Warfarin in haemodialysis patients with atrial fibrillation: what benefit?

Felix Yang1*, Denise Chou2, Paul Schweitzer3, and Sam Hanon3

1Division of Cardiology/Arrhythmia Offices Forman 2, Department of Medicine, Montefiore Medical Center, 111 E. 210th Street, Bronx, NY 10467, USA; 2Department of Neurology, New York Presbyterian Hospital—Cornell, New York, NY, USA; and 3Division of Cardiology, Department of Medicine, Beth Israel Medical Center, New York, NY, USA

Received 24 July 2010; accepted after revision 19 September 2010; online publish-ahead-of-print 2 November 2010

Warfarin is commonly used to prevent stroke in patients with atrial fibrillation; however, patients on haemodialysis may not derive the same benefit from warfarin as the general population. There are no randomized controlled studies in dialysis patients which demonstrate the efficacy of warfarin in preventing stroke. In fact, warfarin places the dialysis patient at increased risk for haemorrhagic stroke and possibly ischaemic stroke. Additionally, warfarin increases the risk of major bleeding and has been associated with vascular calcification. Routine use of warfarin in dialysis for stroke prevention should be discouraged, and therapy should only be reserved for dialysis patients at high risk for thrombo-embolic stroke and carefully monitored if implemented.

Keywords
- Atrial fibrillation
- Haemodialysis
- Stroke

Introduction

Atrial fibrillation is common among haemodialysis patients with a prevalence of 11–27% in cross-sectional studies.1–3 However, it is not known how the risk of stroke in dialysis patients with atrial fibrillation compares to people not on dialysis. The reported annual rates of stroke vary widely between 1 and 15%.4–7 Vazquez et al.8 report that the presence of atrial fibrillation increased the risk of stroke in incident dialysis patients 9.8-fold. Despite this seemingly high rate of stroke in atrial fibrillation, ~75% of patients with atrial fibrillation on dialysis are not anticoagulated.1,9 Here, we review the literature for and against the use of warfarin in haemodialysis patients with atrial fibrillation.

We conducted a literature search of Medline through Ovid (1966 to April 2010). The Medical Subject Heading terms ‘warfarin’, ‘atrial fibrillation’, ‘bleeding’, and ‘stroke’ were combined with ‘end-stage renal disease’, ‘dialysis’, ‘haemodialysis’, and ‘kidney failure’. Additional searches were also conducted for ‘calciphylaxis’ and ‘calcific uremic arteriopathy.”

Haemodialysis patients and the baseline risk of bleeding

Patients on dialysis have an increased risk of bleeding at baseline due to multiple factors. There is an acquired defect in primary haemostasis as a result of defects in platelet secretion, aggregation, and altered interactions between the platelet and vessel walls.10 In particular, uraemia causes altered arachidonic acid metabolism which leads to a multitude of abnormalities: decreased thromboxane A2 production, abnormal intracellular calcium mobilization, and decreased platelet ADP, epinephrine, and serotonin production. Uraemia also impairs binding between IIb–IIIa receptors and the von Willebrand factor, leading to impaired platelet aggregation.11 Finally, uraemia results in increased endothelial production of prostaglandin I2 and nitric oxide, agents which have vasodilatory and antiplatelet properties.10

Patients with very low GFR or on dialysis are at increased risk for haemorrhagic stroke. In a study by Iseki et al.12 of 1609 patients over 4 years, the relative risk increase in dialysis patients vs. the general population for cerebral haemorrhage was 10.7. The relative risk for subarachnoid bleed was 4.0. Additionally, these bleeds occurred 10 years earlier than in the general population. The Rotterdam Study demonstrated similar increased risks for haemorrhagic stroke.13 The age- and sex-adjusted hazard ratio for haemorrhagic stroke was 4.1 (95% CI, 1.25–13.42) for the lowest quartile of the estimated GFR (<53.9 mL/min/1.73 m² for men; <50.4 mL/min/1.73 m² for women) vs. the highest quartile of estimated GFR (>72 mL/min/1.73 m² for men; >70.1 mL/min/1.73 m² for women). The presumed mechanism is the effect of uraemia on platelet function or perhaps the relationship between GFR and cerebral small-vessel disease.14 The devastating effects of cerebral haemorrhage are evident in the fact that among

