

# Should Oral Anticoagulation Be Used in ESKD Patients on Hemodialysis with Atrial Fibrillation?: PRO

Subodh R. Devabhaktuni and J. Paul Mounsey

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## Defining the Magnitude of the Problem

Atrial fibrillation (AF) is the most common cause of stroke, and is a frequent comorbidity in patients with ESKD, affecting as many as one in five (1). The prevalence is 20% and 14% in patients on hemodialysis (HD) and peritoneal dialysis (2), and increases with age from 6% in the 22–44 year age group, 25% between 65 and 74 years, and 33% in patients aged >74 years (3). CKD is associated with an increased risk of ischemic stroke in patients with AF, independent of traditional risk factors for stroke, even in patients who are not on dialysis (4,5). Compared with White patients, Black, Hispanic, and 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 patients with ESKD (21.1 vs. 4.7 per 1000 patient years [7]), and incident AF is associated with increased mortality in patients with ESKD (8). Therefore, oral anticoagulation plays a key role in the management of these patients. In this article, we propose that oral anticoagulants (OAC) are beneficial in patients with AF and ESKD, and examine the evidence supporting it.

## Mitigating the Stroke Risk in Patients with AF and ESKD

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 proinflammatory and procoagulant factors, such as C-reactive protein, cystatin C, IL-6, fibrinogen, factor VII, VIII, IX–XII, TNF- $\alpha$  soluble receptor-1, intracellular adhesion molecule-1, vWf, 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 more common in patients with kidney failure, 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 patients with kidney failure, but more recently, on the basis of pharmacokinetic considerations, apixaban and rivaroxaban have been labeled

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 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 AF. 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 a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  (congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease, and sex category) warfarin was associated with lower risk of all-cause death (5). Similar trends in mortality were noted in patients with CKD who were low and intermediate risk (hazard ratio [HR] 0.62; 95% confidence interval [95% CI], 0.49 to 0.79). Shen *et al.* showed that warfarin use was associated with a reduced risk of ischemic stroke, and there was a signal toward 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 nonsignificant 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 patients on HD with AF (8). Summary of studies demonstrating net clinical benefit of anticoagulating with warfarin are listed in Table 1.

## Role of Direct OAC

Apixaban is the only direct OAC (DOAC) approved by the FDA for use on patients with ESKD that has been studied for efficacy (10,11). In a study by Wang *et al.*, ESKD resulted in a modest increase (36%) in apixaban

Division of Cardiology, University of Arkansas Medical Sciences, Little Rock, Arkansas

**Correspondence:** Dr. J. Paul Mounsey, University of Arkansas for Medical Sciences, #532, 4301 W Markham St, Little Rock, AR 72205. Email: [jpmounsey@UAMS.edu](mailto:jpmounsey@UAMS.edu)

**Table 1. Clinical studies of patients with ESKD and atrial fibrillation treated with warfarin with net benefit**

Study	Type of Study (no. of Patients with ESKD and Atrial Fibrillation)	Outcomes Results Warfarin Versus No Warfarin	Comments
Lai <i>et al.</i> 2009 (9)	Retrospective (93)	Stroke 10% vs 38%; $P < 0.005$ Bleeding 14% vs 9%; $P = \text{NS}$	Patients ESKD with AF treated with warfarin had significant reduction in thromboembolic stroke and an insignificant increase in major bleeding. The same results were noted in patients with ESKD.
Olesen <i>et al.</i> 2012 (4)	Retrospective (901)	S/SE HR 0.44; 95% CI, 0.26 to 0.74; $P = 0.002$ Bleeding HR 1.27; 95% CI, 0.91 to 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 <i>et al.</i> 2014 (5)	Retrospective (1142)	All cause death <sup>a</sup> 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 patients who are high risk.
Shen <i>et al.</i> 2015 (6)	Retrospective (12,284 with new AF)	Ischemic stroke HR, 0.68; 95% CI, 0.47 to 0.99. All-cause mortality HR 1.01; 95% CI, 0.92 to 1.11. Hemorrhagic stroke HR 0.82; 95% CI, 0.37 to 1.81. GI bleeding HR 1.00; 95% CI, 0.69 to 1.44	In addition, as treated analysis showed all-cause mortality was significantly lower for warfarin users (HR, 0.84; 95% CI, 0.73 to 0.97).
Van Der Meersch <i>et al.</i> 2017 (7)	Meta-analysis (17,380)	Ischemic stroke HR 0.74; 95% CI, 0.51 to 1.06 Bleeding HR 1.21, 95% CI, 1.03 to 1.43	Study showed nonsignificant decrease in risk of stroke and nonsignificant increase in risk of bleeding.
Kai <i>et al.</i> 2017 (7)	Retrospective (4286)	All-cause death HR 0.76; 95% CI, 0.69 to 0.84 Ischemic stroke HR, 0.68; 95% CI, 0.52 to 0.91 Hemorrhagic stroke HR 1.2; 95% CI, 0.6 to 2.2 GI bleeding HR 0.97; 95% CI, 0.77 to 1.2	Warfarin use was associated with lower all-cause mortality and ischemic stroke, without significantly increasing the risk of bleeding in patients on hemodialysis with AF.

