Published in final edited form as:

Am J Kidney Dis. 2014 November ; 64(5): 677–680. doi:10.1053/j.ajkd.2014.04.017.

The Debate on Warfarin Use in Dialysis Patients With Atrial Fibrillation: More Fuel for the Fire

Nisha Bansal, MD, MAS

University of Washington, Seattle, WA

Atrial fibrillation (AF) is the most common sustained arrhythmia in the general population. The burden of AF is even greater in patients with chronic kidney disease (CKD). Among patients with end-stage renal disease (ESRD) treated with hemodialysis,¹ the prevalence of AF is estimated to be 7–20% and continues to increase.²

CKD and AF are both associated with thromboembolic disease through endothelial injury, abnormal blood flow and hypercoagulability. The synergistic impact of these conditions enhances the risk of complications such as ischemic stroke.^{3,4} In a study of 132,372 patients with nonvalvular AF, hemodialysis patients had an 83% higher rate of stroke compared to patients without kidney disease.⁵ Although hemodialysis patients have an increased risk for thromboembolism, they also have an increased risk of bleeding. Furthermore, risk of vascular calcification may be enhanced by warfarin use.^{6,7} Thus, decisions on anticoagulation remain challenging in hemodialysis patients. There are clear and evidence-based guidelines for the use of anticoagulation in the prevention of thromboembolic stroke in the general population.⁸ Yet, despite the tremendous burden of AF and associated adverse consequences in patients treated by hemodialysis or peritoneal dialysis, the role of anticoagulation in these high-risk patients remains debated.

What does this important study show?

A recent study by Shah et al adds to the current body of literature on the benefits and risks of warfarin in dialysis patients with AF.⁹ The authors studied patients admitted to hospitals in Quebec and Ontario, Canada with a primary or secondary diagnosis of AF between 1998–2007, a cohort which included 1,626 peritoneal and hemodialysis patients and 204,210 non-dialysis patients. They examined subsequent use of warfarin in the dialysis and non-dialysis groups as well as the association of warfarin use with risk of stroke as well as bleeding events. Stroke was defined as ischemic cerebrovascular disease including transient ischemic

© 2014 The National Kidney Foundation, Inc. Published by Elsevier Inc. All rights reserved.

Address correspondence to Nisha Bansal MD, MAS, University of Washington, Division of Nephrology, Box 359606, 325 Ninth Avenue, Seattle, WA 98104. nbansal@u.washington.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Financial Disclosure: Dr Bansal states that she has no relevant financial interests to declare.

attack (TIA) and retinal infarct. Bleeding was defined by intracerebral bleeding, gastrointestinal bleeding, intraocular bleeding, hematuria or other bleeding.⁹

The authors reported that dialysis patients were as likely as non-dialysis patients to be taking warfarin. Among dialysis patients, warfarin use was not associated with a lower risk of stroke (HR 1.14, 95% CI: 0.78 to 1.67) however it was associated with a 44% increased risk (adjusted HR 1.44, 95% CI: 1.13 to 1.85) of bleeding. In comparison, the non-dialysis patients had a modest reduction in stroke risk (adjusted HR 0.87, 95% CI: 0.85 to 0.90) and an increase in bleeding (adjusted HR 1.19, 95% CI: 1.16 to 1.22) with warfarin use.⁹ Results were similar with propensity score matching.

The study had several strengths. It studied a large group of dialysis patients. The authors adjusted for several key potential confounders for risk of stroke and bleeding. They also used propensity scores to address issues with confounding by indication. Several important limitations must also be noted. The study did not examine the effect of race/ethnicity on outcomes, which is an important well-recognized confounder.^{10,11} The study was conducted in an older population. The authors did not differentiate between peritoneal dialysis versus hemodialysis patients in their analyses, who may differ in terms of their risk for these outcomes. This study was limited to patients with hospitalized AF only, which is likely a subset of the larger AF population. The authors did not have information on international normalized ratio levels or important dialysis characteristics (e.g. use of heparin) that may be important confounders. Finally, this was an observational study, thus there may be biases from residual confounding or confounding by indication.

