In Focus

Balancing thromboembolic risk against vitamin K antagonist-related bleeding and accelerated calcification: is fondaparinux the Holy Grail for end-stage renal disease patients with atrial fibrillation?

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Patients with end-stage renal disease (ESRD) may classically present with highly contrasting derangements of haemostasis, ranging from haemorrhagic diathesis to increased thrombotic risk [1]. Unfortunately, the current guidelines on anticoagulant (AC) therapy do not fully cover the spectrum of thromboembolic conditions potentially affecting ESRD patients [2–4]. These guidelines recommend standard AC treatments for conditions, such as acute deep vein thrombosis, pulmonary embolism, mechanical heart valves and antiphospholipid syndrome, but appear much less clear-cut when dealing with another very common thromboembolic condition, such as atrial fibrillation (AF).

In this regard, the value of conventional oral AC (OAC) therapy with vitamin K antagonists (VKA), such as warfarin, for ESRD patients with AF has been seriously challenged, except for those with prior cardioembolic ischaemic stroke [5]. Other recent data suggest some benefit for VKA use in less-advanced stages of CKD, even though at the price of an increased risk of haemorrhagic complications [6].

Following the demonstration of the better efficacy/manageability compared with conventional OAC, a number of new AC drugs have been introduced that act by direct inhibition of either thrombin (dabigatran etexilate) or factor Xa (rivaroxaban and apixaban) [7]. All of these new drugs have the advantage of oral administration, without needing long-term monitoring; however, they are primarily excreted by the kidney, with a substantial renal clearance [8]. Thus, it is not surprising that renal impairment is one of the putative risk factors for bleeding complications. Unfortunately, a major problem is that renal patients, especially those with ESRD, have been often excluded from randomized controlled trials (RCTs) with these novel AC drugs [8].

Two major issues, specific to the clinical context of ESRD, render conventional OAC therapy even more challenging [9]: (i) the increased bleeding risk notoriously associated with declining kidney function; (ii) the recently discovered side-effect of VKA (the most commonly used conventional OAC drugs), consisting in the acceleration of medial and intimal vascular calcification, a strong and independent risk factor for cardiovascular complications and mortality [10].

Thus, alternatives to VKA with a sound safety profile are urgently required, especially for patients with the most advanced stages of chronic kidney disease (CKD).

In this issue of *Nephrol Dial Transplant.*, Speeckaert et al. [11] suggest that Fondaparinux, a parenteral indirect FXa inhibitor that shows a prolonged half-life in ESRD patients, thus allowing thrice weekly administration, could represent a possible therapeutic option in the conundrum of the prophylaxis against thromboembolic risk in ESRD with AF.

In their observational pilot study on six ESRD patients undergoing a total of 459 treatments, Fondaparinux administered
in the circuit at the start of each dialysis treatment proved to be safe and efficacious in achieving anticoagulation in both the patient and the circuit. Only 2 episodes of major clotting (i.e. premature termination of the dialysis session) out of 459 dialysis sessions were observed, without any major bleeding complications. Their approach is attractive, not only for its simplicity and low costs, but also because Fondaparinux—at least on the basis of its mechanisms of action—does not share with coumarin derivatives a negative impact on the vascular calcification process.

AF is the most common cardiac arrhythmia observed in clinical practice (prevalence >5% in the elderly population) and is associated with both a doubling of all-cause/cardiovascular mortality and a 5-fold increase in age-adjusted stroke rate; this risk is reduced by at least 60% by conventional OAC therapy with adjusted-dose warfarin [12]. Thus, current guidelines strongly recommend the use of VKA for ischemic stroke prophylaxis in AF, provided that stratification for ischemic stroke risk status be performed according to the currently available scores [2–4]. VKAs are indirect OACs that exert their AC effect by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide (vitamin K epoxide), thereby modulating the post-translational gamma-carboxylation of glutamate residues (Gla) on the N-terminal regions of several vitamin K-dependent proteins: treatment with coumarins leads to the hepatic production of partially carboxylated and decarboxylated proteins of the coagulation cascade (factors II, VII, IX and X) with reduced coagulant activity [2, 10]. However, even with careful monitoring of AC therapy, patients with AF and normal renal function may experience major bleeding, at a rate reaching 3.0% per year [7].