AF, atrial fibrillation; S/SE, stroke/systemic embolism; 95% CI, 95% confidence interval; HR, hazard ratio; GI, gastrointestinal.  
<sup>a</sup>Bleeding not assessed separately.

area under the curve and no increase in  $C_{max}$ , and HD had a limited effect on apixaban clearance (10). In a large meta-analysis of around 71,000 patients by Kuno *et al.*, all-cause mortality was lower in apixaban group compared with the no OAC group. There was no difference in stroke rates; however, there was significant heterogeneity in this analysis, as noted the paper. Also, only two 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 with 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 a 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) (12). Table 2 lists the studies demonstrating the 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 (12, 15–17). It should be noted 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 (14).

**Table 2. Clinical studies of patients with ESKD with atrial fibrillation treated with apixaban versus no oral anticoagulants/warfarin with net benefit in apixaban arm**

Study	Type of Study (no. of Patients with ESKD and Atrial Fibrillation)	Outcomes Results Apixaban Versus No Oral Anticoagulants	Comments
Siontis <i>et al.</i> 2018 (13)	Retrospective (25,523)	Sensitivity analysis S/SE HR, 0.64; 95% CI, 0.42 to 0.97, $P=0.04$ Death HR, 0.63, 95% CI, 0.46 to 0.85, $P=0.003$ Major bleeding HR, 0.72; 95% CI, 0.59 to 0.87; $P<0.001$	Sensitivity analysis: outcomes of interest were 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 prespecified sensitivity analysis. There was significant reduction in death, S/SE and major bleeding when compared with warfarin.
Kuno <i>et al.</i> 2020 (14)	Meta-analysis (71,877)	Mortality HR, 0.61; 95% CI, 0.41 to 0.90 S/SE Apixaban vs no OAC Apixaban 5 mg: 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 with the group with no OAC. One of the major limitations of this meta-analysis was that only two observational studies comparing DOACs were included. This might have contributed to no difference in stroke rates between the apixaban and no OAC group.
Mavrakanas <i>et al.</i> 2020 (12)	Retrospective (521 in apixaban group)	All-cause mortality HR, 0.58; 95% CI, 0.43 to 0.78 Composite outcome of mortality or S/SE HR, 0.56; 95% CI, 0.41 to 0.76)	All-cause mortality was lower in apixaban group.

S/SE, stroke/systemic embolism; HR, hazard ratio; 95% CI, 95% confidence interval; OAC, oral anticoagulants.

As said before, some studies support this idea (4–6,8) others do not (12,15–17). So, why is it anticoagulants are not universally beneficial in this cohort of patients? Several possibilities exist. Uremia is associated with an elevated risk of bleeding, and patients on HD 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 (international normalized ratio) in patients on warfarin because of dysregulation of hepatic cytochrome P450, the main pathway for warfarin metabolism, in kidney failure (18). Uremia is associated with a vasculopathy, and this may elevate stroke risk, independent of any mitigation by anticoagulation (19).

High-quality evidence in terms of randomized clinical trials is lacking. The RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation (RENAL-AF) study 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 nonmajor bleed, for apixaban versus warfarin was 32% versus 26% ( $P>0.05$ ). Secondary outcomes were intracranial bleeding 1% versus 1%; gastrointestinal bleeding 2% versus 8%; International Society on Thrombosis and Haemostasis major bleed 9% versus 10%; stroke 2% versus 3%; and cardiovascular death 11% versus 6%. Importantly, this trial was stopped early due to loss of funding, and it is unclear if bleeding outcomes would have been better with a lower dose of 2.5 mg and without aspirin use (approximately 40% usage).

In summary, we think OAC is indicated in these patients on the basis of the data presented in this article, with studies showing a reduction in stroke and, more importantly, a reduction in all-cause mortality. Clinical trials such as the Compare Apixaban and Vitamin-K Antagonists in Patients with Atrial Fibrillation and End-Stage Kidney Disease study (NCT02933697) and the Strategies for the Management of Atrial Fibrillation in Patients Receiving Hemodialysis (NCT03987711) study are underway. The Compare Apixaban and Vitamin-K Antagonists in Patients with Atrial

Fibrillation and End-Stage Kidney Disease study will randomize patients to apixaban 2.5 mg twice daily versus warfarin. The Strategies for the Management of Atrial Fibrillation in Patients Receiving Hemodialysis trial will randomize patients to warfarin, apixaban, and no anticoagulation. Hopefully, these trials will guide us on this highly debated topic. We are 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 these studies will lend a promising solution to this clinical conundrum.

#### Disclosures

J.P. Mounsey reports having consultancy agreements with Boston Scientific Inc. and Medtronic Inc. S.R. Devabhaktuni reports being a scientific advisor or member of the editorial board of Cardiology Cases and Systematic Reviews, the International Journal of Cardiac Science and Research, the Journal of Clinical Cardiology and Cardiovascular Therapy, and the Journal of Innovations in Cardiac Rhythm Management.

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#### Author Contributions

J. Mounsey reviewed and edited the manuscript; and S. Devabhaktuni wrote the original draft.

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