Apixaban for Atrial Fibrillation in Patients with End-Stage Renal Disease on Dialysis

Caitlin Reedholm, PharmD
PGY1 Pharmacy Resident
St. David’s South Austin Medical Center
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Objectives

- State why patients with chronic kidney disease are at a higher risk of bleeding and thromboembolism
- Summarize the evidence for apixaban in patients with ESRD on dialysis
- Recommend an anticoagulant regimen for patients with atrial fibrillation and ESRD on dialysis

Question

KJ is a 62 year old male with diabetes, hypertension, and is on dialysis for ESRD. He weighs 80 kg and was recently diagnosed with non-valvular atrial fibrillation. His physician has decided to initiate anticoagulation therapy. Which medication would you recommend?

A. Warfarin titrated to an INR of 2-3
B. Apixaban 2.5 mg BID
C. Apixaban 5 mg BID
D. Aspirin 81 mg daily

Epidemiology of Atrial Fibrillation

- Most common arrhythmia
- Affects up to 2% of the general population
- 15-40% of patients on dialysis also have AF
- AF increases risk of stroke 4-5 fold compared to those without AF

Abbreviations

- ALT= alanine aminotransferase
- AF= atrial fibrillation
- AST= aspartate aminotransferase
- AP= alkaline phosphatase
- BID= twice a day
- DAPT= dual antiplatelet therapy
- DVT/PE= deep venous thrombosis/pulmonary embolism
- EHRA= European Heart Rhythm Association
- ESRD= end-stage renal disease
- GI= gastrointestinal
- INR= international normalized ratio
- KDIGO= Kidney Disease: Improving Global Outcomes
- NOAC= novel oral anticoagulant
- NSAID= nonsteroidal anti-inflammatory drug
- NVAF= non-valvular atrial fibrillation
- SCr= serum creatinine
- SE= systemic embolism
- TIA= transient ischemic attack
- TTR= time in therapeutic range
- VKA= vitamin K antagonist
- VTE= venous thromboembolism
**CHA₂DS₂-VASc**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>+1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+1</td>
</tr>
<tr>
<td>Age (≥75 years)</td>
<td>+2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>+1</td>
</tr>
<tr>
<td>Previous stroke, TIA, VTE</td>
<td>+2</td>
</tr>
<tr>
<td>Age (65-74 years)</td>
<td>+1</td>
</tr>
<tr>
<td>Female</td>
<td>+1</td>
</tr>
</tbody>
</table>

0 = low risk  
1 = low-moderate risk  
≥2 = moderate-high risk

**HAS-BLED**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
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</tr>
<tr>
<td>Abnormal liver function</td>
<td>+1</td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>+1</td>
</tr>
<tr>
<td>Stroke</td>
<td>+1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>+1</td>
</tr>
<tr>
<td>Labile INR</td>
<td>+1</td>
</tr>
<tr>
<td>Elderly</td>
<td>+1</td>
</tr>
<tr>
<td>Drugs</td>
<td>+1</td>
</tr>
</tbody>
</table>

**Score**

0  
1  
2  
3  
4  
5

**Rate of major bleed per 100 patient years**

0  
1  
2  
3  
4  
5
Factors that increase risk of bleeding:
- Hemorrhagic diathesis
- Thrombocytopenia
- Reduced hepatic function

Factors that increase risk of thromboembolism:
- Presence of traditional risk factors
- Presence of non-traditional risk factors
- Increased venous turbulence during dialysis
- Inflammation and endothelial damage

Note: For NVAF, apixaban is dosed 2.5 mg BID if 2 of the following 3 criteria are present:
- Age > 80 years
- Weight < 60 kg
- SCr > 1.5


Apixaban Package Insert
- ESRD on dialysis patients not enrolled in clinical efficacy and safety studies
- Similar concentrations of apixaban and pharmacodynamic activity as in ARISTOTLE study when using apixaban at usually recommended dose
- Unknown if similar stroke reduction and bleeding risk that was seen in ARISTOTLE study

Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients
- Apixaban 2.5 mg BID x 8 days
  \( n=7 \)
- 5 day washout period
- Apixaban 5 mg BID x 8 days
  \( n=5 \)
Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients

- Results:
  - Apixaban 2.5 mg BID for 8 days: AUC ↑ 2-5.4 fold compared to first dose
  - Apixaban 5 mg BID for 8 days: AUC ↑ 2-5.7 fold compared to apixaban 2.5 mg BID
  - Only 4% of apixaban was removed by dialysis

- Author's conclusion:
  - Apixaban 2.5 mg BID provides drug exposure that is comparable to 5 mg BID in patients with normal renal function
  - Apixaban 5 mg BID should be avoided

Clinical Question: In patients with atrial fibrillation and ESRD on dialysis in which anticoagulation is warranted, is apixaban a safe alternative to warfarin?