* Corresponding author. Tel: +1 718 920 7383; fax: +1 646 292 5187, Email: fey2002@gmail.com

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2010. For permissions please email: journals.permissions@oxfordjournals.org.
anticoagulated patients in the general population, 76% of patients with intracranial haemorrhage either died or had severe disability at hospital discharge. The risk of bleeding is not limited to haemorrhagic stroke. In fact, the most serious source of bleeding is gastrointestinal bleeding. It accounts for 3–7% of all deaths in the dialysis population. The incidence of major bleeding was 2.5% per person-year. In a cross-sectional study of dialysis patients, the prevalence of a history of gastrointestinal bleeding was 24.3%. This may be because dialysis patients are at increased risk for gastrointestinal mucosal abnormalities which are found macroscopically on autopsy in 50% of dialysis patients. Given that most dialysis patients are exposed to anticoagulation of extracorporeal circuit three times a week, the high rate of bleeds is not a surprise. Finally, dialysis patients frequently have an increased need for invasive procedures and therefore are at risk of additional bleeding complications.

Warfarin in haemodialysis patients with atrial fibrillation

Given that the background rates of bleeding are increased in the dialysis patient, such a patient who has atrial fibrillation presents a treatment dilemma. Do the risks of anticoagulation outweigh its benefits? Importantly, there are no randomized trials conducted of full-intensity anticoagulation for any indication in patients with very low GFR. Dialysis patients were excluded from anticoagulation trials for atrial fibrillation such as the Atrial Fibrillation Follow-up Investigation of Rhythm Management study (AFFIRM) and the Stroke Prevention in Atrial Fibrillation study (SPAF). Warfarin in haemodialysis patients

### Table 1 Stroke risk scoring systems

<table>
<thead>
<tr>
<th>Scoring system</th>
<th>Low-risk score</th>
<th>Intermediate-risk score</th>
<th>High-risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHADS</strong>&lt;sup&gt;22,24&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One point each: recent congestive heart failure, hypertension, age over 75, diabetes</td>
<td>Score = 0; ischaemic stroke risk/year without treatment: 1.9%</td>
<td>Score = 1; ischaemic stroke risk/year without treatment: 2.8%</td>
<td>Score = 2–3; ischaemic stroke risk/year without treatment: 4.0–5.9%</td>
</tr>
<tr>
<td>Two points: history of prior stroke/TIA</td>
<td>Recommendation: ASA (81–325 mg)</td>
<td>Recommendation: ASA (81–325 mg) or warfarin (INR 2–3)</td>
<td>Score = 4–6; ischaemic stroke risk/year without treatment: 8.5%+</td>
</tr>
<tr>
<td><strong>CHA2DS2-VASc</strong>&lt;sup&gt;27,29&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One point each: congestive heart failure/LV dysfunction, hypertension, diabetes, vascular disease, age 65–74 years, sex category (female)</td>
<td>Score = 0; thrombo-embolic risk/year without treatment: 0%</td>
<td>Score = 1; thrombo-embolic risk/year without treatment: 0.7%</td>
<td>Score = 2–9; thrombo-embolic risk/year without treatment: 1.9%+</td>
</tr>
<tr>
<td>Two points each: history of prior age ≥75, stroke/TIA</td>
<td>Recommendation: no antithrombotic therapy or ASA (81–325mg)</td>
<td>Recommendation: ASA (81–325 mg) or warfarin (INR 2–3)</td>
<td>Recommendation: warfarin (INR 2–3)</td>
</tr>
</tbody>
</table>

