EXPERT OPINION

End-stage renal disease with atrial fibrillation: uncharted territory in the modern world of anticoagulants

Sandra D Browne, Justin McMaster, Syed A Rizvi & Sultan Ahmed[†]
[†]*JAS Medical Management LLC, Miramar, FL, USA*

Introduction: End-stage renal disease (ESRD) and atrial fibrillation are increasingly common concurrent findings among many patients. Coexisting ESRD and atrial fibrillation can further exacerbate each disease process; thus, evidence-based medicine protocols are needed for the treatment of patients with both ESRD and new-onset atrial fibrillation to clarify the appropriate anticoagulant management of such patients.

Areas covered: The manuscript surveys the literature to look for a suitable answer to the pressing question that requires development of an evidence-based protocol: 'Which anticoagulant is best for the patient with ESRD and atrial fibrillation?'

Expert opinion: Unlike many disease processes that have ample evidence available in order to better manage the patient, in the patient with end-stage kidney disease and new onset of atrial fibrillation, the situation becomes much more complicated. We believe randomized controlled trials for both the classical and the newer oral anticoagulants could provide evidence-based medicine protocols for the treatment of patients with ESRD and new-onset atrial fibrillation.

Keywords: anticoagulant, atrial fibrillation, dialysis, end-stage kidney disease

Expert Opin. Pharmacother. (2014) ***15****(12):1639-1642*

Both chronic kidney disease (CKD) and atrial fibrillation are increasingly common conditions. Recent estimates suggest that 6 – 8% of non-institutionalized American adults have an estimated glomerular filtration rate < 60 ml/min, which classifies them as Stage 3 CKD [1]. The onset of atrial fibrillation increases with the severity of CKD, and, conversely, patients with atrial fibrillation are more likely to develop CKD or worsening kidney disease [1]. While it is estimated that > 1.5 million people have end-stage renal disease (ESRD) internationally, the percentage that also have atrial fibrillation is less well known with estimates varying widely from 10.9 to 27%. The mortality in patients with both of these conditions is almost double that of patients with ESRD alone [2,3].

Warfarin has been used for decades in the general population for the treatment of venous thromboembolism and for stroke prophylaxis in patients with atrial fibrillation [4]. Observational data for patients with ESRD taking warfarin show an increased risk of hemorrhagic stroke, but the outcomes for ischemic stroke are unclear [5]. Recently, Shah *et al.* reported 'that warfarin use is not beneficial in reducing stroke risk but is associated with a higher bleeding risk in patients with AF undergoing dialysis' [6]. Unfortunately, as of yet there have been no randomized trials of warfarin in patients with CKD and atrial fibrillation [4].

10.1517/14656566.2014.936379 © 2014 Informa UK, Ltd. ISSN 1465-6566, e-ISSN 1744-7666

Suboptimal conditions exist with the use of warfarin including the slow onset of action, inconsistent pharmacological effects and copious food and drug interactions. Due to these deficiencies, newer oral anticoagulants have come onto the market in recent years with dabigatran, a direct thrombin inhibitor, being the first approved in the US followed by rivaroxaban and apixaban, which are both Xa inhibitors [7]. For patients with atrial fibrillation and Stage 3 kidney disease, data show evidence for dabigatran 150 mg twice daily to be superior to warfarin in preventing stroke [8]. In the same publication, apixaban was reported to have fewer incidents of major hemorrhaging when compared with warfarin. Overall, the new oral anticoagulants have performed well in randomized clinical trials for those patients with up to Stage 3 kidney disease; however, anticoagulant options for hemodialysis patients still requires testing in randomized trials [9]. Despite the numerous clinical trials, which show beneficial outcomes for those with Stage 3 kidney disease, the outlook is less promising for those with severe ESRD. Trials with dabigatran revealed that for patients with creatinine clearance (CrCl) < 30 ml/min extreme caution should be used and most physicians recommend dabigatran be avoided [7]. A large review by the Mayo Clinic in 2013 reported that until further data become available, the new anticoagulants should be avoided in patients with severe kidney disease who have a GFR < 30 ml/min since they are primarily renally cleared [7]. Recommendations from this same review suggest moving from the new oral anticoagulants to warfarin when the CrCl falls below 30 ml/min. Furthermore, it has been noted that diminished renal function will affect the pharmacokinetics of new anticoagulants (e.g., dabigatran), since its excretion is via the renal route, while some (e.g., betrixaban), would be least affected, as their metabolism is mainly affected by variations in liver function [10].

