Renal Function Considerations for Stroke Prevention in Atrial Fibrillation

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Presenters:
John Fanikos, RPh, MBA
Curt Mahan, PharmD
Paul Dobesh, PharmD, FCCP, BCPS
Presenters

John Fanikos, RPh, MBA  
Director, Pharmacy Business & Financial Services  
Brigham and Women’s Hospital  
Assistant Professor of Clinical Pharmacy Practice  
Northeastern University  
Massachusetts College of Pharmacy  
Boston, MA

Charles E. Mahan, PharmD, RPh, PhC  
Clinical Pharmacist, Pharmacist Clinician  
Presbyterian Healthcare Services  
Clinical Assistant Professor of Pharmacy  
University of New Mexico College of Pharmacy  
Albuquerque, New Mexico

Paul Dobesh, PharmD, FCCP, BCPS  
Associate Professor of Pharmacy Practice  
College of Pharmacy  
University of Nebraska Medical Center  
Omaha, NE

Michael Streiff, MD  
Associate Professor of Medicine  
Johns Hopkins University  
Medical Director, AMS & Outpatient Clinics &  
Staff Physician  
Johns Hopkins Comprehensive Hemophilia  
Treatment Center  
Baltimore, MD, USA
Background

Renal dysfunction is common in atrial fibrillation (AF)

- Mild to moderate (eGFR 30-89 ml/min): 60%
- Severe (eGFR < 30 ml/min): 4%
- Normal (eGFR > 90 ml/min): 36%

eGFR = estimated glomerular filtration rate


Anticoagulation FORUM
**Background**

Renal dysfunction increases complications in AF patients

Increased risk of systemic embolic events (hazard ratio [HR] 1.49; P < .001) and bleeding (HR 2.24; P < .001) relative to those without CKD.\(^6\)

\[\text{eGFR} < 60 \text{ mL/min/1.73 m}^2 \text{ associated with 43\% higher risk of incident stroke.} \quad \text{8,9} \]

Proteinuria & reduced eGFR associated with higher rates of thromboembolism in patients with non-valvular AF, independent of other stroke risk factors.\(^3\)

NHANES survey: patients with CKD had additional stroke risk factors, including diabetes (40.4\%), hypertension (31.0\%), and cardiovascular disease (39.5\%).\(^{10}\)

CKD=chronic kidney disease

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9. Lee M. BMJ. 2010;341:c4249  
Background

Renal dysfunction increases complications in AF patients (cont.)

CKD patients with AF 67% more likely to progress to end-stage renal disease than those without AF.\textsuperscript{11}

Patients with CKD have higher risk of death from any cause (HR 2.37; P < .001) and myocardial infarction (HR 2.00; P < .001) than those without CKD.\textsuperscript{6}

Survival after incident AF decreases progressively with decreasing renal function (P < .0001).\textsuperscript{12}

Disruptions in platelet function and platelet-vessel wall interactions in patients with renal impairment may result in increased bleeding.

Oral Anticoagulants for Non-valvular AF (NVAF)

Warfarin

“No dose adjustment necessary for renal impairment”

Renal impairment associated with need for reduced doses and less stability*

Down regulation of hepatic CYP₄₅₀ isoenzymes?

Conflicting evidence re: utility for stroke prevention in AF patients with CKD

Direct oral anticoagulants (DOACs)

All renally eliminated to some degree

Large AF RCTs excluded patients with severe renal impairment

Estimation of renal function necessary for patient selection and dosing

Performance vs. warfarin at varying degrees of renal function helpful in selecting optimal AF therapy

Estimating Renal Function

May be estimated with:

- Modification of Diet in Renal Disease (MDRD) equation (eGFR)\textsuperscript{13}
- Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (eGFR)\textsuperscript{14}
- Cockcroft-Gault (C-G) equation, which estimates creatinine clearance (CrCl)\textsuperscript{15}

C-G, using actual body weight, used in all phase 3 direct oral DOAC trials.\textsuperscript{16-20}

Estimated Renal Function

Renal function cutoffs varied between trials\textsuperscript{17-20}

- Calculated CrCl $\leq 30$ mL/min for dabigatran
- Calculated CrCl $< 30$ mL/min for edoxaban and rivaroxaban,
- Serum creatinine $> 2.5$ mg/dL or a calculated CrCl of $< 25$ mL/min for apixaban

Use of equations other than C-G may result in incorrect DOAC dosing

Large database study showed renal function estimations other than C-G would result in failure to reduce rivaroxaban or edoxaban doses in 28% of patients, and 18%-21% of doses among dabigatran patients.\textsuperscript{23}

