Paroxysmal Atrial Fibrillation in a Patient on Hemodialysis

Charmaine E. Lok


Introduction
For most American Society of Nephrology (ASN) Kidney Week attendees, case-based clinical nephrology talks are one of the most exciting venues. The Nephrology Quiz and Questionnaire (NQQ) is the essence of clinical nephrology and represents what drew all of us into the field of nephrology. This year’s NQQ in surprisingly temperate Chicago, with full-house attendance, was no exception. The expert discussants prepared vignettes of puzzling cases, which illustrated some topical, challenging, or controversial aspect of the diagnosis or management of key clinical areas of nephrology. These eight interesting cases were presented and eloquently discussed by our four expert ASN faculty. Subsequently, each discussant prepared a manuscript summarizing his or her case discussions, which serves as the main text of this article. (Mark A. Perazella and Michael Choi, Comoderators).

Case
A 66-year-old man is transferred from another dialysis unit, and you review his medical history and medications. His ESRD is of unknown etiology but you note that he has a history of noncompliance, hypertension (systolic BP can be as high as 170 mmHg), and is a one pack per day smoker. He complains of leg pain: cramping on dialysis and claudication pain with walking. His medications include metoprolol 50 mg twice a day, nifedipine extended-release 90 mg/d, atorvastatin 40 mg (every night at bedtime), a multivitamin once per day, vitamin D 1000 as directed, sevelamer carbonate 800 mg (two tablets with each meal), a sleeping pill as needed, and an anxiolytic as needed. You are called to see him during your rounds as he becomes diaphoretic and describes a choking sensation in his throat. He feels his heart “thumping wildly” in his neck and his BP drops.

His vital signs are as follows: BP has dropped from 140/80 to 105/68 mmHg. His heart rate ranges between 88 and 140 beats/min. An electrocardiogram is performed, which shows atrial fibrillation. It suddenly resolves and he completes dialysis uneventfully. At the end of his dialysis, his BP is 138/78 mmHg and his heart rate is 78 beats/min (regular).

Question 1: Which Statement Is True?
1. Cardiac arrhythmias occur more frequently in patients on hemodialysis compared with the general population.
2. Primary and secondary medical prevention for myocardial infarction is proven effective in patients on dialysis using statins and β-blockers.
3. Primary medical prevention for myocardial infarction is proven effective in patients on dialysis using statins.
4. Secondary medical prevention for myocardial infarction is proven effective in patients on dialysis using β-blockers.
5. Smoking cessation would reduce this patient’s risk of myocardial infarction by 35%.

Correct Answer: A

Individuals with CKD and ESRD requiring dialysis are at increased risk of cardiovascular disease (CVD), which may affect any or all components of the cardiovascular system: pericardial, muscular, valvular, vasculature, and the electrical system. This is reflected by the varied manifestation of CVD in CKD including pericarditis, heart failure, myocardial infarction, stroke, and ventricular and atrial arrhythmias. Cardiac arrhythmias occur more frequently in patients with CKD/ESRD than in the general population. For example, the prevalence of atrial fibrillation is 8%–18% in the nondialysis CKD population, 7%–27% in hemodialysis, and 0.4%–1.0% in the non-CKD general population (varying by age) (1). The management of CVD in CKD/ESRD is particularly challenging because of the presence of both traditional (atherosclerotic) and nontraditional CVD risk factors, the change in their relative importance as patients progress through the stages of CKD to ESRD, and the lack of true understanding of how they interact, especially in the unique circumstances of hemodialysis. For example, although statins and β-blockers have been proven effective in primary and secondary prevention of myocardial infarction in the general population, it has not been shown to be true in the hemodialysis population. In the general population, every 1 mmol/L (38.7 mg/dl) decrease in LDL is associated with a 21% decrease risk in cardiovascular events (2). However, this is not true for patients on dialysis, with large clinical trials of statins revealing no clear benefit.
Also, in the general population, smoking cessation reduces the risk of death by approximately 36% and the risk of a recurrent nonfatal myocardial infarction by approximately 32% (3). In patients on dialysis, smoking is associated with a significant increased risk of all-cause mortality but there may not be specific additional increased risks of cardiovascular events (4); whether smoking cessation reduces the risk of myocardial infarction in this population is unstudied and unknown. Until then, smoking cessation serves to reduce other risks, such as lung cancer.