Another common pharmacological option for the management of atrial fibrillation in a patient without CKD is the use of clopidogrel, an antiplatelet, which works through irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets. However, numerous studies suggest that patients with CKD are more likely to be clopidogrel resistant, with one study finding a platelet inhibition rate of only 21.3 ± 16.0 in patients receive standard dosing of clopidogrel. When the dosage of clopidogrel was doubled, the platelet inhibition rate improved slightly to 23.4 ± 14.4 but was still significantly higher than in the control group, which had a platelet inhibition rate of 35.2 ± 20.2 [11]. This clopidogrel resistance can be overcome by switching to ticagrelor, another P2Y12 inhibitor, which has no suggested dose modifications needed for CKD [12]. However, there is currently a lack of long-term randomized controlled trials to access the safety of this drug in dialysis patients [13].

A novel non-pharmacological approach to the management of this patient population involves blocking the left atrial appendage from systemic circulation, which evidence suggests is the main site of thrombus formation in atrial fibrillation patients [14]. The appendage can be blocked using a small device implanted via a catheter. The device consists of a self-expanding metal mesh covered with a thin permeable polyester material, which prevents any formed clots from leaving the left atrial appendage. Within the first year of a 2.3-year clinical trial in patients with atrial fibrillation but no kidney disease, 93.2% of the 408 patients with left atrial appendage closure were able to stop taking warfarin. Based on the results of the 2.3-year trial totaling 1588 patient years, left atrial appendage closure was proven to be non-inferior to warfarin treatment. As with any implantable device, there was an increased number of procedure-related events such as pericardial tamponade and procedure-related stroke. However, once the left atrial appendage was successfully closed this treatment was proven to be superior to ongoing anticoagulant therapy with warfarin [15]. The procedure recently began clinical trials to see if these results can be extrapolated to patients with a GFR < 30 ml/min [16].

The common usage of warfarin in the patient with ESRD and atrial fibrillation is not, however, without concern and caution needs to be maintained as warfarin appears to enhance the already high risk of hemorrhagic stroke in patients with ESRD with the effects on ischemic stroke still uncertain [5,17]. In one large retrospective study consisting of 1626 patients with atrial fibrillation and on dialysis, 756 were prescribed warfarin, and the remainder were not, it was found that the patients on warfarin had a 44% increased bleeding risk with no reduction in the risk of stroke [16]. In addition to the increased bleeding risk, warfarin may also promote vascular calcification in this patient population [5]. Vascular calcification has been noted in young patients receiving dialysis and warfarin, and this calcification increased over time. Other studies of patients taking warfarin who did not have ESRD had increased vascular calcification compared to those not taking warfarin [5]. Therefore, neither age nor the direct results of dialysis seem to promote the vascular calcification, implicating warfarin usage as the catalyst in this pathology.

The lack of protocol for anticoagulant usage in hemodialysis patients with atrial fibrillation is reflected in the varied treatment approaches by physicians internationally. The literature is lacking in clear evidence on how to balance warfarin therapy to prevent thrombotic strokes without increasing the occurrence of bleeding within this population [4]. Due to this lack of clear benefit, some physicians have chosen to avoid the use of anticoagulation therapy altogether within this patient population. In European countries, it has been reported that only 9% of atrial fibrillation patients who are also receiving dialysis receive anticoagulants, while in the United States 25% of this patient population do and in Canada 37% [5]. As mentioned, recent international guidelines do not recommend the use of warfarin in ESRD; however, due to lack of evidence for alternative choices ~ 85% of Canadian nephrologists would continue the administration of warfarin in ESRD patients [5].

In the immediate future, it is essential to have randomized controlled trials for both the classical oral anticoagulants (warfarin) and also the newer oral anticoagulants (dabigatran, rivaroxaban, apixaban) in order to provide evidence-based medicine protocols for the treatment of patients with ESRD and new-onset atrial fibrillation. Until such studies are conducted, no concrete recommendations can be made as to whether this patient population should receive anticoagulation or not.