Guidelines

2018 CHEST Guideline General Recommendation
- Anticoagulation is recommended for patients with a single non-sex
  CHA₂DS₉-VASc stroke risk factor
- NOACs preferred over VKA
- If using VKA, time in therapeutic range (TTR) should be at least 65%
- Apixaban, edoxaban, or dabigatran 110 mg BID preferred over VKA for patients at high risk of bleeding

2018 CHEST ESRD on Dialysis Recommendation
- Individualized decision making is appropriate
- Suggest using well-managed VKA with TTR > 65-70%
- NOACs should generally not be used
2018 EHRA Guideline

- Routine use of NOACs in patients on dialysis is best avoided
- Lack of strong evidence for using VKA
- Decision to anticoagulate is very individualized

Chronic Kidney Disease and Arrhythmias: Conclusions from a KDIGO Controversies Conference

- Insufficient high-quality evidence to recommend warfarin
- Consider apixaban 2.5 mg BID

Guideline Summary

- Lack of strong evidence for warfarin/anticoagulation in patients with dialysis
- Treatment should be individualized
- Only KDIGO suggests using apixaban, but at a reduced dose

Primary Literature

Comparison of the Safety and Effectiveness of Apixaban versus Warfarin in Patients with Severe Renal Impairment

Stanton et al

Methods

- Retrospective, single-center, matched cohort study
- Adults who received at least one dose of apixaban or warfarin while hospitalized
- CL Cr < 25 mL/minute, SCR > 2.5 mg/dL, or on dialysis
- Unable to assess dose or renal function
- Receiving continuous renal replacement therapy
- Major bleeding
- Composite of bleeding (major bleeding, clinically relevant non-major bleeding, and minor bleeding), ischemic stroke (in NVAF patients) or recurrent VTE (in patients treated for a PE or DVT)
Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (n=73)</th>
<th>Warfarin (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>79 ± 11.8</td>
<td>79 ± 13.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82 ± 24.5</td>
<td>81.5 ± 23.7</td>
</tr>
<tr>
<td>Female [n, %]</td>
<td>44 (60.3%)</td>
<td>43 (58.9%)</td>
</tr>
<tr>
<td>Mean CHA2DS2-VASc score</td>
<td>6.1 ± 1.5</td>
<td>5.6 ± 1.5</td>
</tr>
<tr>
<td>Mean HAS-BLED score</td>
<td>3.4 ± 0.9</td>
<td>3 ± 0.9</td>
</tr>
<tr>
<td>Renal impairment [n, %]</td>
<td>Severe ESRD</td>
<td>ESRD on dialysis</td>
</tr>
<tr>
<td></td>
<td>46 (63%)</td>
<td>46 (63%)</td>
</tr>
<tr>
<td></td>
<td>7 (9.6%)</td>
<td>7 (9.6%)</td>
</tr>
<tr>
<td>Indication [n, %]</td>
<td>NVAF</td>
<td>VTE</td>
</tr>
<tr>
<td></td>
<td>53 (72.6%)</td>
<td>19 (26%)</td>
</tr>
<tr>
<td></td>
<td>19 (26%)</td>
<td>19 (26%)</td>
</tr>
<tr>
<td></td>
<td>1 (1.4%)</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Aspirin and/or clopidogrel [n, %]</td>
<td>47 (64.4%)</td>
<td>36 (49.3%)</td>
</tr>
</tbody>
</table>

Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban (n=73)</th>
<th>Warfarin (n=73)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding [n, %]</td>
<td>7 (9.6%)</td>
<td>13 (17.8%)</td>
<td>0.149</td>
</tr>
<tr>
<td>GI</td>
<td>7</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Intracerebral</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Intramuscular</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Composite bleeding [n, %]</td>
<td>16 (21.9%)</td>
<td>20 (27.4%)</td>
<td>0.442</td>
</tr>
<tr>
<td>Stroke in NVAF [n, %]</td>
<td>4 (7.5%)</td>
<td>4 (7.5%)</td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE [n, %]</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Note: TTR during hospitalization for patients on warfarin was 67.5%

Results Continued

In a sub-analysis of patients on dialysis, there was no statistically significant difference in major and composite bleeding

- All patients on dialysis compared to those not on dialysis (P = 0.663 and P = 0.549)
- Apixaban patients on dialysis compared to those not on dialysis (P = 0.99 and P > 0.99)
- Warfarin patients on dialysis compared to those not on dialysis (P = 0.742 and P = 0.384)