Indeed, the beneficial effect of medical management of traditional atherosclerotic cardiovascular risk factors in the general population may not be applicable to the dialysis population who may suffer additional nonatherosclerotic, nontraditional risk factors. Such nontraditional risk factors include uremia and inflammation; abnormalities in multiple factors such as volume, electrolytes, mineral metabolism, anemia, myocardial hypertrophy and fibrosis; and others. The degree of additional contribution to CVD risk and whether their modification(s) would result in improved CVD outcomes are areas of ongoing and much needed study. For now, each patient deserves, and is dependent on, the clinician’s best assessment of the individual patient’s traditional and nontraditional cardiovascular risks and their appropriate management.

Case Continued

Six months later, the dialysis unit calls you as he did not show up for dialysis. After investigation, he was found on the floor unconscious after a drinking binge. He develops another episode of paroxysmal atrial fibrillation and you send him to a cardiologist. A two-dimensional echocardiogram is done that demonstrates an enlarged right atrium and a left ventricular ejection fraction of 38%. The cardiologist recommends anticoagulation with warfarin.

Question 2: Which Is True?

1. He has a CHA2DS2VASc score of 2.
2. He has a HAS-BLED score of 6.
3. The harms of warfarin are likely higher than the benefits of reducing ischemic stroke in this patient.
4. Dabigatran would be a good alternative in this patient, and it can be easily monitored by the International Normalized Ratio (INR).
5. In case of significant bleeding complications with dabigatran, it can be quickly removed by dialysis.

Correct Answer: C

Atrial fibrillation in the hemodialysis population presents a unique set of management challenges because of the unique circumstances of a patient on hemodialysis whereby the mechanisms of atrial fibrillation and its response to therapy can be highly influenced by hemodialysis itself. Furthermore, the nephrologist does not have the “baseline certainty” that we might take for granted when managing a patient with atrial fibrillation who is not on dialysis. For example, the data on the increased risks of ischemic stroke in patients on dialysis with atrial fibrillation are conflicting—from no increased risk to risks as high as 35% per year (5). If such elevated risks exist, they must be balanced by the greater risks of bleeding noted in patients on hemodialysis; for example, risk of gastrointestinal bleeding at approximately nine-fold higher and intracerebral bleeding at 4–6.5-fold higher than the nonhemodialysis population (6). In this case, our patient has the additional increased bleeding risks associated with falls.

The critical question in our case is, should we anticoagulate this patient with (paroxysmal) atrial fibrillation to prevent ischemic (thromboembolic) stroke, given the inherent increased risk of bleeding in patients on dialysis? In the general population, risk scores have been developed and validated to assist with risk stratification and to provide guidance via quantitation of the potential benefits (e.g., CHADS2, the CHA2DS2VASc), and risks (e.g., HAS-BLED) of an anticoagulation strategy.

Our patient’s CHA2DS2VASc score is 4, with an estimated risk of stroke of 4% per year. His HAS-BLED score is 4, with an estimated risk of 8.7 bleeds per 100 patient-years. However, these scoring systems were developed and validated exclusively in patients not receiving dialysis; major components of the scores, such as hypertension, diabetes, and congestive heart failure in CHA2DS2VASc, may not reliably predict strokes in patients on dialysis (7). Similarly, key components of the HAS-BLED score may not be discriminatory; for example, advanced age and hypertension are common in patients on dialysis and the variable CKD is, by definition, present in all patients on dialysis. Indeed, in a study of 12,284 patients on dialysis in the United States, <10% of patients had a CHA2DS2VASc score <2 (8), indicating a low risk of ischemic stroke. Furthermore, recent studies have demonstrated that CHADS2, CHA2DS2VASc (9,10), and HAS-BLED (9) scores can predict ischemic strokes but not bleeding events in patients on dialysis (9). Thus, nephrologists are left with knowing that few patients (<10%) with atrial fibrillation have a low risk of ischemic stroke but the majority have unclear risks of both ischemic stroke and bleeding.

