 67.7   | 78.3     | <0.01 |
| Mean number of anti-arrhythmic drugs used | NA  | NA   | NA   | NA   | 3.4±1.2 | 3.2±1.3 | NA   | NA   | NA   | NA   | 3.4±1.2 | 3.2±1.3 | 0.66 |
| Duration of AF, years | 4.3±3.9 | 4.1±3.9 | NA   | NA   | NA   | NA   | NA   | NA   | 4.75±3.5 | 4.3±3.9 | 4.5±3.7 | 4.2±3.9 | 0.55 |
| Male, % | 55.6 | 75.5  | 57.1   | 73.6  | 78.2  | 82.7  | 60.1  | 78.8  | 72.9  | 58.2  | <0.01 |
| BMI, kg/m² | 22.9±3.0 | 25.3±3.1 | 24.7±4.0 | 24.2±3.2 | 24.1±3.4 | 24.6±3.3 | NA   | NA   | 23.8±2.9 | 24.1±2.4 | 24.2±3.6 | 24.6±3.1 | 0.11 |
| HTN, % | 55.6 | 31.6  | 55.7   | 34.4  | 72.2  | 53.3  | 75.4  | 57.4  | 27.6  | 24.6  | 61.4   | 38.1     | <0.01 |
| Diabetes mellitus, % | 11.1 | 5.6   | 15.7   | 9.7   | 7.4   | 9.0   | 25.7  | 14.0  | NA   | 16.4  | 9.5    | <0.01 |
| LA diameter, mean, mm | 40.3±5.0 | 37.8±6.2 | 38.1±5.5 | 38.8±5.3 | NA   | NA   | NA   | NA   | 38.4±4.9 | 37.6±5.3 | 38.6±5.4 | 37.0±5.4 | <0.01 |
| LVEF, % | 59.3±7.8 | 60.0±8.0 | 61.4±6.5 | 64.8±6.1 | NA   | NA   | NA   | NA   | 66.4±6.3 | 67.1±6.6 | 61.4±8.5 | 60.9±7.6 | 0.37 |
| CAD, % | 25   | 13.8  | 15.7   | 6.7   | NA   | NA   | 28.1  | 14.1  | NA   | 21.3  | 7.5    | <0.01 |
| CHF, % | NA   | NA   | 12.2   | 4.4   | NA   | NA   | NA   | NA   | NA   | NA   | 14.7   | 6.8     | <0.01 |

AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CHF, chronic heart failure; eGFR, estimated glomerular filtration rate; LA, left atrial; LVEF, left ventricular ejection fraction; HTN, hypertension. § Deng reported 80% and 84.1% in <60 eGFR and >60 eGFR groups, respectively, failed anti-arrhythmic drug therapy. * Naruse reported 16.7% and 8.4% of patients in <60 eGFR and >60 eGFR groups, respectively, have structural heart disease.