**Stroke and bleeding risk assessment**

The decision to anticoagulate patients for atrial fibrillation is often guided by the CHADS<sub>2</sub> scoring system (Table 1). In the general population, treatment with warfarin reduces the annual stroke rate by 50% compared with no treatment. One of the major limitations to the CHADS<sub>2</sub> scoring system is that the majority of patients are classified as intermediate risk, including patients who may actually be at low risk. As a result, a fair number of individuals may be recommended for anticoagulation where there may be little or no benefit. A recent modification to the CHADS<sub>2</sub> scoring system has been proposed by Lip et al. to identify patients who are at truly low risk for thrombo-embolism. This scheme, referred to as the CHA2DS<sub>2</sub>-VASc scoring system, places weight on major (definitive) risk factors such as prior stroke or TIA and age ≥75, while recognizing the clinically relevant non-major risk factors of heart failure, hypertension, diabetes, and additionally, female gender, age 65–75 years, and atherosclerotic vascular disease (Table 1). These low-risk patients with a CHA2DS<sub>2</sub>-VASc score of 0 had a 0% thrombo-embolic rate at 1 year follow-up and thus could be managed with no antithrombotic therapy. In the validation population, the CHA2DS<sub>2</sub>-VASc scoring system identified ∼9% of the patients as being low risk (score = 0). The vast majority of the population had scores of 1 or greater and therefore was recommended anticoagulation therapy.

It should be noted that the CHADS<sub>2</sub> score was developed using data from the Atrial Fibrillation Investigators and SPAF, and validated using the National Registry of Atrial Fibrillation. These studies dealt with the general population and not the dialysis population. Similarly, the CHA2DS<sub>2</sub>-VASc scoring system was based upon the Euro Heart Survey on Atrial Fibrillation which included...
renal failure in only 5.8% of its study population, of which dialysis patients were not specifically subcategorized. Application of the CHADS2 or CHA2DS2-VASc scoring system to a dialysis patient with atrial fibrillation would result in the recommendation of anticoagulation in the vast majority of cases despite its unproven efficacy in such a population.

The benefit of stroke prevention in any patient is counterbalanced by the risk for haemorrhage. A pooled analysis of five trials with warfarin in atrial fibrillation demonstrated an annual rate of major bleeding of 1.0% in the control patients vs. 1.3% in non-dialysis patients treated with warfarin. The annual rate of intracranial haemorrhage was 0.1% in controls vs. 0.3% in non-dialysis patients treated with warfarin. Determining the risk of bleeding in a dialysis patient on warfarin is difficult. A number of scoring systems have been created to predict bleeding with warfarin treatment (Table 2). However, none of these bleeding risk models were created or validated specifically using a dialysis population.

A bleeding risk model by Shireman et al. incorporates age over 70, female gender, history of bleeding, alcohol/drug abuse, diabetes, anaemia, and antiplatelet use as bleeding risk factors. However, only 0.6% of the development and validation cohorts had a history of hepatic or renal failure. The outpatient bleeding risk index (OBRI) by Beyth et al. incorporates a creatinine >1.5 mg/dL in the index. While ~20% of the derivation and validation population had renal insufficiency (Cr >1.5 mg/dL), patients with end-stage renal disease requiring dialysis were not described. Gage et al. developed the HEMORR2HAGES scoring system to predict the risk of major bleeding among patients prescribed warfarin. Renal failure is a recognized risk factor in this classification.

However, this system was developed from the National Registry of Atrial Fibrillation in which only 10% of patients had hepatic or renal failure. Finally, a recent bleeding scoring system developed from the Euro Heart Survey with the acronym HAS-BLED also incorporates renal failure in the score, but it only had a small sample of renal failure patients as mentioned previously.