Another scoring system called R2CHADS2, derived from the The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) study, adds two points for renal dysfunction to the original CHADS2 score and was validated among patients in the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study (11). However, data on whether adding renal function independently improves stroke prediction is conflicting (11). In future, scoring systems might incorporate dialysis-specific risk factors, such as potassium and calcium dialysate concentrations and intradialytic changes, occurrences of hypo- and hypertension, ultrafiltration rates, and anticoagulant use to predict risks of atrial fibrillation, stroke, and bleeding in patients on hemodialysis.

To summarize what we know above: (1) strokes occur more frequently in patients on dialysis than in the nondialysis population, regardless of whether a patient has atrial fibrillation; (2) atrial fibrillation occurs more frequently in the hemodialysis population than in the nondialysis population; (3) patients with atrial fibrillation on dialysis likely have a higher risk of stroke than patients without atrial fibrillation, although the association is
less apparent than in the nondialysis population; and (4) predictive risk scores for stroke and bleeding used in the nondialysis population may not be discriminatory and are less useful in patients on dialysis (they are unhelpful in predicting the risk of bleeds). So, the question remains, should we prophylactically anticoagulate our patient with warfarin?

In the general nondialysis population with atrial fibrillation receiving warfarin, the incidence rate of ischemic stroke/thromboembolism has been estimated to be 1.66% per year, with an acceptable bleeding risk of major bleeding of 1.4%–3.4% (12). In patients on dialysis with atrial fibrillation, bleeding events have been consistently shown to be higher than ischemic-embolic events by approximately 1.5–2-fold (9). Further, the increased risk of hospitalization because of bleeding is greater in patients on dialysis at 7.8/100 patient-years compared with 2.1/100 patient-years in the general population.

Reasons for the increased risk of major bleeding in hemodialysis include clinical and practice factors, such as uremic platelet dysfunction and accelerated turnover, gastrointestinal comorbidities, advanced age/frailty, prior bleed or stroke, peri-dialysis hypotension and risk of falls, and additional antiplatelet and anticoagulant use inter- and intradialysis. Because many of these underlying risk factors are nonmodifiable, clinicians must use caution and individually consider and balance the risks and benefits of anticoagulation in patients on dialysis with atrial fibrillation.

The secondary question in this case is, if we decide to anticoagulate, should we use warfarin or a nonvitamin K antagonist oral anticoagulant (NOAC)? In addition to the lack of randomized clinical trial support for warfarin use to prevent ischemic-embolic stroke in patients on hemodialysis with atrial fibrillation, there are other concerns surrounding warfarin use. These include the ability to properly monitor INR and attain the correct therapeutic target given the use of heparin anticoagulation during dialysis, and the risks of vascular calcification and calciphylaxis. Studies have demonstrated that the risk of stroke is reduced when the time in therapeutic range is >70%, yet patients on dialysis receiving daily warfarin have a therapeutic range of <50% (13). The uncertainty and challenges of its use are reflected by the range of warfarin use: from 2% in Germany to 26% in the United States and 37% in Canada (7). Even with this relatively high use in Canada, a national survey of nephrologists revealed consistent uncertainty about its role in the balance of risks between ischemic stroke and bleeding (14).

NOACs provide an alternative to warfarin as oral anticoagulation for atrial fibrillation. They inhibit either thrombin (dabigatran) or activated factor X (Xa) (apixaban, betrixaban, edoxaban, eribaxaban, rivaroxaban). Details of these agents are in Table 1. Of note, NOACs have not undergone the rigor of clinical trials in the hemodialysis population and are sensitive to different comedications in P-glycoprotein and cytochrome metabolic pathways, so NOAC dosing may need to be reduced or not used at all (e.g., as in most triazole antifungals).