In the case of CKD patients, a complex bidirectional relationship exists with AF. About 20% of patients with CKD have AF, and one-third of AF outpatients have CKD [13, 14]. Moreover, Stage 3 CKD is an independent predictor of stroke in patients with AF [15] and, finally, AF in CKD patients has been recently demonstrated as a factor of progression towards ESRD [16]. Warfarin reduces stroke risk by 76% in Stage 3 CKD, yet at the cost of about twice the rate of major bleeding episodes (average about 5–6% per year in recent clinical trials), compared with non-CKD patients [12]. All recent Phase 3 trials evaluating novel AC in patients with AF have included patients with Stage 3 CKD, supporting a role for these drugs as reasonable alternatives to VKA for stroke prevention; the Food and Drug Administration (FDA), Health Canada and European Medicines Agency (EMA) have, in fact, approved dabigatran and rivaroxaban for use in AF patients with Stage 3 CKD, while apixaban is currently undergoing evaluation by these regulatory agencies.

Notwithstanding the indications of some recent guidelines [3], no robust data support the safety and efficacy of VKA for Stage 4 CKD patients with AF; in fact, Stage 4 CKD emerged as an independent predictor of major bleeding during warfarin AC in one large study on an outpatient cohort with AF [17]. Among the novel AC drugs, only dabigatran (FDA) and rivaroxaban (FDA and EMA) have been approved for use in Stage 4 CKD patients, although data supporting the efficacy and safety of these drugs in this specific clinical context are lacking [12].

All of these problems are magnified in the case of ESRD patients on haemodialysis (HD), who have an AF prevalence of 7–20%, rising up to 22.5–37% in older subjects [12, 18].

It is uncertain if AF per se in ESRD increases thromboembolic risk, since the high background risk of stroke in these patients represents a powerful confounder; however, AF is associated with remarkable excess mortality in this clinical setting [19, 20]. Wide variations in the use of conventional AC in ESRD patients on dialysis are observed among different countries (from 5% in Germany, Spain or Japan to as high as 26–37% in the USA and Canada) [21]. OAC dose in ESRD must be carefully adjusted based on close INR monitoring, due to both lower dose requirement (20–25% less), and increased variability of INR, with inherent difficulties in keeping it within the therapeutic range [12].

ESRD patients have a significantly increased risk of major bleeding and haemorrhagic stroke with OAC [12]. Moreover, keeping a fine balance between ischaemic stroke risk against haemorrhagic risk is not easy, since cardioembolic stroke risk scores and bleeding risk stratification tools have not been validated in this clinical setting [9].

In summary, guidelines and risk score tools suggest that ESRD patients with AF represent a high-risk subgroup likely needing OAC. However, given their heavy haemorrhagic risk, a high degree of caution is warranted when implementing VKA in this clinical setting. Unfortunately, no RCTs exist on this topic, with decision-making being based on observational data and experts’ opinions.

The uncertain balance between increased ischaemic stroke risk and the high rate of bleeding complications is not the only reason of concern associated with VKA use in CKD/ESRD patients. In fact, acceleration of arterial medial and valvular calcification (i.e. extraskeletal calcification) may also represent a potential adverse effect of long-term treatment with coumarin derivatives. Vascular calcifications are found in 60–80% of HD patients [22] and are associated with arteriolosclerosis and increased arterial stiffness, altered left ventricular (LV) diastolic function and LV hypertrophy, as well as with an increased risk of cardiovascular events and mortality, independently from the traditional atherogenic risk factors [23]. Vascular calcification is a highly active process driven by different coexisting factors (high CaXP product, high Parathormon levels, inflammation etc.) and is effectively controlled by a number of regulatory proteins produced in the vascular wall [10]. Vitamin K acts as a local regulator of vascular calcification, being the main co-factor in the activation by gamma-glutamyl carboxylase of the most important local calcification inhibitor in the arterial media, namely the matrix-Gla protein (MGP), which is secreted by osteoclasts, chondrocytes and vascular smooth muscle cells of the arterial media [10]. The protein sequence of MGP includes nine glutamate residues, five of which need to be carboxylated to yield bioactive MGP. This activation depends on vitamin K availability, resembling the biosynthesis of coagulation factors II, VII, IX and X in the liver; thus, by blocking vitamin K recycling, VKA also decrease the inhibitory activity of anti-calcification proteins, while adequate intake of vitamin K1 favours fully carboxylated, and active, MGP [10].
In this regard, the side-effects of VKA on the extraskeletal calcification process are likely to be potentiated by the peculiar vitamin K status of patients with CKD/ESRD. These patients, in fact, and especially those with ESRD on HD, have a high prevalence of subclinical vitamin K deficiency. This is due to exhaustion of vitamin stores secondary to the high requirements by vitamin K-dependent proteins inhibiting calcification. Moreover, also dietary restrictions, such as diets low in potassium (fewer leafy green vegetables that are rich in vitamin K1) and phosphorus (fewer dairy products rich in vitamin K2) are likely to play an important role [24, 25].