How does this study compare with prior studies?

Prior observational studies in various dialysis populations have yielded conflicting results regarding the overall risk versus benefit of warfarin therapy in dialysis patients. In a study of 1,671 incident hemodialysis patients with pre-existing AF from Fresenius Medical Care North America, warfarin use was associated with almost a 2-fold *increased* risk in stroke (a composite outcome that included both hemorrhagic and ischemic strokes), but had no association with all-cause mortality.¹² In a study of the international Dialysis Outcomes and Practice Patterns Study (DOPPS), warfarin use was associated with a 2.2 fold higher risk of stroke or death only among hemodialysis patients >75 years in age (with no association in the younger age groups).⁴ Among Medicare hemodialysis patients with incident AF, there was no difference in occurrence of ischemic stroke among warfarin vs. no warfarin users (HR=0.92; 95% CI: 0.61 to 1.37), however warfarin use was associated with a 2.38-fold greater risk of hemorrhage stroke (HR 2.38; 95% CI: 1.15 to 4.96).¹³ In this study, there was no difference in mortality or gastrointestinal hemorrhage between the two groups.¹³

Two studies have suggested that warfarin use is associated with a reduced risk of complications in dialysis patients. In a study of 901 Danish dialysis patients with AF, warfarin use was associated with a 56% reduction in risk of stroke or systemic thromboembolism compared to non-warfarin users and warfarin users did not have an increased risk of bleeding.⁵ This risk reduction was similar to patients without CKD or not on dialysis. However, the generalizability of this study has been questioned due to the low

burden of comorbidity in this cohort.⁵ A recent study using a Swedish registry observed that among 24,317 survivors of myocardial infarction with AF, warfarin use after hospital discharge was associated with lower risk of death, myocardial infarction and ischemic stroke with no increased risk of bleeding.¹⁴ These associations were consistent across all stages of CKD. Specifically, among 478 patients with estimated glomerular filtration rate 15 ml/min/1.73 m², warfarin use was associated with a 43% reduction (95% CI: 14%–63%) in risk of subsequent death, myocardial infarction and ischemic stroke and there was no increased risk of bleeding (HR 0.52 [95% CI: 0.16–1.65]).¹⁴ The data from these previous investigations and the recent one from Shah et al have revealed that the debate regarding risks versus benefits of warfarin therapy in dialysis patients with AF is far from resolved.

What should clinicians and researchers do?

While observational data on warfarin use and outcomes in dialysis patients with AF has yielded important results, the conflicting messages have left clinicians, patients and guideline writers uninformed - so much so that the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines advised against warfarin therapy for stroke prevention in dialysis patients due to lack of evidence and called for clinical trials in this area.¹⁵ Observational studies suffer from issues of unmeasured or residual confounding or selection bias, even when utilizing sophisticated statistical methodology such as propensity scores. More definite answers through randomized clinical trials are necessary to guide clinicians in the care of this high-risk population. Prior clinical trials of anticoagulation in patients with AF have largely excluded patients with advanced CKD.¹⁶ This point was articulately made in an accompanying editorial by Granger and Chertow, who state: “It is ironic that we are routinely treating many patients with renal disease and atrial fibrillation every day with great uncertainty as to benefit or harm without their consent, and at the same time, major regulatory and ethical barriers exist that prevent efficient enrollment of patients into clinical trials that are needed to answer this (and other) important questions.”¹⁷