### Table 4. Baseline characteristics of HD and control group in studies of catheter ablation in HD patients

| Investigators | Hayashi | Sairaku | Takamiya | Takigawa | Total | p value |
|-------------|---------|---------|----------|----------|-------|---------|
| Status      | HD      | Non-HD  | HD       | Non-HD   | HD    | Non-HD  | HD    | Non-HD  | HD    | Non-HD  | HD vs. non-HD |
| Participants, n | 16     | 111     | 30       | 60       | 38    | 50     | 32    | 1,332   | 116   | 1,553   |
| Mean age, years | 63.8±7.4 | 58.6±10.0 | 65.8±8.9 | 64±11 | 67.8±6.7 | 62±11 | 67±7 | 61±11 | 64.7±7.8 | 61.0±11.0 | <0.01 |
| Paroxysmal AF, % | 93.8 | 74.8   | 100      | 100      | 100   | 100   | 100   | 100    | 100    | 99.1   | 98.5     | 0.70 |
| Duration of AF, years | NA   | NA     | 38±3.7   | 4.8±4.8  | NA    | 3.2±2.8 | 50±5.4 | 3.5±3.3 | 50±5.4 | <0.01 |
| Male, % | 75    | 78.4   | 57       | 57       | 55.3  | 60     | 68.8  | 77     | 62.2   | 75.8   | <0.01 |
| BMI, kg/m² | NA   | NA     | 20.5±2.6  | 23.5±3.5 | 22±4 | 23±4 | 20.4±2.2 | 23.6±3.0 | 21.0±3.2 | 23.6±3.1 | <0.01 |
| Mean number of anti-arrhythmic drugs used | 1.25±0.93 | 1.57±0.75 | 1.4±1.0 | 1.9±1.3 | NA   | NA   | 1.7±1.6 | 1.8±1.4 | 1.5±1.3 | 1.8±1.4 | 0.05 |
| HTN, % | 56.3 | 53.2   | 60       | 38       | 68.4  | 48    | 71.9  | 43.6   | 65.5   | 44.2   | <0.01 |
| Diabetes mellitus, % | 43.8 | 8.1    | 10       | 7        | NA    | NA    | 15.6  | 10.4   | 19.2   | 10.1   | 0.01 |
| LA diameter, mean, mm | 45.6±4.0 | 39.2±6.8 | 40.5±5.5 | 37±5    | 41±8  | 34±8  | 43.1±5.3 | 37.6±5.0 | 42.0±6.3 | 37.6±5.3 | <0.01 |
| Structural heart disease, % | NA² | NA²   | 17       | 12      | NA    | NA    | 46.9  | 16.3   | 32.4   | 10.1   | <0.01 |
| LVEF, % | 63±9.2 | 66.7±8.3 | 62±8    | 63±6    | 62±13 | 67±8  | 63.0±10.1 | 66.2±7.3 | 62.4±10.5 | 66.1±7.4 | <0.01 |
| CHADS2 score | 1.25±0.93 | 0.73±0.83 | NA   | NA   | NA   | NA    | 1.2±0.9 | 0.8±1.0 | 1.2±0.9 | 0.8±1.0 | <0.01 |

AF, atrial fibrillation; BMI, body mass index; HTN, hypertension; LA, left atrial; LVEF, left ventricular ejection fraction; CHF, chronic heart failure. § Hayashi reported their HD and non-HD patient groups had 25% and 6.3% with coronary artery disease, respectively.

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eGFR <60: 24.3%) [42] and Chao (eGFR ≥90: 6.9%, 90 > eGFR ≥ 60: 14.5%, eGFR <60: 38.9%) [43].

Meta-analysis of studies with CKD patients: the meta-analysis of these studies showed patients with CKD had a significant risk of AF recurrence after catheter ablation (RR 2.34; 95% CI: 1.36–4.02, p < 0.01) (Fig. 2). The heterogeneity test showed that there were significant differences between individual studies ($I^2 = 91\%, 95\% \text{ CI: 82.2–95.6\%}$). Sensitivity analysis was done to detect the origin of the heterogeneity, which was visualized using a baujat plot (Fig. 3). After removing Navaravong et al. [48], heterogeneity remained significant ($I^2 = 83\%, 95\% \text{ CI: 55.6–93.2\%}$). The overall risk ratio remained similar (RR 2.82, 95% CI: 1.80–4.42, p < 0.01).

**Fig. 2.** Risk ratio of AF recurrence post-ablation in CKD patients compared to the general population. eGFR, estimated glomerular filtration rate.

**Fig. 3.** Baujat plot of studies with CKD patients.
Publication bias was evaluated via a funnel plot (Fig. 4). The funnel plot showed no publication bias, although it is difficult to interpret due to the small number of studies evaluated by this meta-analysis.