Barring a bleeding scoring system specifically designed for dialysis patients, the existing risk models do estimate a significant bleeding risk for dialysis patients on warfarin. Using the HAS-BLED system, a dialysis patient would already have a score of 3 for renal disease, anaemia, and labile INR. This would predict 3.7 bleeds per 100 patient-years. Many dialysis patients at baseline have a HEMORR2-HAGES score of 3 given reduced platelet function, renal disease, and anaemia. This puts the predicted annualized major bleeding rate at a high 8.4%. A similar number is obtained by the OBRI which predicts an annualized major bleeding rate of 8% for patients with just one point for renal insufficiency. One would expect that the existing risk models would underestimate the rates of bleeding in a dialysis population given the increased baseline risk of bleeding as discussed previously. Indeed, observational studies suggest that there is an increased bleeding risk with anticoagulation in this population. According to four cohort studies, rates of major bleeding in dialysis patients with full-intensity anticoagulation is 10–54% per patient year of exposure. This is at least twice that of dialysis patients not exposed to warfarin. Using retrospective data, Sood et al. developed a modified OBRI which estimates very high rates of bleeding specifically in dialysis patients on warfarin (10% annual risk of bleeding for OBRI score = 0; 32% annual risk of bleeding for OBRI score = 1 or 2; 54% annual risk of bleeding for OBRI score = 3 or 4).

---

### Table 2 Bleeding risk scoring systems

<table>
<thead>
<tr>
<th>Scoring system</th>
<th>% Annual bleeding risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low bleed risk</td>
</tr>
<tr>
<td>OBRI (outpatient bleeding risk index)&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Score = 0; 3%</td>
</tr>
<tr>
<td><strong>One point each:</strong> age ≥ 65, history of stroke, history of GI bleed</td>
<td></td>
</tr>
<tr>
<td><strong>One point (max) for any of the following:</strong> recent MI, Hct &lt;30%, Cr &gt;1.5 mg/dL, diabetes</td>
<td></td>
</tr>
<tr>
<td>HEMORR2-HAGES&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Score = 0–1; ~2–2.5%</td>
</tr>
<tr>
<td><strong>One point each:</strong> hepatic or renal disease, ethanol abuse, malignancy, older age (age &gt;75 years), reduced platelet count or function, uncontrolled hypertension, anaemia, genetic factors, excessive fall risk, stroke</td>
<td></td>
</tr>
<tr>
<td><strong>Two points:</strong> rebleeding risk</td>
<td></td>
</tr>
<tr>
<td>Shireman et al.&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Score ≤ 1.07; 1%</td>
</tr>
<tr>
<td>Score = 0.49(X&lt;sub&gt;Age&lt;/sub&gt; × 70 + 0.32(X&lt;sub&gt;FEMALE&lt;/sub&gt;) + 0.58(X&lt;sub&gt;Recent MI&lt;/sub&gt;) + 0.62(X&lt;sub&gt;Hct&lt;/sub&gt; &lt; 30%) + 0.71(X&lt;sub&gt;Alcohol/Drug Abuse&lt;/sub&gt;) + 0.27(X&lt;sub&gt;Diabetes&lt;/sub&gt;) + 0.86(X&lt;sub&gt;Anaemia&lt;/sub&gt;) + 0.32(X&lt;sub&gt;Antiplatelet&lt;/sub&gt;)</td>
<td></td>
</tr>
<tr>
<td>X = 1 when the specific characteristic is present and 0 if absent</td>
<td></td>
</tr>
<tr>
<td>HAS-BLED&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Score = 1–2; ~1–2%</td>
</tr>
<tr>
<td><strong>One point each:</strong> hypertension, abnormal renal function, abnormal liver function, stroke, bleeding, labile INRs, elderly age &gt;65, drugs, alcohol</td>
<td></td>
</tr>
</tbody>
</table>
Warfarin and antiplatelet drugs

When warfarin is combined with antiplatelet agents, the risk of bleeding in dialysis patients is even higher. Since many dialysis patients are already on aspirin for coronary artery disease, the addition of warfarin poses an additive risk. Roughly one-third of dialysis patients are on aspirin.3,42 Holden et al.17 reported that the incidence of major bleeding on warfarin alone is 3.1% per person-years vs. 4.4% per patient-years on aspirin alone vs. 6.3% per patient-years on warfarin with aspirin. The overwhelming majority of bleeding occurred in the gastrointestinal tract. Although the absolute rates of bleeding vary widely between studies, the combination of warfarin and aspirin places the dialysis patient at high risk for bleeding.