<table>
<thead>
<tr>
<th>Dabigatran&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Rivaroxaban&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Edoxaban</th>
<th>Apixaban&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CrCl mL/min</strong></td>
<td><strong>Dose</strong></td>
<td><strong>CrCl mL/min</strong></td>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td>&gt;30</td>
<td>150 mg BID</td>
<td>&gt;50</td>
<td>20 mg QD</td>
</tr>
<tr>
<td>30–15</td>
<td>75 mg BID</td>
<td>50–15</td>
<td>15 mg QD</td>
</tr>
<tr>
<td>&lt;15</td>
<td>Avoid Use</td>
<td>&lt;15</td>
<td>Avoid Use</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>15 mg QD&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
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</tr>
</tbody>
</table>

**BID =** twice daily; **CrCl =** creatinine clearance; **P-gp =** P-glycoprotein; **QD =** once daily; **SCr =** serum creatinine.  
<sup>a</sup>Not recommended for patients with CrCl <30 mL/min taking concomitant P-gp inhibitors; the dose should be reduced or avoided in patients with CrCl 30-50 mL/min who use concomitant P-gp inhibitors.  
<sup>b</sup>Should be taken with the evening meal.  
<sup>c</sup>Apixaban should be reduced to a dose of 2.5 mg BID in patients for whom 2 of the following apply: serum creatinine >1.5 mg/dL, age ≥80 years old, body weight ≤60 kg; apixaban may be administered to patients on hemodialysis at a dose of 5 mg unless dose administration is warranted based on reduction criteria.  
<sup>d</sup>Labeling suggests rivaroxaban may be administered to patients on hemodialysis at a dose of 15 mg unless dose administration is warranted based on reduction criteria; however, as it has not been adequately studied in a large-scale clinical trial, use in this population should be avoided whenever possible.  
<sup>e</sup>Labeling suggests apixaban may be administered to patients on hemodialysis at a dose of 5 mg unless dose administration is warranted based on reduction criteria; however, as it has not been adequately studied in a large scale clinical trial, use in this population should be avoided whenever possible.
Methods

Evaluation of existing evidence as to safety and efficacy of oral anticoagulants for NVAF at varying levels of renal function

• Pre-specified subgroup analyses
• Metanalyses

Patient populations enrolled in phase 3 NVAF studies also differed in:

• Risk for cardiac dysfunction
• Diabetes and heart failure (riva and edox > apixa and dabi)
• Mean CHADS₂ score (riva 3.5; edox 2.8, apixa and dabi 2.1)
• Inclusion of patients with atrial flutter
• Timing of documentation of atrial fibrillation²¹,²²

### SSE relative to warfarin for the DOACs stratified by renal function

<table>
<thead>
<tr>
<th></th>
<th>CrCl &gt;80 mL/min</th>
<th>CrCl 50–95 mL/min</th>
<th>CrCl 50–80 mL/min</th>
<th>CrCl 30–50 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of enrolled</td>
<td>HR a (95% CI)</td>
<td>% of enrolled</td>
<td>HR a (95% CI)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25,32,39,b</td>
<td>31.2</td>
<td>0.69 (0.43, 1.12)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27,36,39,e</td>
<td>22.0</td>
<td>0.93 (0.67, 1.31)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24,33,39,f</td>
<td>26.0g</td>
<td>0.87 (0.60, 1.26)g</td>
<td>NR</td>
<td>0.79 (0.61, 1.02)g</td>
</tr>
<tr>
<td>Edoxaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26,34,39,h</td>
<td>37</td>
<td>1.33 (0.97, 1.81)</td>
<td>58.3</td>
<td>0.78 (0.64, 0.96)</td>
</tr>
</tbody>
</table>

aComparisons should not be made across drugs within CrCl ranges; HR presented are for each DOAC vs warfarin within the CrCl range provided. b150-mg dose c eGFR >50–≤80 mL/min d eGFR≥30–≤50 mL/min e20 mg daily or 15 mg daily if CrCl 15–50 mL/min once daily with evening meal f5 mg twice daily or 2.5 mg twice daily if ≥ 2 of: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL gIn patients with stable renal function over time h60 mg daily or a 50% dose reduction to 30 mg daily for CrCl 30–50 mL/min, body weight of ≤60 kg, or use of a potent P-gp inhibitor

25. http://docs.boehringer-ingelheim.com/Prescribing%20Information/Pis/Pradaxa/Pradaxa.pdf
33. Hohnloser SH. Eur Heart J. 2012;33:2821-2830
SSE: CrCl >80 mL/min

SSE event rates for rivaroxaban, apixaban and dabigatran similar, and slightly numerically lower, compared with warfarin. 32,33,36

SSE events for edoxaban were similar, but slightly numerically higher compared with warfarin.34