HD patients have AF recurrences far earlier in follow-up compared with the general population after catheter ablation. Takigawa et al. [46] showed at 5-year follow-up, 19.7% of HD patients remained AF-free compared to a 61.7% AF-free survival rate in non-HD patients. Sairaku et al. [47] showed similar results with 54% HD patients remaining free from AF recurrences compared to 78% of non-HD patients after mean 821 ± 218 days. Hayashi et al. [45] showed that, after the single-ablation procedure, 25% of HD patients remained AF-free, while 59% of non-HD patients remained AF-free. The study also conducted multiple-ablation procedures and showed 81.3% of HD patients and 82.9% of non-HD patients were free of atrial arrhythmias after multiple-ablation procedures at 5-year follow-up. Takamiya et al. [22] showed 50% of HD patients undergoing either cryoballoon or radiofrequency ablation remained AF-free within the follow-up period of 41.1 ± 38.1 months compared to 86% of non-HD patients within a follow-up period of 32.6 ± 26.7 months.
Meta-analysis of studies with HD patients: the meta-analysis of studies investigating HD patients suggested that HD patients suffered a greater risk of AF recurrence post-ablation; however, the overall result did not reach statistical significance (RR 1.50, 95% CI: 0.84–2.67, \( p = 0.17 \)) (Fig. 5). Heterogeneity analysis showed that the studies were heterogeneous (\( I^2 = 90.1\% , \) 95% CI: 77.5–95.6%, \( p < 0.01 \)). A Baujat plot was plotted to locate the source of heterogenicity (Fig. 6). After removing Sairaku et al. [47], there remained significant heterogeneity across the studies (\( I^2 = 79.0\% , \) \( p < 0.01 \)). Similarly, a funnel plot was also completed to show publication bias (Fig. 7). No conclusions were drawn on publication bias as the funnel plot was difficult to interpret due to the low numbers of HD studies included in this meta-analysis.

Discussion

This meta-analysis demonstrates that CKD patients are significantly more likely to have AF recurrence post catheter ablation than those without CKD. There is a stepwise increase in risk for AF recurrence after ablation as eGFR decreases [44, 48]. Deng et al. [21] showed that eGFR <82.5 mL/min/1.74 mm² is a significant risk factor for AF recurrence after ablation (HR 1.79, 95% CI: 1.54–2.08, \( p < 0.01 \)). Chao et al. [43] also showed that patients with lower renal functions have a higher risk of AF recurrence after catheter ablation (HR 2.09, 95% CI: 1.16–3.77, \( p = 0.014 \)). Tokuda et al. [42] demonstrated that patients with eGFR <60 mL/min/1.74 mm² suffered an increased risk of AF recurrence even after repeated catheter ablation (HR 4.4, 95% CI: 1.2–6.0, \( p < 0.01 \)). Both Hayashi et al. [45] and Tokuda et al. [42] have shown that multiple-ablation procedures increase the proportion of patients in sinus rhythm in follow-up. However, the studies were heterogeneous and small; more studies with larger sample size are necessary to confirm whether repeated abla-
Catheter Ablation for AF in CKD and HD Patients

In the general population, studies with repeated AF ablation procedures report a higher procedure success rate compared with studies analysing single-AF ablation [55]. This is similar to the result shown by Tokuda and Hayashi, where a higher proportion of patients remained in sinus rhythm after multiple-ablation procedures [55].

There is no study in CKD patients comparing catheter ablation and pharmaceutical drug therapy. However, drug therapy for rate and rhythm control has potential disadvantages, including clearance and side effects, in contrast to the “relatively safe,” single time-point, catheter ablation procedure [11]. Catheter ablation may potentially provide additional survival benefit, regardless of the success in maintaining sinus rhythm in the case of patients with heart failure [56]. Furthermore, there is evidence to suggest that patients who underwent catheter ablation have reduced symptom frequency and severity and a better quality of life, when compared to patients on anti-arrhythmic drug therapy, even in patients who have AF recurrences during follow-up [57–59].

Fig. 7. Funnel plot of studies with HD patients.

In the general population, patients with CKD and HD have larger LA diameters when compared to controls in this meta-analysis. A larger LA diameter has been shown to be associated with higher rates of AF recurrence after catheter ablation in both CKD and HD patients [21, 22, 43, 44, 46]. This is similar to what was in the general population, where LA diameter is a risk factor for AF and associated with increase AF recurrence after catheter ablation [21, 42–47].

Furthermore, some studies saw minor improvements in eGFR following AF ablation [30, 33, 48, 52]. Catheter ablation has also been shown to be safe for CKD patients in a large retrospective study, with the most common side effect being vascular complications such as haemorrhage or haematoma formation [28]. As anticoagulants and anti-arrhythmics have their respective drawbacks [53, 54], especially within CKD and HD population, ablation is a possible alternative treatment for AF. Most studies [21, 42–47] evaluated in this meta-analysis recruited patients with drug-refractory AF, and this may have contributed to the high occurrence rate found in this meta-analysis.