Warfarin pharmacokinetics

Warfarin use is complicated by a narrow therapeutic index and multiple drug–drug and drug–food interactions. These issues are magnified in the dialysis patient. Patients with severe chronic kidney disease (CKD) (GFR <30 mL/min/1.73 m²) require significantly lower warfarin doses. Additionally, they spend less time within their target range and are at a higher risk of over- or underanticoagulation when compared with patients with no, mild, or moderate CKD.43 Although warfarin is primarily metabolized by CYP2C9 in the liver, CKD can significantly reduce the non-renal clearance and bioavailability of warfarin.18 Animal studies have shown that there is a significant 40–85% downregulation of hepatic cytochrome P-450 metabolism in CKD.44 Dreisbach et al.45 demonstrated a 50% increase in the plasma warfarin S-enantiomer/R-enantiomer ratio among patients with ESRD relative to control subjects, which may reflect a selective decrease in hepatic CYP2C9 activity in renal failure. Since the S-enantiomer of warfarin is five times as powerful as the R-enantiomer, this would explain the lower dosage requirements for warfarin in dialysis patients. Owing to the decrease in CYP2C9 activity in dialysis patients, maintaining a therapeutic range of warfarin may be more difficult, especially when these patients may periodically be on other medications which inhibit, induce, or compete with CYP2C9 metabolism. Dialysis patients should therefore be monitored more closely while on warfarin therapy.

Specific studies of warfarin in dialysis patients

Studies specifically dealing with the efficacy of warfarin in dialysis patients with atrial fibrillation are limited (Table 3). In two studies comparing an undertreated population of dialysis patients with atrial fibrillation with patients without atrial fibrillation, there was no difference in stroke incidence.9,46 Recently, a retrospective cohort analysis of 1671 haemodialysis patients with pre-existing atrial fibrillation suggested that warfarin may actually increase stroke risk.47 After an average follow-up of 1.6 years, warfarin was noted to double the risk for stroke vs. non-warfarin use. Even patients with the highest CHADS2 scores or those with a history of stroke or TIA did not benefit from warfarin. An examination of the specific types of strokes encountered in the study reveals that haemorrhagic and, more importantly, ischaemic strokes significantly increased in warfarin users. The crude ischaemic stroke rate among warfarin users was 5.8 strokes per 100 patient-years (95% CI 4.6–7.4) vs. 2.3 strokes per 100 patient-years among non-users (95% CI 1.5–3.6). The crude haemorrhagic stroke rate among warfarin users was 1.2 strokes per 100 patient-years (95% CI 0.7–2.1) vs. 0.5 strokes per 100 patient-years among non-users (95% CI 0.2–1.4). The authors also demonstrated a dose–response relationship between warfarin and new stroke; higher INR levels resulted in a significantly higher stroke risk (P = 0.04 for trend).

Although the study by Chan et al. is a retrospective analysis, it raises the possibility that warfarin in dialysis patients puts the patient at increased risk for the outcome we sought to prevent—stroke. No study has subclassified ischaemic stroke into thrombo-embolic, thrombotic, and lacunar infarcts.47 Given the high rates of hypertension and diabetes in the dialysis population, it is possible that most of the ischaemic strokes in such