On the basis of the mechanisms of action of these NOAC agents, the use of prothrombin time (INR levels) is unhelpful. Thrombin time (TT) has the greatest sensitivity for measuring the anticoagulant activity of dabigatran; a normal TT indicates low drug levels and therefore is only useful to exclude the presence of a clinically relevant concentration of dabigatran. The diluted TT and ecarin clotting time can provide quantitative assessments of drug concentrations if necessary. However, the advantage of NOACs is not having to monitor blood levels, as required with warfarin. These levels may be requested in urgent situations, such as bleeding emergencies or unexpected surgery.

If excessive bleeding occurs, there are limited reversal agents for NOACs. Idarucizumab is a humanized monoclonal antibody fragment specifically directed at dabigatran. The active site of idarucizumab is structurally similar to the dabigatran binding site of thrombin, although the antibody lacks enzymatic activity and therefore lacks prothrombotic activity. Idarucizumab binds dabigatran with approximately 350 times the avidity with which thrombin binds dabigatran. In sufficient doses, idarucizumab displaces dabigatran from thrombin and tightly binds it, allowing fibrin formation to ensue normally. Idarucizumab is distributed solely within the intravascular space and draws dabigatran from the extravascular space. It has an elimination half-life of approximately 45 minutes and is predominantly eliminated by renal excretion. No dosing adjustments are required for renal impairment and there are currently no published data available describing its use specifically in patients on dialysis. Approximately 50% of dabigatran can be removed by dialysis in a 4-hour dialysis session. Thus, it would require approximately four dialysis sessions (each of 4 hours duration) to completely remove dabigatran from the patient’s blood.

Currently there are no factor Xa inhibitor antidotes. Andexanet alfa and ciraparantag are in various stages of development. Andexanet alfa is a recombinant protein analog of factor Xa that binds to factor Xa inhibitors and the antithrombin–low molecular weight heparin complex but does not trigger prothrombotic activity. In ex vivo animal and volunteer human studies, andexanet alfa was able to dose-dependently reverse factor Xa inhibition and restore thrombin generation for the duration of drug administration (15). Ciraparantag is a small synthetic and cationic molecule that binds to direct factor Xa inhibitors, thrombin inhibitors, and unfractonated and low molecular weight heparin through noncovalent hydrogen bonds and charge–charge interactions, but there is little published data on the exact mechanism of this molecule. Both agents are awaiting US Food and Drug Administration approval. Dialysis is ineffective in removing factor Xa inhibitor anticoagulants.

Given all of the considerations above, in this particular patient, the risks of bleeding are greater than the risk of ischemic-embolic stroke from his paroxysmal atrial fibrillation; thus, it would not be unreasonable to manage this patient without prophylactic anticoagulation with either warfarin or an NOAC. However, in the management of atrial fibrillation in a patient on dialysis, it would be prudent to clearly discuss the risks and benefits of this and other approaches with the patient and ensure that he fully understands and agrees with the proposed management and follow-up plans. Given how common clinicians need to make decisions on anticoagulation for stroke prophylaxis in patients on dialysis with atrial fibrillation and the
Table 1. Oral anticoagulation in ESRD for atrial fibrillation and stroke prophylaxis (16,17)

