

Should Oral Anticoagulation be used in ESKD Patients on Hemodialysis with Atrial Fibrillation? PRO

Subodh R. Devabhaktuni¹ and John P. Mounsey¹

1. University of Arkansas Medical Sciences

Corresponding author:

John P Mounsey, MD PhD

University of Arkansas for Medical Sciences

#532, 4301 W Markham St, Little Rock, AR 72205

Email: jpmounsey@UAMS.edu

Voice: 501 296 1401

Fax: 501 686 6439

Defining the magnitude of the problem:

Atrial fibrillation (AF) is the commonest cause of stroke, and is a frequent comorbidity in patients with end stage kidney disease (ESKD) affecting as many as 1 in 5 patients (1). Prevalence is 19.6% and 14.1% in patients on hemodialysis (HD) and peritoneal dialysis (PD) (2) and increases with age from 5.5% in age group 22 to 44 years, 24.6% between 65 and 74 years and 33.2% in patients >74 years (3). Chronic kidney disease (CKD) is associated with an increased risk of ischemic stroke in patients with AF independent of traditional risk factors for stroke, even in non-dialysis patients (4,5). Compared with white patients, black, Hispanic, or Asian patients with ESKD are more likely to experience stroke (13%, 15%, and 16% more, respectively), and this is related to low warfarin prescription fill (6). The risk of ischemic stroke is much higher than the risk of hemorrhagic stroke in ESKD patients (21.1 vs. 4.7 per 1,000 patient years (7), and incident AF is associated with increased mortality in ESKD patients (8). Therefore, oral anticoagulation plays a key role in management of these patients. In this article, we propose that OAC is beneficial in patients with AF and ESKD and go over the evidence supporting it.

Mitigating the stroke risk in AF and ESKD patients:

ESKD by itself is a prothrombotic state even in the absence of AF. Patients with kidney disease have an increased level and/or activity of numerous pro-inflammatory and pro-coagulant factors such as C-reactive protein, cystatin C, interleukin 6, fibrinogen, factor VII, VIII, IX-XII, tumor necrosis factor α soluble receptor-1, intracellular adhesion molecule-1, von- Willebrand factor, plasminogen activator inhibitor-1, homocysteine, thromboplastin, and fibrinopeptide. There is also a decreased level of protein C, an anticoagulant(2,3).

If AF and stroke are each commoner in kidney failure patients, and kidney failure itself is prothrombotic, it would be logical that anticoagulation in AF would be associated with a reduction in stroke risk. Traditionally, warfarin has been the mainstay for anticoagulation in kidney failure patients, but more recently, on the basis of pharmacokinetic considerations, apixaban and rivaroxaban have been labelled for use at all stages of kidney failure. But only apixaban has been studied for efficacy so we will confine ourselves to consideration of the evidence for warfarin and apixaban.

It should be noted that there are no good prospective randomized trials available. Patient management is guided by retrospective analyses and meta-analyses.

Role of Warfarin:

Several studies showed the benefit of warfarin in these patients. In a large Danish registry, warfarin treatment was associated with reduced risk of stroke and thromboembolism (4). In this study, ESKD was associated with an increased risk of stroke/systemic embolism and bleeding among patients with atrial fibrillation. Warfarin treatment decreased risk of stroke/systemic embolism with no increase in bleeding. In another study by Bonde et al., in patients with ESKD on dialysis with CHA₂DS₂-VASc score ≥ 2 , warfarin was associated with lower risk of all-cause death (5). Similar trends in mortality were noted in CKD patients in low and intermediate risk patients [HR 0.62 (0.49-0.79)]. Shen et al., showed that warfarin use was associated with a reduced risk of ischemic stroke, and there was a signal towards reduced mortality in as-treated analyses (6). In a meta-analysis of 12 prospective or retrospective cohort studies, treatment with warfarin was associated with a nonsignificant 26% reduction of the risk of ischemic stroke and also non-significant increase in bleeding (7). Another study by Kai et al. warfarin use was associated with lower all-cause mortality and ischemic stroke, without significantly increasing

the risk of bleeding in hemodialysis patients with atrial fibrillation (8). Summary of studies demonstrating net clinical benefit of anticoagulating with warfarin are listed in Table 1.

