Atrial fibrillation, moderate chronic kidney disease, and stroke prevention: new anticoagulants, new hope

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This editorial refers to ‘Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment’†, by K.A.A. Fox et al., on page 2387

Chronic kidney disease (CKD) affects up to 10% of adults1 and carries a high risk for cardiovascular disease, including atrial fibrillation (AF).2 In a large population-based long-term follow-up study involving 10 328 patients with impaired renal function, there was a strong association between the degree of impaired renal function and the risk of development of AF.3 Specifically, the hazard ratio for development of AF increased from 1.3 [95% confidence interval (CI) 1.1–1.6] in patients with normal renal function to 3.2 (95% CI 2.0–5.0; P < 0.0001) in those with an estimated glomerular filtration rate (eGFR) of 15–29 mL/min.3 This increase in HR was independent of other known risk factors for AF. The mechanisms by which CKD leads to AF are not completely understood, but increased likelihood of development of hypertension, fluid overload, pathological activation of the intrarenal renin–angiotensin–aldosterone system with subsequent enhanced myocardial fibrosis, and other factors are likely to play an important role. Whereas it is well appreciated that stroke risk in end-stage renal disease is elevated,4 the issue of AF-associated thrombo-embolic risk is more controversial in patients with CKD not on renal replacement. Recently, Go and colleagues utilized a large administrative database containing data from 10 908 AF patients to demonstrate that a lower level of eGFR was associated with a graded, increased risk of ischaemic stroke and other systemic embolism which was independent of known risk factors in AF.5 In patients with an eGFR of <45 mL/min, stroke risk was 4.22 per 100 patient-years. Mechanisms underlying the increased stroke risk in CKD are likely to be multifactorial but include augmentation of the underlying prothrombotic diathesis by several pathways.5

Despite this increased risk for AF-associated thromboembolism, many patients with CKD are not receiving oral anticoagulation therapy,6 mostly because of fear of bleeding with warfarin. In fact, it has been shown that the risk of bleeding associated with warfarin therapy is particularly high in patients with CKD.7 Hence, there is a formidable clinical dilemma in AF patients who are concomitantly suffering from renal disease.

Recently, several new oral anticoagulants have been tested in large trials involving thousands of patients with AF.8–10 All of these new anticoagulants are partially eliminated by renal clearance. In CKD patients, therefore, the half-lives of these novel anticoagulants may be prolonged, resulting in enhanced antithrombotic efficacy. On the other hand, there might be a higher than normal bleeding risk in CKD patients with these compounds.

The ROCKET-AF study tested the efficacy and safety of rivaroxaban, a novel factor Xa inhibitor, in 14 264 patients with non-valvular AF and additional stroke risk factors compared with standard warfarin therapy aiming at an international normalized ratio (INR) of 2.0–3.0.10 Rivaroxaban is predominantly metabolized by the liver, but approximately one-third of the drug is cleared by the kidneys.11,12 The ROCKET-AF trial excluded patients with an eGFR <30 mL/min, whereas the daily dose of rivaroxaban was reduced from 20 to 15 mg in patients with an eGFR of 30–49 mL/min based on available pharmacodynamic data and pharmacokinetic modelling.12 Fox and colleagues have now reported the results from a substudy of ROCKET-AF in 2950 subjects with moderate renal impairment.14

In agreement with previous studies, patients with moderate kidney dysfunction had at baseline more concomitant disease burden including higher prevalence of prior myocardial infarction, heart failure, and peripheral vascular disease. Compared with subjects with normal renal function, patients with CKD had a higher incidence of stroke and systemic embolic events, irrespective of the treatment assignment (i.e. warfarin or rivaroxaban). This observation confirms results of studies evaluating the direct thrombin inhibitor dabigatran8 or the novel factor Xa inhibitor apixaban9 where strokes and systemic embolic events were reduced compared with standard warfarin therapy.
more frequent among patients with impaired renal function. In ROCKET-AF, the efficacy results in patients with impaired eGFR were consistent with the results observed in the overall study population (see Table 1) with a non-significant interaction P-value of 0.76. Specifically, the HR for the primary outcome measure of stroke/systemic embolic events was 0.84 in patients with reduced and 0.78 in patients with normal eGFR.