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CKD and AF are inextricably linked by multiple pathophysiological mechanisms. These mechanisms differ from AF pathophysiology in the general population. Consideration of these alternative mechanisms and non-traditional risk factors may provide new avenues of research for treatment to prevent and manage AF in this particularly vulnerable group of patients.

Pathophysiology of AF in CKD Patients

Several mechanisms thought to connect CKD and AF are outlined in Figure 8. Relevant studies are summarized in Tables 5–7.

Inflammation

CKD is associated with low-grade inflammation, with higher interleukin-6 and C-reactive protein levels compared to healthy controls [60, 61]. Inflammation in turn contributes to the development of AF [62, 63]. High-sensitivity C-reactive protein, soluble intercellular adhesion molecule-1, and fibrinogen are significantly associated with increased risk of AF after controlling for traditional risk factors [64]. TNF-α, a proinflammatory cytokine, has been shown to alter calcium handling within the pulmonary vein (PV) cardiomyocytes, inducing arrhythmogenic activity in PV cardiomyocytes [65]. In addition, low-dose methylprednisolone for 4 weeks has been shown to reduce AF incidence compared to the placebo, suggesting suppression of inflammation reduces AF incidence [66]. These data are summarized in Table 5.

High Renin-Angiotensin-Aldosterone System Activity

CKD patients have been shown to have inappropriately high renin-angiotensin-aldosterone system (RAAS) activity (Table 6) [67]. The RAAS molecules act as inflammatory signalling molecules [68]. RAAS stimulates cell adhesion molecules and upregulates inflammatory cytokines such as interleukin-6 [69, 70]. In addition to contributing to inflammation, RAAS has been shown to result in atrial enlargement and fibrosis in transgenic mice with overexpression of angiotensin-converting enzyme...
Catheter Ablation for AF in CKD and HD
Patients

Although the mechanism by which RAAS contributes to atrial fibrosis is not known, Goette et al. [72] suggest that RAAS may contribute to atrial fibrosis via an increase in the amounts of activated Erk1/Erk2 in the atrial interstitial cells. A more recent study using transgenic mice suggested that cadherin 11 contributes to atrial fibrosis through stimulation of Smad2/4, ERK1/2, and JNK pathway [73]. Furthermore, animal studies have shown ACE inhibitors, such as enalapril and cilazapril, to reduce the atrial fibrosis and AF incidence [74, 75]. Patients with chronic AF have been shown to have reduced atrial fibrosis with ACE inhibitor therapy [76]. ACE inhibitors have also been shown to reduce AF incidence, although this is limited to patients with left ventricular dysfunction [77].

Angiotensin II has been shown to activate Rac1 and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, causing an up-regulation of connexin43, N-cadherin, and interstitial fibrosis, ultimately leading to atrial remodelling [78]. An animal model has also shown in-

| Year | Author | Study type/models | Methods | Findings | Reference |
|------|--------|-------------------|---------|----------|-----------|
| 2001 | Chung MK | Case-control study | AF versus non-AF patients | There is a stepwise increase in CRP elevation with higher AF burden, suggesting inflammation promotes AF persistence. | [43] |
| 2004 | Dernellis J | Prospective cohort study | Patients with persistent AF | CRP concentration is a risk factor for AF. Administration of low-dose methylprednisolone reduces AF incidence. | [46] |
| 2004 | Landray MJ | Cross-section analysis | Group of patients with serum creatinine >1.47 mg/dL versus 2 age- and sex-matched control groups | CKD is associated with low-grade inflammation, demonstrated by higher CRP and fibrinogen concentrations when compared to controls. | [40] |
| 2010 | Conen D | Prospective cohort study | Female healthy health professionals in the USA aged 45 years or older randomized to receive both aspirin and vitamin E every other day or placebo | Higher CRP, soluble ICAM-1, and fibrinogen are associated with AF after 14.4 years follow-up | [44] |
| 2012 | Gupta J | Cross-section analysis | Age-based eGFR inclusion criteria | Inflammatory markers, such as IL-6, TNF-α, CRP, and fibrinogen is higher in patients with lower eGFR and higher urine ACR | [41] |
| 2016 | He G | Cross-section analysis | Patients with rheumatic mitral stenosis undergoing valve replacement | Infiltration of macrophages and over-activation of NLRP3 inflammasome may play a role in atrial inflammation in patients with AF. | [68] |
| 2018 | Yao C | Cross-section analysis | Enhanced cardiomyocyte NLRP3 inflammasome signalling promotes AF | Right atrial appendages of patients undergoing open-heart surgery for coronary bypass grafting and/or valve replacement | Cardiomyocytes NLRP3 inflammasome contributes to pathogenesis of AF. Transgenic mice with constitutively active NLRP3 displayed ectopic activity, abnormal sarcoplasmic-reticulum Ca2+-release, AERP shortening, and atrial hypertrophy. | [66] |
| 2019 | Guo Y | Cross-section analysis | eGFR < 60 and/or proteinuria versus eGFR >60 without proteinuria | Raised CRP is a risk factor for AF in CKD populations. | [42] |