Role of Direct Oral Anticoagulants (DOACs):

Apixaban is the only DOAC approved by FDA for use on ESKD patients that has been studied for efficacy (9,10). In a study by Wang et al., ESKD resulted in a modest increase (36%) in apixaban AUC and no increase in Cmax, and hemodialysis had a limited impact on apixaban clearance(9). In a large meta analysis of around 71000 patients by Kuno et al., all cause mortality was lower in apixaban group compared to no OAC group. There was no difference in stroke rates, however there was significant heterogeneity in this analysis as noted the paper. Also, only 2 studies of patients taking DOACs were included in this analysis. In another large study by Siontis et al.; apixaban was associated with significant reduction in death, stroke and major bleeding when compared to warfarin. In another study, comparing apixaban with no OAC, apixaban use was associated with lower all-cause mortality rates compared with no anticoagulation (HR, 0.58; 95% CI, 0.43 to 0.78). Similarly, apixaban use was associated with lower incidence of the composite outcome of all-cause mortality or stroke or systemic thromboembolism compared with no treatment (HR, 0.56; 95% CI, 0.41 to 0.76) (11).Table 2 lists the studies demonstrating clinical benefit of anticoagulating with apixaban.

Evidence supporting the role of OAC comes from observational and meta analysis of these studies. But evidence pointing against the role of OAC also comes from observational studies and meta analyses (11–14). It should be noted that these meta analyses too were limited by study heterogeneity including

the inability to account for a number of important confounders such as the time in the therapeutic range (12). As said before, some studies support this idea(4–6,8) others do not (11–14). So why is it that anticoagulants are not universally beneficial in this cohort of patients? Several possibilities exist. Uremia is associated with an elevated risk of bleeding, and hemodialysis patients routinely receive heparin during dialysis. Taken together this elevation of bleeding risk may offset the potential benefit of anticoagulation. Uremia complicates regulation of the INR in warfarin patients because of dysregulation of hepatic cytochrome P450, the main pathway for warfarin metabolism, in kidney failure (15). Uremia is associated with a vasculopathy and this may in itself elevate stroke risk independent of any mitigation by anticoagulation(16).

High quality evidence in terms of randomized clinical trials are lacking. The RENAL-AF, presented at American Heart Association annual scientific sessions in November 2019, randomized patients to apixaban 5 mg twice daily or 2.5 mg twice daily in select patients versus warfarin with an international normalized ratio of 2–3. The primary outcome of the study, clinically relevant non major bleed, for apixaban vs. warfarin was: 31.5% vs. 25.5% ($p > 0.05$). Secondary outcomes were- intracranial bleeding: 1.2% vs. 1.4%; gastrointestinal bleeding: 2.4% vs. 8.3%; International Society on Thrombosis and Haemostasis (ISTH) major bleed: 8.5% vs. 9.7%; stroke: 2.4% vs. 2.8%, cardiovascular death: 11% vs. 5.6%. Importantly this trial was stopped early due to loss of funding and it is unclear if bleeding outcomes would have been better with lower dose of 2.5mg and without aspirin use (~ 40% usage).

In summary, we think OAC is indicated in these patients based on the data presented in this article with studies showing reduction in stroke and more importantly reduction in all cause mortality. Clinical

trials such as AXADIA study (NCT02933697) and SAFE HD (NCT03987711) study are underway. AXADIA (Compare Apixaban and Vitamin-K Antagonists in Patients with Atrial Fibrillation and End-Stage Kidney Disease), will randomize patients to apixaban 2.5 mg twice daily versus warfarin. Strategies for the Management of Atrial Fibrillation in Patients Receiving Hemodialysis (SAFE HD trial), will randomize patients to warfarin, apixaban, and no anticoagulation. Hopefully these trials will guide us on this highly debated topic. We are well aware that the major hurdle is to balance risk of stroke and bleeding in this patient population. A potential therapeutic option could be the left atrial appendage closure techniques. Clinical trials (NCT03446794) in this realm are underway. We believe that these studies will lend a promising solution to this clinical conundrum.