Vitamin K status seems to be critical in the predisposition of blood vessels to calcification, at least in experimental models of CKD. Specifically, recent data suggest that therapeutic levels of warfarin may increase the vascular calcification severity in a vitamin K-dependent way, while a diet rich in vitamin K1 largely prevented the development of vascular calcification in a CKD rat model [26]. Taken together, these data indicate that the effects of therapeutic warfarin on the top of an already low vitamin K status could be important in accelerating the vascular calcification rate. Along this line, it has been demonstrated that the levels of inactive (uncarboxylated) MGP predict survival in ESRD patients [27], and that vitamin K2 supplementation is able to improve the carboxylation status (activity) of vitamin K-dependent proteins in a dose-dependent fashion, suggesting that restoration of MGP functionality may be important in preventing the vascular calcification process [28]. However, whether increased vitamin K intake is protective against vascular calcifications in patients with CKD/ESRD, and is capable of decreasing their high cardiovascular mortality, remains to be tested in prospective clinical trials.

Fondaparinux is a synthetic, highly sulphated pentasaccharide acting as a selective anti-Xa inhibitor [29], without significant interaction with platelets or platelet factor 4. Thus, unlike heparins, it is not expected to induce thrombocytopenia. Complete pharmacokinetic parameters are summarized in Table 1 [29]. In Phase 3 trials, non-inferiority or superiority has been demonstrated for Fondaparinux in both the prevention and the treatment of venous thromboembolism compared with unfractionated heparin (UFH) or low-molecular-weight heparins (LMWH), with similar or higher safety; recent ACCP guidelines suggest prophylactic or therapeutic doses of Fondaparinux of the drug as safe as a prophylactic or therapeutics dose of UFH or LMWH [30].

The limited data on patients with advanced CKD have been obtained from retrospective cohort studies or post hoc analyses, since patients with serum creatinine of >2 mg/dL have been excluded in most of the trials. Although impaired kidney function was a predictor of bleeding complications, no major differences were found as compared with LMWH [29]. A trend towards drug accumulation with decreasing renal function was documented, as Fondaparinux clearance was decreased by 25% in patients with a GFR of <60 mL/min and by 43% in patients with a GFR of <30 mL/min [12, 29]. Data on the use of Fondaparinux in ESRD patients on chronic dialysis are scanty, since <40 cases are reported in the literature, with different indications (Table 2), the most common being circuit patency, patients with heparin-induced thrombocytopenia included.

The approach proposed by Speeckaert et al. [11], if confirmed, seems to be a reasonable option. First, it is very simple. The drug is administered as a single bolus by dialysis nurses in the inlet blood line of the circuit at the start of dialysis, thereby obviating problems such as poor patient compliance to VKA and dose errors.

Secondly, this approach exploits some apparently unfavourable pharmacokinetic characteristics of Fondaparinux (parenteral-only formulation and prolonged half-life in advanced stage CKD) that actually render the drug very appealing in the specific category of dialysis patients. In the study by Speeckaert et al. [11], a thrice weekly administration in the extracorporeal circuit, at the start of dialysis, allowed an acceptable simultaneous anticoagulation in both the extracorporeal circulation and the patient. In fact, with a 2.5 mg intravenous dose (about 0.03 mg/kg) at dialysis start, anti-Xa levels were within the therapeutic range at the start and at the end of treatment, and also in the longer interdialytic interval.

Thirdly, due to its pentasaccharide structure, Fondaparinux is less immunogenic—if at all—for what concerns the risk of HIT; in fact, for the immunologic reaction of HIT antibodies to occur with PF4-saccharid complexes, 12–16 saccharides are needed [12]. Since the risk of HIT with Fondaparinux is considered extremely low or even inexistent, in many cases the drug has been successfully used for HIT treatment in dialysis patients (Table 2).