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**SSE: CrCl >95 ml/min**

<table>
<thead>
<tr>
<th>Edoxaban post hoc sub-analysis</th>
<th>Trend toward lower efficacy relative to warfarin for SSE (HR 1.36 [0.88-2.1], p=0.08)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Net clinical outcome (SSE + MB + all cause death) at least as favorable as warfarin across renal subgroups.³⁴</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rivaroxaban subgroup analysis</th>
<th>Numerically, although not significantly, higher rate of SSE events relative to warfarin (HR 1.47 [0.81-2.68])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The interaction was significantly different relative to patients with CrCl ≤ 95 mL/min, in whom a stroke risk reduction was observed (p=0.033).³⁶</td>
</tr>
</tbody>
</table>

No peer-reviewed phase 3 subanalyses of dabigatran or apixaban in this population

SSE: CrCl >50-80 mL/min
(Normal to mild renal impairment)

DOACs are associated with a reduced risk of SSE relative to warfarin

<table>
<thead>
<tr>
<th>Drug</th>
<th>CrCl 50–&lt;80 mL/min</th>
<th>DOAC</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>1.25</td>
<td>1.83</td>
<td>1.25</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>2.2</td>
<td>2.4</td>
<td>2.2</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1.16</td>
<td>1.5</td>
<td>1.16</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>1.49</td>
<td>2.17</td>
<td>1.49</td>
</tr>
</tbody>
</table>

SSE: CrCl ≤ 50 mL/min

All DOACs reduced SSE to a greater extent than warfarin in patients with moderate renal impairment (CrCl 30-50 mL/min) in individual trials.

## Major bleeding relative to warfarin for the DOACs stratified by renal function

<table>
<thead>
<tr>
<th>CrCl</th>
<th>% of enrolled</th>
<th>HR(^a) (95% CI)</th>
<th>% of enrolled</th>
<th>HR(^a) (95% CI)</th>
<th>% of enrolled</th>
<th>HR(^a) (95% CI)</th>
<th>% of enrolled</th>
<th>HR(^a) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80 mL/min</td>
<td></td>
<td></td>
<td>&gt;50–95 mL/min</td>
<td></td>
<td>&gt;50–80 mL/min</td>
<td></td>
<td>30–50 mL/min</td>
<td></td>
</tr>
<tr>
<td>Dabigatran 25,32,39,b</td>
<td>31.3</td>
<td>0.90 (0.65, 1.25)</td>
<td>NR</td>
<td>NR</td>
<td>45.8</td>
<td>0.92 (0.75, 1.14)c</td>
<td>18.4</td>
<td>1.02 (0.77, 1.34)d</td>
</tr>
<tr>
<td>Rivaroxaban 27,36,39,e</td>
<td>31.7</td>
<td>1.26 (0.95, 1.67)</td>
<td>NR</td>
<td>NR</td>
<td>45.7</td>
<td>0.94 (0.76, 1.15)</td>
<td>22.4</td>
<td>1.03 (0.79, 1.35)</td>
</tr>
<tr>
<td>Apixaban 24,33,39,f</td>
<td>26.0g</td>
<td>0.80 (0.60, 1.07)g</td>
<td>NR</td>
<td>0.74 (0.61, 0.94)g</td>
<td>48.1g</td>
<td>0.76 (0.62, 0.94)g</td>
<td>15</td>
<td>0.53 (0.39, 0.71)</td>
</tr>
<tr>
<td>Edoxaban 26,34,39,h</td>
<td>37</td>
<td>0.86 (0.60, 1.22)i</td>
<td>58.3</td>
<td>0.89 (0.75, 1.04)</td>
<td>43</td>
<td>0.88 (0.73, 1.07)</td>
<td>19.5</td>
<td>0.76 (0.58, 0.98)</td>
</tr>
</tbody>
</table>

\(^a\)Comparisons should not be made across drugs within CrCl ranges; HR presented are for each DOAC vs warfarin within the CrCl range provided.

\(^b\)150-mg dose \(^c\)eGFR 50–<80 mL/min \(^d\)eGFR ≥30–≤50 mL/min \(^e\)20 mg daily or 15 mg daily if CrCl 15–50 mL/min once daily with evening meal \(^f\)5 mg twice daily or 2.5 mg twice daily if ≥ 2 of: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL \(^g\)In patients with stable renal function over time \(^h\)60 mg daily or a 50% dose reduction to 30 mg daily for CrCl 30–50 mL/min, body weight of ≤60 kg, or use of a potent P-gp inhibitor \(^i\)CrCl>80–95

25. [http://docs.boehringeringelheim.com/Prescribing%20Information/Pls/Pradaxa/Pradaxa.pdf](http://docs.boehringeringelheim.com/Prescribing%20Information/Pls/Pradaxa/Pradaxa.pdf)
**Major Bleeding: CrCl >80 mL/min**

Bleeding rates for dabigatran, apixaban and edoxaban similar, and slightly numerically lower, compared with warfarin\(^{32-34}\)

Bleeding rates for rivaroxaban similar, but slightly numerically higher compared with warfarin\(^{36}\)

Composite of major or non-major clinically relevant bleeding similar for rivaroxaban and warfarin, and no significant treatment interaction\(^{36}\)

![Graph showing bleeding rates for different treatments](image)

**Table:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>DOAC</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>2.04</td>
<td>2.43</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>3</td>
<td>2.4</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1.33</td>
<td>1.66</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>2.44</td>
<td>2.85</td>
</tr>
</tbody>
</table>


DOACs are associated with a lower bleeding risk relative to warfarin.