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Table 1

Clinical studies of ESKD patients with AF treated with warfarin with net benefit

Study	Type of study and no. of patients with ESKD and AF	Outcomes results Warfarin vs no warfarin	Comments
Lai et al. 2009(17)	Retrospective 93	Stroke- 10% vs 38%; p<0.005 Bleeding-14% vs 9%; p- NS	ESKD patients with AF treated with warfarin had significant reduction in thromboembolic stroke and an insignificant increase in major bleeding. Same results were noted in ESKD patients.
Olesen et al. 2012(4)	Retrospective 901	S/SE**-0.44; 95% CI, 0.26-0.74; p- 0.002 Bleeding-1.27 (0.91– 1.77); p=0.15	ESKD was associated with an increased risk of S/SE and bleeding among patients with atrial fibrillation. Warfarin treatment was associated with a decreased risk of S/SE with no increase in bleeding
Bonde et al. 2014(5)	Retrospective 1142	All cause death* HR- 0.85, 95% CI: 0.72 to 0.99 S/SE- 4.8 vs 7.3 per 100 person years	Warfarin was associated with decrease in all cause mortality in high risk patients
Shen et al. 2015(6)	Retrospective 12284 with new AF	Ischemic stroke- HR- 0.68; 95% CI, 0.47-0.99. All-cause mortality- 1.01 (0.92-1.11) Hemorrhagic stroke- 0.82 (0.37-1.81) GI bleeding- 1.00 (0.69-1.44)	In addition, as treated analysis showed all-cause mortality was significantly lower for warfarin users (HR, 0.84; 95% CI, 0.73-0.97).
Van Der Meersch et al. 2017(7)	Meta-analysis 17380	Ischemic stroke-0.74, 95% CI- 0.51-1.06 Bleeding-1.21, 95% CI- 1.03- 1.43	Study showed non-significant decrease in risk of stroke and non-significant increase in risk of bleeding
Kai et al. 2017(7)	Retrospective 4286	All-cause death- HR- 0.76, 95% CI- 0.69–0.84 Ischemic stroke- HR 0.68, 95% CI 0.52–0.91 Hemorrhagic stroke- HR 1.2, 95% CI 0.6–2.2 Gastrointestinal bleeding- HR 0.97, 95% CI 0.77– 1.2	Warfarin use was associated with lower all-cause mortality and ischemic stroke, without significantly increasing the risk of bleeding in hemodialysis patients with atrial fibrillation

*Bleeding not assessed separately; ** S/SE- Stroke/ Systemic embolism

Table 2

Clinical studies of ESKD patients with AF treated with apixaban versus no OAC/ warfarin with net benefit in apixaban arm

Study	Type of study and no. of patients with ESKD and AF	Outcomes results Apixaban vs no OAC	Comments
Siontis et al. 2018 (18)	Retrospective 25,523	Sensitivity analysis: S/SE* - HR 0.64, 95% CI 0.42–0.97, P=0.04 Death- HR 0.63, 95% CI 0.46–0.85, P=0.003 Major bleeding- HR, 0.72; 95% CI, 0.59-0.87; P<0.001	Sensitivity analysis- Outcomes of interest was also performed with multivariable Cox regression analysis in the overall (unmatched) apixaban and warfarin cohorts. Some patients in the apixaban group who were initially given warfarin were excluded in the pre specified sensitivity analysis. There was significant reduction in death, S/SE and major bleeding when compared to warfarin.
Kuno et al. 2020(19)	Meta-analysis 71,877	Mortality- HR: 0.61; 95% CI: 0.41 to 0.90 S/SE- Apixaban vs no OAC: Apixaban 5mg HR: 0.59; 95% CI: 0.30 to 1.17; apixaban 2.5 mg, HR: 1.00; 95% CI: 0.52 to 1.93 Major Bleeding- HR: 1.41; 95% CI: 1.07 to 1.88	Apixaban 5 mg dose resulted in lower all cause mortality compared to the group with no OAC. One of the major limitations of this meta-analysis was that, only 2 observational studies comparing DOACs were included. This might have contributed to no difference in stroke rates between apixaban and no OAC group.
Mavrakanas et al. 2020 (11)	Retrospective 521 in apixaban group	All cause mortality HR, 0.58; 95% CI, 0.43 to 0.78 Composite outcome of mortality or S or SE- HR, 0.56; 95% CI, 0.41 to 0.76)	All cause mortality was lower in apixaban group with

*S/SE- Stroke/Systemic embolism