### Table 3 Studies of warfarin in dialysis patients with atrial fibrillation

<table>
<thead>
<tr>
<th>Study (year, design)</th>
<th>Number of dialysis patients with AF (no. of patients with AF on warfarin)</th>
<th>Mean follow-up</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>To et al.16 (2007, retrospective)</td>
<td>40 (10)</td>
<td>26 months</td>
<td>Cerebrovascular events did not differ between patients with AF from those without AF (5.0%/year vs. 2.4%/year; NS)</td>
</tr>
<tr>
<td>Genovesi et al.44 (2008, prospective multicentre)</td>
<td>127 (31 at enrolment)</td>
<td>36 months</td>
<td>No difference in stroke incidence when comparing an undertreated population of dialysis patients with AF (only 24% of AF patients were on warfarin at enrolment) compared with patients without AF (15.4 vs. 12.4%; P = 0.4).</td>
</tr>
<tr>
<td>DOPPS3 (2010, retrospective)</td>
<td>3245 (509)</td>
<td>Not reported</td>
<td>Warfarin use was associated with higher stroke risk; significantly in patients &gt;75 years of age (HR = 2.17; 95% CI 1.04–4.53, P = 0.04).</td>
</tr>
<tr>
<td>Chan et al.42 (2010, retrospective)</td>
<td>1671 (746)</td>
<td>19 months</td>
<td>Warfarin use increased haemorrhagic stroke risk (1.2%/year among warfarin users vs. 0.5%/year among non-users) and ischaemic stroke risk (5.8%/year among warfarin users vs. 2.3%/year among non-users) without increasing all-cause mortality or hospitalization</td>
</tr>
</tbody>
</table>

---

1669 Warfarin in dialysis patients
patients are small-vessel lacunar infarcts rather than thrombo-embolic in origin.41 We may be anticoagulating a population where the risk of haemorrhagic stroke may possibly exceed that of a thrombo-embolic event secondary to atrial fibrillation. In addition, warfarin might actually increase the risk of non-thrombo-embolic ischaemic stroke through its possible deleterious effects on vasculature.

The failure of warfarin to prevent strokes was also demonstrated in the observation of 3245 dialysis patients with atrial fibrillation in the Dialysis Outcomes and Practice Patterns Study (DOPPS).4 In fact, warfarin use was associated with higher stroke risk, particularly in those over 75 years of age. For patients ≤65 years, the HR = 1.29 (95% CI = 0.45–3.68; P = 0.63), for patients 66–75 years, the HR = 1.35 (95% CI = 0.69–2.63; P = 0.30), and for patients ≥75, the HR = 2.17 (95% CI = 1.04–4.53; P = 0.04). Although the study did not discriminate between ischaemic and haemorrhagic strokes and may be confounded (patients received warfarin because they have elevated risk of thrombo-embolic stroke) and/or causal (anticoagulation resulted in higher rates of haemorrhagic stroke), the use of warfarin in this patient population warrants caution as its benefit is uncertain.3

We cannot assume that the dialysis patient will derive the same benefit from treatments that have been demonstrated to be beneficial in the general population. This is illustrated in the belief that statins reduce cardiovascular mortality in dialysis patients. Observational studies had suggested that statin therapy reduced mortality in dialysis patients.48 However, two randomized controlled trials, 4D49 and AURORA,50 have failed to demonstrate a significant reduction in cardiovascular endpoints despite reductions in cholesterol in this specific patient population. Recognizing the problem in applying treatments to untested patient populations, there is clearly a need for randomized trials of warfarin in dialysis patients for atrial fibrillation.

## Warfarin and vascular calcification

Warfarin has been linked to ectopic calcification, which may adversely affect vascular health. Warfarin, a vitamin K antagonist, prevents the hepatic formation of clotting factors. However, vitamin K-dependent proteins occur in a number of extrahepatic tissues including arterial walls and bone. There is increasing evidence that subclinical deficiency of vitamin K has an effect on bone health and vascular calcification.51 Warfarin, through its ability to interfere with vitamin K remodelling, is therefore a model of peripheral vitamin K deficiency.18

In the hyperphosphataemic environment such as renal failure, vascular smooth muscle cells (VSMCs) have the capacity to transform into osteoblast-like cells capable of producing ectopic bone.52 These VSMCs initiate and regulate vascular calcification. Matrix Gla protein (MGP) inhibits the calcification process above; however, the protein is activated by a process which requires vitamin K.53–55 Warfarin therefore may lead to vascular calcification. In the murine model, MGP-deficient mice develop extensive vascular calcification in the aorta and die early from aortic rupture. Administration of vitamin K antagonists in rodents also induces vascular calcification. Even in non-CKD human patients, vitamin K antagonists significantly increase the prevalence and extent of aortic valve and coronary calcifications.56