While the nephrology community continues to inform the debate on using warfarin in dialysis patients with only observational data, several novel, direct acting oral anticoagulants have been tested for prevention of stroke in patients with AF in large randomized trials of the general population.^{18–21} These novel anticoagulants include two direct thrombin inhibitors (ximelagatran and dabigatran) and two factor Xa inhibitors (apixaban and rivaroxaban) and have the benefit of not requiring regular anticoagulation monitoring and frequent dose adjustments. Yet, all have substantial kidney clearance with prolonged half-life in patients with CKD. Three of these novel anticoagulants have recently been approved for clinical use for non-valvular AF (dabigatran, apixaban and rivaroxaban) and have been shown to be non-inferior or superior to adjusted-dose warfarin for stroke prevention, and, in some cases, carry reduced risk of major hemorrhagic complications.^{18–21} While major clinical trials of these agents have excluded patients with advanced CKD, many have included patients with moderate CKD (Table 1). Overall, evidence from these trials support the use of these novel agents in patients with moderate CKD (Table 1). However, there remains a paucity of data on the efficacy and safety of these agents in more advanced stages of CKD.

In summary, while important, the recent studies on the efficacy and risks of warfarin to prevent complications related to AF in patients with dialysis simply add fuel to the fire. The debate on how best to treat this high-risk group of patients will continue until randomized clinical trials to study warfarin and novel direct acting anticoagulants in patients with advanced CKD are prioritized.

Acknowledgments

Support: None.

REFERENCES

1. Wetmore JB, Mahnken JD, Rigler SK, et al. The prevalence of and factors associated with chronic atrial fibrillation in Medicare/Medicaid-eligible dialysis patients. *Kidney Int.* 2012; 81:469–476. [PubMed: 22189842]
2. Winkelmayer WC, Patrick AR, Liu J, et al. The increasing prevalence of atrial fibrillation among hemodialysis patients. *J Am Soc Nephrol.* 2011; 22:349–357. [PubMed: 21233416]
3. Genovesi S, Vincenti A, Rossi E, et al. Atrial fibrillation and morbidity and mortality in a cohort of long-term hemodialysis patients. *Am J Kidney Dis.* 2008; 51:255–262. [PubMed: 18215703]
4. Wizemann V, Tong L, Satayathum S, et al. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. *Kidney Int.* 2010; 77:1098–1106. [PubMed: 20054291]
5. Olesen JB, Lip GY, Kamper AL, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med.* 2012; 367:625–635. [PubMed: 22894575]
6. McCabe KM, Booth SL, Fu X, et al. Dietary vitamin K and therapeutic warfarin alter the susceptibility to vascular calcification in experimental chronic kidney disease. *Kidney Int.* 2013; 83:835–844. [PubMed: 23344475]
7. Zhang YT, Tang ZY. Research progress of warfarin-associated vascular calcification and its possible therapy. *Journal of cardiovascular pharmacology.* 2014; 63:76–82. [PubMed: 24072176]
8. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation.* 2014
9. Shah M, Avgil Tsadok M, Jackevicius CA, et al. Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. *Circulation.* 2014; 129:1196–1203. [PubMed: 24452752]
10. Wetmore JB, Phadnis MA, Mahnken JD, et al. Race, Ethnicity, and State-by-State Geographic Variation in Hemorrhagic Stroke in Dialysis Patients. *Clin J Am Soc Nephrol.* 2014
11. Wetmore JB, Ellerbeck EF, Mahnken JD, et al. Stroke and the "Stroke Belt" in Dialysis: Contribution of Patient Characteristics to Ischemic Stroke Rate and Its Geographic Variation. *J Am Soc Nephrol.* 2013
12. Chan KE, Lazarus JM, Thadhani R, et al. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. *J Am Soc Nephrol.* 2009; 20:2223–2233. [PubMed: 19713308]
13. Winkelmayer WC, Liu J, Setoguchi S, et al. Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. *Clin J Am Soc Nephrol.* 2011; 6:2662–2668. [PubMed: 21959598]
14. Carrero JJ, Evans M, Szummer K, et al. Warfarin, kidney dysfunction, and outcomes following acute myocardial infarction in patients with atrial fibrillation. *Jama.* 2014; 311:919–928. [PubMed: 24595776]
15. Herzog CA, Asinger RW, Berger AK, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2011; 80:572–586. [PubMed: 21750584]