AF, atrial fibrillation; Ca2+, calcium; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ICAM-1, intercellular adhesion molecule-1; IL-6, interleukin-6; NLRP3, nucleotide-binding oligomerization domain 3; PV, pulmonary vein; TGF β1, transforming growth factor beta 1; TNF-α, tumour necrosis factor-alpha; urine ACR, urine-albumin-to-creatinine ratio.

Table 5. Studies showing inflammation as a mechanism to increase incidence of AF
creased NADPH oxidase atrial fibrosis in post-nephrectomy rats, suggesting that oxidative stress may link CKD and AF [79]. In addition, the authors found a potent antioxidant, sodium zinc dihydrolipoylhistidinate, that attenuates atrial fibrosis caused by nephrectomy in rats. This suggests both RAAS and CKD cause additional oxidative stress which increase atrial remodelling, increasing the risk of aberrant atrial currents forming. However, it is not yet known whether the atrial remodelling described above causes gap junction changes, affecting atrial cardiomyocytes’ cell-to-cell electrical coupling [80].

Both RAAS and CKD have been shown to increase transforming growth factor beta 1 (TGF-β1) levels [81–83]. Overexpression of TGF-β1 has been shown to result in selective fibrosis, causing increased conduction heterogeneity and AF vulnerability in transgenic mice [84]. In post-nephrectomy rats, CKD induced severe atrial interstitial fibrosis via the TGF-β1 pathway, causing increased AF inducible rates and AF duration [85]. Pirfenidone, an anti-fibrotic drug that works by interfering with the TGF-β1 pathway, has also been shown to reduce cardiac fibrosis in animal models [86], further implicating the TGF-β1 pathway in the pathogenesis of atrial fibrosis.

**Uraemic Toxins**
Recent studies have demonstrated the role of uraemic toxins as a novel cardiovascular risk factor for patients in CKD (Table 7) [87]. In rabbits treated with uraemic toxin...
indoxyl sulphate (IS), there was higher AF occurrence and longer AF duration in the LA compared to healthy rabbits [88]. This effect was attenuated with administration of the antioxidant ascorbic acid, suggesting that IS contributes to AF occurrence via oxidative stress. Aoki et al. [89] showed that not only were IS levels increased in post-nephrectomy rats but also it increases atrial interstitial fibrosis and AF inducibility. Atrial fibrosis and AF inducibility were shown to be reduced with AST-120, a therapeutic agent commonly used as an absorbent of uraemic toxins.

Abnormal Calcium Handling

Abnormal calcium handling has also been shown to contribute to AF pathophysiology [93, 94]. Patients with CKD have altered bone and calcium metabolism. Concentration of fibroblast growth factor 23 is higher in CKD patients, which has shown to be associated with incident AF, highlighting an additional link between CKD and AF [95]. Furthermore, increased serum calcium and phosphate in renal disease are thought to predispose patients to valvular heart disease such as aortic valve calcifications [96]. These valvular diseases may contribute to AF development via pressure overload. In rabbits induced to CKD, significant calcium homoeostasis abnormalities were found within the PV cardiomyocytes with the activation of protein kinase A and