In dialysis patients, warfarin has been linked to calcific uraemic arteriopathy (calciphylaxis) as well as aortic valve calcification.57–59 Calcific uraemic arteriopathy occurs in 1–4% of dialysis patients and portends a poor prognosis (45% mortality at 12 months).60 It is a small- and medium-vessel vasculopathy that involves mural calcification with intimal proliferation, fibrosis, and thrombosis which is usually associated with chronic renal disease and secondary hyperparathyroidism.61,62 Most often, it affects the skin and leads to non-healing ulcers and subcutaneous calcification; however, it can manifest as a rapidly progressive, cutaneous necrosis, and be seen as extensive calcification of small and medium-sized arteries even on X-ray.62 Calcific uraemic arteriopathy has also been described in visceral organs such as the heart, lungs, pancreas, intestines, and skeletal muscle. Significant infectious morbidity can be seen within weeks of diagnosis and death commonly results within months due to sepsis or visceral involvement by the vasculopathy.62 Warfarin is a recognized precipitant of calcific uraemic arteriopathy in addition to other risk factors such as a high calcium-phosphate product, hypercalcaemia, hyperphosphataemia, hyperparathyroidism, low serum albumin, vitamin D treatment, corticosteroids, immunosuppression, diabetes, and dialysis dependency.62 The dialysis patient is already at increased risk for calcific uraemic arteriopathy and the addition of warfarin may add additional risk. Recognizing the negative effects of warfarin upon vascular health from animal models and the link between warfarin and calcific uraemic arteriopathy, one might hypothesize that warfarin could induce calcification in cerebral vasculature and perhaps may have a role in the development of stroke in these patients.

### Table 4 Risk stratification for warfarin use in stroke prevention in dialysis patients with atrial fibrillation

<table>
<thead>
<tr>
<th>Risk stratification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favours warfarin</td>
<td>Known atrial thrombus Prosthetic heart valve CHADS2 score greater than or equal to the OBI score by two points Mitral stenosis Previous TIA or stroke Patient preference</td>
</tr>
<tr>
<td>Favours no warfarin*</td>
<td>Age &lt;65 years with no risk factors Uncontrolled hypertension Concurrent antiplatelet use History of active calciphylaxis Previous life-threatening haemorrhage Severe malnutrition Non-compliance Frequent falls</td>
</tr>
</tbody>
</table>

*Consider the use of antiplatelet agents in patients not suitable for warfarin.

Adapted from Sood et al.51
Conclusion

All decisions regarding anticoagulation depend on an assessment of risk and benefit in the individual patient. In the dialysis patient with atrial fibrillation, the risks of warfarin are many and the benefits are unproven. Not only is there a lack of evidence for the efficacy of warfarin in preventing strokes in the dialysis patient with atrial fibrillation, but data show that warfarin increases the risk of hemorrhagic stroke, major gastrointestinal bleed, vascular calcification, and possibly ischaemic stroke. There are certain situations where the decision to start warfarin should be straightforward, such as a patient with a known atrial thrombus or a patient pericardioversion. However, the long-term perceived efficacy of anticoagulation based on a high CHADS2 or CHA2DS2-VASc score, or even prior stroke or TIA in dialysis patients with atrial fibrillation may ultimately prove to be false.

A risk–benefit analysis based on the CHADS2 or CHA2DS2-VASc score is simply not applicable in the dialysis patient. Sood et al.41 suggested parameters to help guide the decision between anticoagulating vs. not anticoagulating dialysis patients with atrial fibrillation (Table 4). In the majority of dialysis patients with atrial fibrillation but without multiple compelling risk factors for anticoagulation, the case for avoiding warfarin would be clear. Until we have randomized prospective data to guide our management of such patients, warfarin should only be reserved for those patients at highest risk for thrombo-embolic stroke and the INR should be closely monitored if implemented.

Conflict of interest: none declared.

Authorship: All authors had access to the data and a role in writing the manuscript.

References