Fourthly, cost issues seem not to be disadvantageous compared with conventional OAC, even including more intensive

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**Table 1: Mechanism of action, pharmacokinetics and dose of Fondaparinux**

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>High affinity inactivation of factor Xa, due to strong binding to ATIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>107% (95% CI 102–112) at 2 h from subcutaneous administration</td>
</tr>
<tr>
<td>Terminal half-life</td>
<td>17 h in young healthy subjects</td>
</tr>
<tr>
<td>Elimination</td>
<td>Almost completely (80%) excreted unchanged in the urine</td>
</tr>
<tr>
<td>Within-subject variability</td>
<td>Low (4.4–5.5%)</td>
</tr>
<tr>
<td>Inter-subject variability</td>
<td>Low (11.6–17.5%)</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Unnecessary in patients with normal renal function</td>
</tr>
<tr>
<td>Doses for VTE</td>
<td>Prevention of VTE (2.5 mg subcutaneously once daily)</td>
</tr>
<tr>
<td></td>
<td>Therapy of VTE (7.5 mg subcutaneously once daily, 5 mg if BW of &lt;50 kg, 10 mg if BW of &gt;100 kg)</td>
</tr>
</tbody>
</table>

ATIII, anti-thrombin III; BW, body weight; VTE, venous thromboembolism.
<table>
<thead>
<tr>
<th>Study</th>
<th>Indication to Fondaparinux</th>
<th>Design</th>
<th>No of patients</th>
<th>Age (years)</th>
<th>Dose (mg)</th>
<th>Anti-Xa (IU/mL or s)</th>
<th>Duration of treatment</th>
<th>Safety/efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haase et al., Nephrol Dial Transplant 2005; 20: 444–446</td>
<td>HD circuit patency in HIT</td>
<td>Case report</td>
<td>1</td>
<td>52</td>
<td>2.5 mg in the circuit</td>
<td>70–110 s</td>
<td>10 weeks</td>
<td>No bleeding complications, good patency of the circuit</td>
</tr>
<tr>
<td>Kalicki et al., Blood Coag, Fibrinolysis Cell Haemost 2007; 98: 1200–1207</td>
<td>HD circuit patency</td>
<td>Cohort study</td>
<td>12</td>
<td>57.7 (∓18.6)</td>
<td>0.05 mg/kg in the circuit</td>
<td>0.61 (∓0.14)–0.89 (∓0.24)</td>
<td>9 sessions each patient</td>
<td>Clot formation comparable with UFH, few minor bleeding events. High-flux filters used</td>
</tr>
<tr>
<td>Sharathkumar et al., J Pediatr Hematol 2007; 28: 581–584</td>
<td>PE treatment</td>
<td>Case report</td>
<td>1</td>
<td>15</td>
<td>0.0125–0.05 mg/kg in the circuit</td>
<td>0.66–2.05</td>
<td>21 days</td>
<td>Minor bleeding events, dose adjustments needed</td>
</tr>
<tr>
<td>Sombolos et al., Int J Clin Pharmacol Ther 2008; 46: 198–203</td>
<td>HD circuit patency</td>
<td>Cohort study</td>
<td>16</td>
<td>Not specified</td>
<td>2.5 mg single dose in the circuit</td>
<td>0.12–0.58 pre-HD</td>
<td>Single dose</td>
<td>Increased clot formation with high-flux polysulphone filters compared with low-flux polysulphone</td>
</tr>
<tr>
<td>Montagnac et al., Nephrol Therapeut 2010; 6:581–584</td>
<td>HD circuit patency in HIT</td>
<td>Case report</td>
<td>1</td>
<td>58</td>
<td>2.5 mg s at each HD, 67 kg</td>
<td>0.35 pre-HD, – 0.75 post-HD</td>
<td>Four months</td>
<td>No bleeding; adequate prevention of circuit clotting. High-flux filters used</td>
</tr>
<tr>
<td>Mahieu et al., Artif Org 2013; 37:482–494</td>
<td>HDF circuit patency in HIT</td>
<td>Observational dose-finding study</td>
<td>4</td>
<td>74.5 (±10) (range 63–84)</td>
<td>0.03–0.05 mg/kg in the circuit</td>
<td>0.46 (0.33–0.63)</td>
<td>3 months 160 sessions</td>
<td>No bleeding; Fondaparinux therapy at a dose of 0.03–0.04 mg/kg prevented circuit clotting (severe clotting 4 of 160, 2.5%). Post-dilution HDF</td>
</tr>
<tr>
<td>Ho et al., Am J Kidney Dis 2013; 61: 523–526</td>
<td>HD circuit patency in HIT, or in previous anaphylactoid reaction to heparin</td>
<td>Case series</td>
<td>3</td>
<td>71.6</td>
<td>2.5 mg OD</td>
<td>0.17 (0.11–0.25) pre-HD, 0.31 (0.24–0.64) post-HD</td>
<td>Maximum 126 HD sessions</td>
<td>No bleeding complications, adequate anticoagulation of the circuit</td>
</tr>
<tr>
<td>Speeckaert et al. [11]</td>
<td>Substitute of conventional OAC for AF and HD circuit patency</td>
<td>Case series</td>
<td>6</td>
<td>73.8 (68.9–76)</td>
<td>2.5 mg at each dialysis in the circuit</td>
<td>0.36 (0.30–0.42) pre-HD, 0.75 (0.65–0.80) post-HD</td>
<td>459 sessions in six patients</td>
<td>2 of 459 cases of major clotting (premature restitution needed). No major bleeding observed</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; HD, haemodialysis; HDF, haemodiafiltration; HIT, heparin-induced thrombocytopenia; OAC, oral anticoagulant therapy; sc, subcutaneously; UFH, unfractionated heparin.
Data presented as mean (±SD) or median (range).
monitoring by anti-Xa activity measurements in the first 4–6 weeks of the implementation phase.