**Major Bleeding: CrCl >50-80 mL/min**

**CrCl 50–<80 mL/min**

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>3.35</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>3.5</td>
</tr>
<tr>
<td>Apixaban</td>
<td>2.14</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>2.44</td>
</tr>
</tbody>
</table>

n = 188 n = 209 n = 176 n = 191
n = 136 n = 176 n = 136 n = 176

Major Bleeding: CrCl ≤ 50 mL/min

- In patients with moderate renal impairment (CrCl 30-50 ml/min), MB reduced with apixaban (HR 0.53 [0.39-0.71]) and edoxaban (HR 0.76 [0.58-0.98]) relative to warfarin\(^{33, 34}\).
- Similar to warfarin for dabigatran or rivaroxaban.\(^{32, 36}\)

<table>
<thead>
<tr>
<th></th>
<th>DOAC</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>5.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>4.7</td>
<td>4.6</td>
</tr>
<tr>
<td>Apixaban</td>
<td>3.15</td>
<td>5.3</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>4</td>
<td>5.3</td>
</tr>
</tbody>
</table>

CrCl ≤ 50 mL/min

% / year

Severe Renal Dysfunction
(CrCl 15-30 ml/min)

**Edoxaban 15 mg daily in NVAF patients with CrCl 15 - <30 mL/min**

- Compared to 60 mg (30-mg reduced dose) in CrCl ≥ 50 mL/min over a 12-week period.\(^\text{40}\)
- At 2 weeks, pre-dose edoxaban concentrations in severe renal impairment significantly higher than in normal or mild renal impairment administered 30 mg edoxaban.
- Similar to normal/mild renal impairment receiving 60 mg edoxaban.

**Apixaban open-label, parallel-group, single-dose study**

- CrCl >80 vs. >50-80 vs. 30-50 vs. <30 not yet on dialysis\(^\text{41}\)
- No effect on max apixaban concentrations after single 10-mg dose
- Apixaban exposure increased with increasing renal impairment

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40. Koretsune Y. Circ J. 2015;79:1486-1495  
Patients on Hemodialysis

Small (n= 8-10) single-dose studies of apixaban, rivaroxaban and edoxaban \(^{42,44,45}\)

- Suggest comparable pharmacokinetics and pharmacodynamics to patients with moderate to severe renal dysfunction
- Did not evaluate repeat dosing, accumulation or effects at steady state
- Apixaban and rivaroxaban FDA-approved for use in NVAF patients on intermittent hemodialysis \(^{24,27}\)
- As they have not been adequately studied in this population, use of all DOACs should be avoided until better evidence is available

Emerging Evidence in Hemodialysis

Mavrakanas, et el. 2017

- Repeat doses of apixaban 2.5 mg and 5 mg twice daily evaluated in patients on hemodialysis
- At steady-state, apixaban 5 mg BID increased exposure 2-5.7 times relative to 2.5 mg twice daily
- Results suggest the approved 5-mg twice daily dose for this patient population may lead to supratherapeutic drug exposure

Ongoing trials

- RENAL-AF (NCT02942407)

Patients with Worsening Renal Function

DOACs may be associated with better preservation of renal function compared to warfarin *

- May be related to decrease in vascular inflammation via FIIa and Fxa inhibition

26.3% and 13.6% of rivaroxaban and apixaban NVAF patients, respectively, had decreasing renal function (≥ 20% decrease in CrCl)31,47

Rivaroxaban and apixaban associated with lower relative risk of SSE and MB compared with warfarin in patients with decreasing renal function over time31, 47

Dabigatran and rivaroxaban showed significantly slower decrease in renal function compared to warfarin46,47

Conclusions

Patients with renal impairment are at increased risk for thromboembolic and bleeding events, a risk that increases over time.

Following DOAC dosing recommendations as calculated by C-G, utilizing actual body weight, is critical for avoiding improper dosing of patients.

In mild or moderate renal impairment, DOACs are associated with reduced SSE and MB relative to warfarin.

Until we have more data, DOACs should be avoided in severe renal impairment or hemodialysis whenever possible, despite labeling.

The DOACs may confer a better renal risk-benefit profile than warfarin in those with decreasing renal function over time.

Additional assessments may be warranted to ensure optimal use of DOACs in patients with very high or low renal function.
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