Importantly, the benefit of rivaroxaban in terms of stroke prevention did not come at the expense of a higher bleeding rate. Major and clinically relevant bleeds (primary safety outcome in ROCKET-AF) were more frequently observed in CKD patients irrespective of treatment assignment. However, there was no excess bleeding on rivaroxaban compared with warfarin. Of note, critical organ bleeding and fatal bleeds were actually less frequently encountered with rivaroxaban than with warfarin.

In summary, therefore, we now have important data from three novel anticoagulants regarding stroke prevention in AF patients with CKD. The benefits of these new anticoagulants in patients with CKD were consistent with those in the overall study populations. Of note, rivaroxaban, dabigatran, and apixaban were not associated with higher bleeding rates in CKD. In all three studies, however, patients with an eGFR < 30 mL/min were excluded. Accordingly, there is still a paucity of data in AF patients with more severe degrees of CKD and in those on renal replacement therapy.

**Conflict of interest:** none declared.

**References**


### Table 1

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stroke/SEE in patients without CKD (eGFR ≥ 50 mL/min)</th>
<th>HR, 95% CI</th>
<th>Stroke/SEE in patients with CKD (eGFR 30–49 mL/min)</th>
<th>HR, 95% CI</th>
<th>P-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>RELY</td>
<td>Dabigatran 110 mg b.i.d., 1.35%/year</td>
<td>0.92, 0.71–1.14</td>
<td>Dabigatran 110 mg b.i.d., 2.33%/year</td>
<td>0.78, 0.53–1.15</td>
<td>0.27</td>
</tr>
<tr>
<td>ROCKET</td>
<td>Rivaroxaban 20 mg o.d., 1.57%/year</td>
<td>0.88, 0.35–2.45</td>
<td>Rivaroxaban 15 mg o.d., 2.57%/year</td>
<td>0.78, 0.29–2.31</td>
<td>0.84</td>
</tr>
</tbody>
</table>

**Note:** Rivaroxaban was administered 2.5 mg b.i.d. in patients who met two of the following criteria: age > 80 years, body weight > 61 kg, serum creatinine > 1.5 mg/dL.

CI, confidence interval; HR, hazard ratio; SEE, systemic embolic events.


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**CARDIOVASCULAR FLASHLIGHT**

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**Chest pain with spurious ST-segment elevation**

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A 46-year-old male, ex-smoker, with hypertension and hypercholesterolemia, was attended by the emergency mobile service (EMS) because of retrosternal chest pain lasting for 30 min. The initial electrocardiogram (ECG), with waning symptoms (Panel A), showed sinus tachycardia, anterior ST-segment elevation and J point descent in inferior leads and V5-V6. A second ECG (Panel B) showed no ST changes.

The patient was admitted to our hospital with presumptive diagnosis of acute coronary syndrome with transient ST-segment elevation. He remained asymptomatic under treatment with intravenous nitroglycerin, aspirin, clopidogrel, and enoxaparin. Physical examination was normal. Blood analysis including serial CPK and troponin-T determinations was normal. Repeated ECG and telemetry did not show ST changes. Chest X-ray and transthoracic echocardiogram were normal. Coronary angiography showed non-significant stenosis and intravenous metilergonovine did not promote coronary vasospasm.

Retrospective analysis of ECGs revealed different high-pass filters in ECG with ST-segment elevation (band-pass filters 1–30 Hz) with respect to ECG without ST changes (0.05–40 Hz). New ECG obtained with the same EMS monitor/recorder, in the asymptomatic patient, again displayed marked ST changes. Inadequate high-pass filters programmed for monitor and 3-lead manual strips (1 Hz) reproduced ST-segment elevation that disappeared instantaneously during 12-lead automatic ECG (Panel C) with standard high-pass filters (0.05 Hz).

ST-segment changes are important for the diagnosis of acute ischaemia, pericarditis, Brugada syndrome, and other electrical diseases, but ST-segment configuration can be spuriously changed by electronic means. This case underscores the importance of adequate technical standards in ECG recordings.

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