| Year | Author | Study subjects | Findings | Reference |
|------|--------|----------------|----------|-----------|
| 2015 | Aoki K | 5/6 nephrectomy Sprague-Dawley rats | IS induces atrial fibrosis by upregulating makers of oxidative stress, inflammation, and profibrotic factors. | [65] |
| 2017 | Chin LH | Partial nephrectomy on mice | Uraemic toxins upregulates NLRP3 inflammasome, IL-1β, IL-18 axis, leading to cardiac contractile dysfunction | [67] |
| 2004 | Verheule S | Cardiac overexpression of TGF β1 in transgenic Mice | Increased TGF β1 expression increases atrial interstitial fibrosis. Atrial fibrosis, caused by increased TGF β1, is sufficient to increase AF inducibility. | [53] |
| 2006 | Lee KW | CHF induced by rapid right ventricular pacing for 3 weeks in Mongrel dogs | Treatment with pirfenidone reduces atrial fibrosis and AF vulnerability by suppressing TGF β1 expression | [55] |
| 2018 | Qiu H | 5/6 nephrectomy in Sprague-Dawley rats | CKD induces severe interstitial fibrosis via activation of the TGF β1 pathway and induced an inflammatory cascade by maturing the NLRP3 inflammasome. | [54] |

**Calcium handling**

| Year | Author | Study subjects | Findings | Reference |
|------|--------|----------------|----------|-----------|
| 2014 | Mathew JS | Prospective cohort study in patients 45–84 years of age with no baseline cardiovascular disease | Higher serum FGF-23 associated with incident AF | [60] |
| 2017 | Huang S | Neomycin and cefazolin every other day for 4 weeks to induce CKD in rabbits | CKD causes PV cardiomyocytes to have calcium-handling abnormalities via protein kinase A and reactive oxygen species | [62] |

**Oxidative stress**

| Year | Author | Study subjects | Findings | Reference |
|------|--------|----------------|----------|-----------|
| 2012 | Fukunaga N | 5/6 nephrectomy in Sprague-Dawley rats | There is an increase in atrial fibrosis and slowing of interatrial conduction in nephrectomy rats. These changes were partially reversible with administration of sodium DHLHZn, an antioxidant agent. | [56] |

AF, atrial fibrillation; CKD, chronic kidney disease; FGF-23, fibroblast growth factor 23; IL-1B, interleukin 1 beta; IL-18, interleukin 18; NLRP3, nucleotide-binding oligomerization domain 3; PV, pulmonary vein; DHLHZn, zinc dihydrolipoamidehistidinate.
reactive oxygen species, suggesting that CKD increases PV arrhythmogenesis by altering calcium homeostasis in PV [97].

Management of AF in CKD

Management of AF involves a choice of rate or rhythm control with or without anticoagulation. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines state the indications for rate control over rhythm control in CKD patients are similar to the general population [11]. Patients who are older with more comorbidities should be managed with rate control. Rate control also uses more familiar agents that are already used clinically for blood pressure control in CKD patients [98].

Rhythm control should be considered for patients who are younger, symptomatic, or who have fewer comorbidities. There are 3 options for rhythm control: direct current cardioversion, anti-arrhythmic drugs, or catheter ablation. As the risk of AF recurrence increases as eGFR decreases, direct current cardioversion is often not sufficient alone to maintain sinus rhythm [99]. The choice of anti-arrhythmic is often difficult due to the high prevalence of structural heart disease within the CKD population and reduced renal clearance of the drug in CKD patients. Amiodarone has been shown to be safe to use regardless of eGFR and does not appear to negatively affect survival [15]. However, it is unknown whether CKD patients treated with amiodarone have a higher risk of side effects or organ toxicity. Catheter ablation appears to be a safe procedure for patients regardless of eGFR [28]. Although, as this review shows, CKD and HD patients do indeed have a higher risk of recurrence compared to the general population, there is potential for increased quality of life and survival benefit for selected groups of patients [57–59].