16. Charytan D, Kuntz RE. The exclusion of patients with chronic kidney disease from clinical trials in coronary artery disease. *Kidney Int.* 2006; 70:2021–2030. [PubMed: 17051142]
17. Granger CB, Chertow GM. A pint of sweat will save a gallon of blood: a call for randomized trials of anticoagulation in end-stage renal disease. *Circulation.* 2014; 129:1190–1192. [PubMed: 24452751]
18. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med.* 2011; 364:806–817. [PubMed: 21309657]
19. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009; 361:1139–1151. [PubMed: 19717844]
20. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011; 365:981–992. [PubMed: 21870978]
21. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011; 365:883–891. [PubMed: 21830957]
22. Hart RG, et al. Anticoagulants in atrial fibrillation patients with chronic kidney disease. *Nat. Rev. Nephrol.* 2012 Oct; 8(10):569–578. (2012) Epub 2012 Jul 24. [PubMed: 22825670]

Table 1

Overview of phase III randomized trials of new oral anticoagulants

Study (n)	Agents	Design features	Exclusion criteria related to CKD	Dose adj. related to CKD	Stage 3 CKD (%)	Mean time in therapeutic range (INR 2–3)	Main results
RE-LY ¹⁹	Dabigatran 150 mg or 110 mg 2×/d vs. warfarin	Warfarin given open-label	eCler<30 ml/min	None	10% eCler 30–49 ml/min	64%	Stroke, non-CNS embolism and CV mortality reduced by dabigatran 150 mg vs. warfarin; major hemorrhage reduced by dabigatran 110 mg vs. warfarin; intracranial bleeding reduced by both doses of dabigatran vs. warfarin; no significant differences in total mortality
AVERROES ¹⁸ (5,599)	Apixaban 5 mg 2×/d vs. aspirin	Double-blind; restricted to those deemed unsuitable for warfarin	Ser >221 umol/L or eCler<25 ml/min	2.5 mg twice daily if Ser 133 umol/L plus age 80 years or weight 60 kg	30% eCler 30–59 ml/min	NA	Stroke and non-CNS embolism reduced by apixaban vs aspirin; major hemorrhage and intracranial bleeding comparable with both agents; no significant difference in CV or total mortality
ROCKET AF ²¹ (14,264)	Rivaroxaban 20 mg/d vs. warfarin	Double-blind; restricted to those at high risk of stroke	eCler<30 ml/min	15 mg per day if Cler<50 ml/min	21% eCler 30–49 ml/min	55%	Rivaroxaban noninferior to warfarin for stroke and non-CNS embolism; major hemorrhage comparable with both agents; intracranial bleeding reduced by rivaroxaban vs. warfarin; no significant difference in CV or total mortality
ARISTOTLE ²⁰	Apixaban 5 mg 2×/d vs. warfarin	Double-blind	Ser >221 umol/L or eCler <25 ml/min	2.5 mg twice daily if Ser 133 umol/L plus age 80 years or weight 60 kg	15% eCler 30–50 ml/min	62%	Stroke, non-CNS embolism, major hemorrhage, intracranial bleeding and total mortality reduced by apixaban vs. warfarin; no significant difference in CV mortality

Abbreviations: CKD=chronic kidney disease; cardiovascular, CV; CNS=central nervous system; Ser= serum creatinine; eCler=estimated creatinine clearance; INR=international normalized ratio; NA=not available; RE-LY, Randomized Evaluation of Long-term Anticoagulant Therapy; AVERROES, Apixaban versus Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patient Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; ARISTOTLE, Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment.

Conversion factors for Units: serum creatinine in μmol/L to mg/dL, ×0.01132.
Based on data from Hart et al²².