Some limitations of the study by Speeckaert et al. [11] should be underscored.

(i) This is a pilot study, suggesting a high degree of caution in interpreting the results.

(ii) While it is true that new ACs including Fondaparinux do not require routine and prolonged coagulation monitoring [31], yet in special situations such as renal failure and obesity, in children and, more broadly, in non-licensed indications, at least anti-factor Xa activity with a chromogenic assay calibrated with Fondaparinux, should be recommended in the first 4–6 weeks of therapy.

(iii) Albeit extravascular accelerated calcification associated with VKA is avoided with Fondaparinux, data on its putative long-term adverse effects are quite scarce, as in none of the published studies the duration of therapy lasted more than 3–8 months (Table 2).

(iv) The operational characteristics of specific dialysis modalities must be taken into account, as they may significantly affect the pharmacokinetic properties of the drug. For example, as Fondaparinux is a solute having a relatively low molecular weight (1728 Da), and an apparently low distribution volume (7–11 L), the use of high-flux membranes has been associated with a trend to increased circuit clotting in some studies (Table 2), indirectly suggesting a more efficient drug removal.

(v) Residual renal function is also to be taken into account, as a trend to relatively higher predialytic anti-Xa activity levels was observed in anuric compared with non-anuric patients [29].

(vi) The long half-life of Fondaparinux would make it necessary to have an antidote in case of major haemorrhagic complications. However, the proposed antidotes (recombinant factor VIIa and recombinant antithrombin variant) [32–33] are not available for routine use, nor have they been tested in controlled clinical trials. In case of overdose and/or haemorrhagic complications, high-efficiency (convective) treatments are obviously an option.

(vii) At present, the use of Fondaparinux as proposed in the study of Speeckaert et al. [11] should be considered as off-label. In fact, the drug is currently contraindicated in patients with GFR of <20 mL/min by the EMA, and in patients with <30 mL/min by the FDA. However, the extremely high risk for accelerated calcification in ESRD patients on VKA could represent be a potent argument to modify this formal contraindications.

On the basis of recent data on accelerated cardiovascular calcification risk associated with conventional OAC with VKA, Fondaparinux could represent a reasonable option for ESRD patients with AF who have the indication for ischaemic stroke prevention. However, more data are needed from RCTs directly comparing Fondaparinux with VKA in renal patients.

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CONFLICT OF INTEREST STATEMENT

The content of this paper has not been published previously in whole or part. None declared.

(See related article by Speeckaert et al. Fondaparinux as an alternative to vitamin K antagonists in haemodialysis patients. Nephrol Dial Transplant 2013; 28: 3090–3095.)

REFERENCES


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