Review: In renal failure, direct oral anticoagulants reduce risk for hemorrhagic stroke compared with VKAs

Clinical impact ratings: ★★★★★☆☆☆☆

**Question**
In patients with renal failure, do direct oral anticoagulants (DOACs) reduce risks for hemorrhagic stroke and major bleeding compared with vitamin K antagonists (VKAs)?

**Review scope**
Included studies compared DOACs (apixaban, dabigatran, edoxaban, or rivaroxaban) with VKAs in adults with nonvalvular atrial fibrillation (AF) or venous thromboembolism (VTE) and reported safety outcomes separately for those with different levels of renal impairment (estimated creatinine clearance [ eCrCl ] < 50 mL/min or 50 to 80 mL/min). Exclusion criteria included use of placebo control. Outcomes were intracranial hemorrhage, and major bleeding or a composite of major bleeding or clinically relevant nonmajor bleeding. PROSPERO registry CRD42014013730.

**Review methods**
MEDLINE, EMBASE/Excerpta Medica, and Cochrane Library (all to Nov 2015); ClinicalTrials.gov; Web sites; conference abstracts; and other systematic reviews were searched for randomized controlled trials (RCTs). 9 RCTs ( eCrCl < 50 mL/min, n = 13 996; eCrCl 50 to 80 mL/min, n = 40 681) met the inclusion criteria. 5 RCTs were done in patients with AF (follow-up 1.6 to 2.8 y) and 4 in those with acute VTE (follow-up 0.25 to 1 y). 4 RCTs evaluated rivaroxaban, 2 each evaluated apixaban or edoxaban, and 1 evaluated dabigatran. DOACs were compared with warfarin in 6 RCTs and enoxaparin followed by warfarin in 3 RCTs. All 9 RCTs had adequate allocation concealment and adequate outcome data, and 6 blinded patients, study staff, and outcome assessors. All RCTs were funded by pharmaceutical companies.

**Main results**
DOACs reduced hemorrhagic stroke compared with VKAs in patients with eCrCl < 50 mL/min or 50 to 80 mL/min (Table). DOACs reduced major bleeding compared with VKAs in patients with eCrCl 50 to 80 mL/min; groups did not differ for major bleeding in patients with eCrCl < 50 mL/min (Table).

**Conclusions**
In patients with atrial fibrillation or venous thromboembolism and renal failure, direct oral anticoagulants reduce risk for hemorrhagic stroke compared with vitamin K antagonists. Direct oral anticoagulants reduce risk for major bleeding in those with estimated creatinine clearance 50 to 80 mL/min.

**Direct oral anticoagulants (DOACs) vs vitamin K antagonists (VKAs) in patients with atrial fibrillation or venous thromboembolism and renal failure**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Renal function levels</th>
<th>Number of trials (n)</th>
<th>Weighted event rates</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DOACs</td>
<td>VKAs</td>
<td>eCrCl &lt; 50 mL/min</td>
<td>eCrCl 50 to 80 mL/min</td>
<td>eCrCl &lt; 50 mL/min</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>5 (12 352)</td>
<td>5 (32 213)</td>
<td>5 (12 352)</td>
<td>5 (32 213)</td>
<td>0.62%</td>
</tr>
<tr>
<td>Major bleeding§</td>
<td>9 (13 996)</td>
<td>9 (40 681)</td>
<td>9 (13 996)</td>
<td>9 (40 681)</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

* eCrCl = estimated creatinine clearance; other abbreviations defined in Glossary. Weighted event rates, RRR, NNT, and CI calculated from VKA event rates and risk ratios in article using a fixed-effect (hemorrhagic stroke) or random-effects (major bleeding) model.

† Includes a small number of patients with eCrCl < 30 mL/min (n ≤ 476).

‡ eCrCl > 50 mL/min with no upper limit in 2 trials.

§ Major or clinically relevant nonmajor bleeding in 3 trials.

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**Commentary**

The decision to use anticoagulation therapy, whether in patients with AF or VTE, weighs the potential benefits for preventing or treating thrombosis against the risks for hemorrhage, especially intracranial hemorrhage. Patients with renal disease have an increased risk for hemorrhage when receiving anticoagulation therapy (1) but are also at higher risk for arterial or venous thromboembolic disease.

In the past, VKAs, including warfarin, were the only available oral anticoagulants. However, they require frequent blood draws and dose adjustments to maintain therapeutic activity and have multiple food and drug interactions. Newer DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) allow fixed dosing with few modifications for age or organ failure and have fewer drug interactions. Large, multicenter RCTs have found the newer DOACs to be noninferior or superior to warfarin for preventing stroke in AF and noninferior to warfarin for preventing recurrent VTE, with lower risks for major hemorrhage, especially intracranial bleeding (2). DOACs are also more cost-effective than warfarin (3). However, clinicians may be reluctant to use DOACs in patients with renal insufficiency because these drugs have substantial renal excretion and dosing may need to be reduced.

In the most comprehensive and rigorous meta-analysis of DOAC safety in patients with AF or VTE and renal failure, Raccah and colleagues found that DOACs were associated with less major hemorrhage (especially hemorrhagic stroke) than warfarin, including in patients with eCrCl < 50 mL/min. In indirect network comparisons, apixaban, which has the least renal excretion among DOACs, had the lowest risk for major bleeding in patients with eCrCl < 50 mL/min. The absence of patients with severe renal insufficiency (eCrCl < 15 mL/min) or on hemodialysis in trials included in the review precluded conclusions about the relative safety of DOACs in end-stage renal disease.

DOACs, especially apixaban, are safer than warfarin in patients with mild to moderate renal insufficiency (eCrCl 30 to 80 mL/min), provide comparable efficacy with important logistic advantages, and have a favorable cost–benefit ratio. Safety is enhanced by dose modification, while efficacy is preserved. Reluctance to prescribe DOACs in general, including in higher-risk patients with renal insufficiency, is no longer justified.

**References**