Anticoagulation is used to reduce the risk of thromboembolic events in patients with AF. Although the CHA2DS2-VASc score does not have a specific renal component, observational data have shown that a treatment threshold of ≥2 is associated with benefit in CKD cohorts [100]. The use of CHA2DS2-VASc is more difficult within ESRD patients. Observational studies within this population have shown the predictive ability is similar to the general population for stroke [101, 102]. However, when in-hospital death was included as a competing risk, the predictive performance of CHA2DS2-VASc was diminished in ESRD patients [103]. Hence, the use of oral anticoagulation (OAC) needs to be carefully weighed for individual ESRD patients. To assess for bleeding risk, the HAS-BLED score is generally used. KDIGO recommends HAS-BLED should be used during the clinical decision-making process of using OAC. There have also been several studies showing it is useful in predicting major bleeding events in patients on dialysis [104, 105].

For anticoagulation, there is a choice between DOACs and warfarin. Recent landmark clinical trials of DOACs showed that dabigatran (RE-LY) [106], rivaroxaban (ROCKET AF) [107], apixaban (ARISTOTLE) [108], and edoxaban (ENGAGE AF_TIMI 48) [109] are safe and similar in efficacy when compared to warfarin in patients with moderate renal impairment. These trials excluded patients with creatinine clearance of <30 mL/min, whereas in ARISTOTLE, the cut-off was <25 mL/min. It is important to note that renal function was estimated using the Cockcroft-Gault criteria in these randomized control trials; therefore, the Cockcroft-Gault formula should be used in considering DOACs for these patients. There are no randomized control trial data on the use of DOACs in patients with CrCl of <25–30 mL/min.

The use of warfarin or DOACs in ESRD is controversial. Previous meta-analyses have shown that warfarin use in ESRD patients is not associated with a statistically significant reduction in stroke amongst patients with ESRD and AF [110, 111]. A retrospective analysis showed that off-label use of dabigatran or rivaroxaban in patients on dialysis was associated with a higher risk of hospitalization or death from bleeding than with the use of warfarin [112]. Due to the lack of data, the decision of whether to use anticoagulation should be approach in a case-by-case basis, weighing the benefits and risks of anticoagulation for an individual ESRD patient.

Limitations

A number of limitations to this meta-analysis must be considered. Firstly, it was composed solely of observational studies with differing protocols and heterogeneity in outcomes. The conclusions drawn from this meta-analysis are also limited by the small number of included studies and the relatively small sample sizes. Subgroup analysis stratified by CKD stages was not performed as only a small number of included studies found. This will be vital in future studies as CKD management is dependent on CKD stage. Within this meta-analysis, we defined eGFR <60 mL/min/1.73 m² as CKD, even though it is not diagnostic of CKD and has its limitations. Due to the lack of detailed data from the included studies, we were also unable to perform multivariate regression to adjust for other risk factors such as valvular disease or ischaemic heart disease, which are well represented within the CKD population. In addition, all the studies regarding catheter ablation in HD patients were performed in Japan, limiting external validity.
Conclusion

This meta-analysis showed that CKD patients are significantly more likely to have AF recurrence after single catheter ablation therapy. The study found that HD patients have a higher risk of AF recurrence compared to the general population, although the results were not statistically significant. Pharmacological management of AF has limited efficacy and significant safety concerns in CKD. Catheter ablation is a potential treatment option for this group, but current evidence is sparse and composed of mainly of heterogeneous observational studies. There is a need for a randomized control trial with a suitable follow-up time, such as 2 years, to compare catheter ablation therapy with use of anti-arrhythmic drugs and anticoagulation in this group. This longer follow-up time would allow comparison of the efficacy, safety, and adverse effects of catheter ablation versus long-term rate or rhythm control. Determining whether catheter ablation therapy is a safer and more effective for AF in the CKD and HD patient group may better inform clinical decision-making for managing these challenging patients. Moreover, consideration of the varying pathophysiological mechanisms of AF in CKD may facilitate alternative pathways for treatment in this group.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

Debasish Banerjee has received speaker fees from AstraZeneca, Pfizer, ViforPharma. The other authors declare they have no competing interest.

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Author Contributions

Isaac Chung and Yasir Khan completed the literature search for the systematic review. The manuscript was written by authors Isaac Chung and Hilary Warrens. The study was supervised by authors Rao Kondapally Seshasai, Manav Sohal, and Debasish Banerjee.

Data Availability Statement

The data for the study are available on request.

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