Expert opinion

Unlike many disease processes that have ample evidence available in order to best manage the patient, for those with ESRD on dialysis with new onset of atrial fibrillation, the situation becomes much more complicated. Thus far, research has provided adequate guidelines regarding the usage of anticoagulants with atrial fibrillation as a sole disease process; choices are numerous and include warfarin, IIa inhibitors like dabigatran, Xa inhibitors like rivaroxaban and apixaban among others. The advantages of using the newer oral anticoagulants over warfarin include rapid onset of action, fewer drug interactions, predictable pharmacokinetics and no need for continuous coagulation level monitoring or body weight adjustment. These newer oral anticoagulants are mostly renally cleared and have proven to be an adequate choice for patients with atrial fibrillation whose CrCl ranges between 25 and 49 ml/min, but what about those patients with concurrent worsening kidney function and/or the need for dialysis? How do physicians systematically approach patient care weighing the risks and benefits of anticoagulation? Even the historically used anticoagulant, warfarin, poses enhanced bleeding risk in those patients undergoing dialysis treatment with concurrent atrial fibrillation as outlined recently by Shah *et al*. So where do we as a team see the field of anticoagulant research going in coming years? We see benefit in conducting randomized controlled research trials (RCTs) for both historical and novel anticoagulation for patients who have coexisting atrial fibrillation and ESRD on dialysis in order to form a systematic approach to patient care. With recent research showing an increased bleeding risk in those patients with ESRD on dialysis prescribed warfarin [6], the ethical issues of enrolling our patients in such future randomized controlled trials surface. But one has to keep in mind that our currently available information is based on observational retrospective study and patients in the ESRD group on dialysis often have higher CHADS2 and HAS-BLED scores compared to those patients not on dialysis and this research only covers warfarin to date and not any of the newer oral anticoagulants. The future appears arduous in setting up equally at-risk patient groups for RCTs (similar CHADS2 and HAS-BLED scores): patients on dialysis with atrial fibrillation receiving a new oral anticoagulant versus patients on dialysis with atrial fibrillation receiving warfarin versus patients on dialysis with atrial fibrillation not on any oral anticoagulant. The outcome of this type of three-tiered patient group RCT is of particular interest to our team and would prove to be highly beneficial in assisting physicians with appropriate prescription protocols for this patient population.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Bibliography

1. Winkelmayer WC, Turakhia MP. Warfarin treatment in patients with atrial fibrillation and advanced chronic kidney disease : sins of omission or commission? JAMA2014311:913-15
2. Szczech L. Atrial fibrillation: the beat is faster than the answers. Kidney Int 2012;81:432-3
3. Vazquez E, Sanchez-Perales C, Garcia-Garcia F, et al. Atrial fibrillation in incident dialysis patients. Kidney Int 2009;76:324-30
4. Juma S, Thomson BK, Lok CE, et al. Warfarin use in hemodialysis patients with atrial fibrillation: decisions based on uncertainty. BMC Nephrol 2013;14:174
5. Brimble KS, Ingram AJ, Eikelboom JW, et al. Anticoagulants in patients with. atrial fibrillation and end-stage renal disease. Postgrad Med 2012;124:17-25
6. Shah M, Avgil TM, Jackevicius CA, et al. Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. Circulation 2014;129:1196-203
7. Gonsalves WI, Pruthi RK, Patnaik MM. The new oral anticoagulants in clinical practice. Mayo Clin Proc 2013;88:495-511
8. Hart RG, Eikelboom JW, Brimble KS, et al. Stroke prevention in atrial fibrillation patients with chronic kidney disease. Can J Cardiol 2013;29:S71-8
9. Hart RG, Eikelboom JW, Ingram AJ, et al. Anticoagulants in atrial fibrillation patients with chronic kidney disease. Nat Rev Nephrol 2012;8:569-78
10. Perez A, Eraso L, Merli G. Implications of new anticoagulants in primary practice. In J Clin Pract 2013;67:139-56
11. Park SH, Kim W, Park CS, et al. A comparison of clopidogrel responsiveness in patients with versus without chronic renal failure. Am J Cardiol 2009;104:1292-5
12. Butler K, Teng R. Pharmacokinetics, pharmacodynamics, and safety of ticagrelor in volunteers with severe renal impairment. J Clin Pharmacol 2012;52:1388-98
13. Alexopoulos D, Xanthopoulou I, Plakomyti TE, et al. Ticagrelor in clopidogrel-resistant patients undergoing maintenance hemodialysis. Am J Kidney Dis 2012;60:332-3

14. Reddy VY, Doshi SK, Sievert H, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. Circulation 2013;127:720-9

15. Lobodzinski SS. New device for stroke prevention in atrial fibrillation as an alternative to anticoagulation drugs. Cardiol J 2009;16:375-8

16. University of Magdeburg. Left atrial appendage occlusion vs. usual care in patients with atrial fibrillation and severe chronic kidney disease (WATCHAFIB). In: ClinicalTrials.gov [Internet]. National Library of Medicine (US), Bethesda (MD); 2000. Available from: http://clinicaltrials.gov/show/NCT02039167NLMIdentifier NCT0203916 [Last accessed 17 March 2014]

17. 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;6:2662-8

Affiliation

Sandra D Browne[1], Justin McMaster[1], Syed A Rizvi*[2] PhD MS MBA & Sultan Ahmed[†3] MD
[†,*]Authors for correspondence
[1]Saba University, School of Medicine, 27 Jackson Road Suite 301, Devens, MA 01434, USA
[2]Nova Southeastern University, College of Pharmacy, 3200 South University Drive, Fort Lauderdale, FL 33328, USA
E-mail: srizvi@nova.edu
[3]JAS Medical Management LLC, 6151 Miramar Pkwy, Miramar, FL 33023, USA
E-mail: cmeahmed@bellsouth.net