<table>
<thead>
<tr>
<th>Considerations</th>
<th>Warfarin</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target inhibition</strong></td>
<td>K-dependent coagulation factors</td>
<td>Xa</td>
<td>IIa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td><strong>Lowest creatinine clearance for use as approved by FDA (Cockroft–Gault)</strong></td>
<td>&lt;15 ml/min or RRT</td>
<td>&lt;15 ml/min or RRT</td>
<td>15–29 ml/min (not RRT)</td>
<td>15–29 ml/min (not RRT)</td>
<td>15–29 ml/min (not RRT)</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>On the basis of INR</td>
<td>5 mg, twice a day$^a$</td>
<td>75 mg, twice a day</td>
<td>30 mg daily</td>
<td>15 mg daily</td>
</tr>
<tr>
<td><strong>Half-life, h</strong></td>
<td>20–60</td>
<td>8–15</td>
<td>12–17</td>
<td>8–14</td>
<td>5–14</td>
</tr>
<tr>
<td><strong>Hours to C-max</strong></td>
<td>2–4</td>
<td>1–3</td>
<td>2</td>
<td>1–2</td>
<td>2–4</td>
</tr>
<tr>
<td><strong>Renal clearance</strong></td>
<td>&lt;1%</td>
<td>27%–40%</td>
<td>80%</td>
<td>35%–50%</td>
<td>33%–66%</td>
</tr>
<tr>
<td><strong>CYP metabolism</strong></td>
<td>CYP 450</td>
<td>CYP 450</td>
<td>0</td>
<td>CYP 450</td>
<td>CYP 450</td>
</tr>
<tr>
<td><strong>Removal with hemodialysis (4-h session)</strong></td>
<td>&lt;1%</td>
<td>7%</td>
<td>50%–60%</td>
<td>&lt;1%</td>
<td></td>
</tr>
<tr>
<td><strong>Antidote</strong></td>
<td>Vitamin K, FFP, 4F-PCC</td>
<td>PCC</td>
<td>Humanized monoclonal antibody antigen-binding fragment e.g., idarucizumab; anti-inhibitor coagulant complex</td>
<td>PCC</td>
<td>PCC</td>
</tr>
<tr>
<td><strong>Key study</strong></td>
<td>AVERROES, ARISTOTLE</td>
<td>FDA approval on the basis of pharmacokinetic and pharmacodynamic studies of eight patients only</td>
<td>Not approved for dialysis</td>
<td>Not approved for dialysis</td>
<td>FDIAntidote approval for patients with ESRD</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>When INR (target 2–3) is within therapeutic range of &gt;70%</td>
<td>Not approved for dialysis</td>
<td>FDA indicates clinical efficacy and safety studies did not enroll patients with ESRD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For PCC, there are four-factor (II, VII, IX, X e.g., Kcentra) and three-factor (II, IX, X e.g., Bebulin) formulations available, but four-factor PCC should be used. Off-label use of these drugs in patients on dialysis has been associated with increased adverse events, including increased hospitalizations (2). Xa, activated factor X; IIa, thrombin; FDA, US Food and Drug Administration; INR, international normalized ratio; C-max, maximum concentration; CYP, cytochrome P450 enzymes; FFP, frozen fresh plasma; 4F-PCC, 4-factor prothrombin complex concentrate; PCC, prothrombin complex concentrate; FEIBA, anti-inhibitor coagulant complex; AVERROES, Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment: A Randomized Double-Blind Trial; ARISTOTLE, Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation; RE-LY, RE-LY: Randomized Evaluation of Long-Term Anticoagulation Therapy; ENGAGE AF-TMI, Edoxaban versus Warfarin in Patients with Atrial Fibrillation; ROCKET AF, The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

$^a$Dose adjusted to 2.5 mg twice a day if two or more of the following criteria are met: serum creatinine $\geq 1.5$ mg/dl (i.e., all patients on dialysis), weight $\leq 60$ kg, or age $\geq$ 80 years old.
current conflicting evidence on both the use of, and clinical effectiveness of anticoagulation in patients with ESRD, clinical equipoise openly invites a much needed randomized clinical trial on this important topic.

Acknowledgments
I wish to thank my good colleagues Dr. Michael Choi and Dr. Mark Perazella for reviewing the cases and Dr. Robert Richardson, Dr. Vandana Niyyar, and Dr. Louise Moist for their insights on this manuscript.

Disclosures
None.

References

Published online ahead of print. Publication date available at www.cjasn.org.