Author’s Conclusion

Apixaban appears to be a reasonable alternative to warfarin in patients with severe renal impairment

Safety and effectiveness of apixaban compared to warfarin in dialysis patients

Reed et al
Methods

Design

• Single-center, retrospective, observational cohort study

Inclusion criteria

• Adults with ESRD requiring peritoneal or hemodialysis
• Received either at least 2 doses of apixaban or 5 days of warfarin for any indication

Exclusion criteria

• Continuous renal replacement or acute kidney injury
• Switching anticoagulant during analysis period

Primary endpoint

• Overall bleeding event rate

Secondary endpoints

• Major bleeding events, clinically relevant non-major bleeding events, minor bleeding, recurrent VTE in patients treated for DVT or PE, and ischemic stroke in patients with NVAF

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (n=74)</th>
<th>Warfarin (n=50)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.5 ± 14.7</td>
<td>62.0 ± 14.4</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>86.1 ± 27.0</td>
<td>75.0 ± 26.5</td>
<td></td>
</tr>
<tr>
<td>Female (%)(n)</td>
<td>36 (48.6%)</td>
<td>19 (38%)</td>
<td></td>
</tr>
<tr>
<td>Mean CHA2DS2-VASc</td>
<td>4.1 ± 1.2</td>
<td>4.0 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>Mean HASBLED score</td>
<td>3.2 ± 1.4</td>
<td>3.4 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>Indication (%)(n)</td>
<td>AF: 29 (32.2%)</td>
<td>AF: 29 (58%)</td>
<td></td>
</tr>
<tr>
<td>VTE: 45 (51.4%)</td>
<td>VTE: 21 (42%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban: 36 (48.6%)</td>
<td>DAPT: 4 (8.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin: 34 (68.2%)</td>
<td>None: 4 (8%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: 79.7% of patients in the apixaban group were on the 5 mg BID dose

Results

Outcome | Apixaban (n=74) | Warfarin (n=50) | P-value |
---------|-----------------|-----------------|---------|
Any bleeding event | 14 (18.9%) | 21 (42%) | 0.01 |
Major bleeding event | 4 (5.4%) | 11 (22%) | 0.01 |
Recurrent VTE | 2 (4.4%) | 8 (16%) | 0.99 |
Ischemic stroke | 0 | 0 | - |

Adjusted Odds of Experiencing a Bleeding Event

<table>
<thead>
<tr>
<th></th>
<th>Adjusted odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>0.15 (0.05-0.46)</td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>1.63 (0.58-4.56)</td>
<td>0.35</td>
</tr>
<tr>
<td>&gt; 70 years of age</td>
<td>3.73 (0.89-15.69)</td>
<td>0.07</td>
</tr>
<tr>
<td>African American</td>
<td>0.31 (0.10-0.99)</td>
<td>0.03</td>
</tr>
<tr>
<td>Prior bleeding event</td>
<td>4.79 (1.30-16.21)</td>
<td>0.01</td>
</tr>
<tr>
<td>History of stroke</td>
<td>0.99 (0.15-6.57)</td>
<td>0.99</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1.13 (0.39-3.36)</td>
<td>0.82</td>
</tr>
<tr>
<td>DAPT</td>
<td>0.99 (0.19-5.11)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Author's Conclusion

Apixaban may be a safe and effective anticoagulation option in patients with ESRD on dialysis

Evaluation of Study

Strengths

• Most patients taking apixaban were on the 5 mg BID dose
• Only included patients with ESRD on dialysis
• Multivariate analysis to assess for potential confounding variables

Limitations

• Small sample size
• Did not assess TTR for warfarin
• Did not compare apixaban dosing
Outcomes Associated with Apixaban Use in End-Stage Kidney Disease Patients with Atrial Fibrillation in the United States

Siontes et al

### Methods

**Design**
- Retrospective cohort study

**Inclusion criteria**
- Medicare beneficiary included in United States Renal Data System (October 2010-December 2015)
- Adults with ESRD and AF undergoing dialysis and treatment with oral anticoagulant

**Exclusion criteria**
- Valvular AF or bioprosthetic valves
- Oral anticoagulant for indications other than AF
- Ischemic stroke or SE, major bleeding, GI bleeding, intracranial bleeding, and death

### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (n=2,351)</th>
<th>Warfarin (n=23,172)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.87 ± 11.49</td>
<td>68.15 ± 11.93</td>
</tr>
<tr>
<td>Male (% )</td>
<td>1,280 (54.4%)</td>
<td>12,572 (54.3%)</td>
</tr>
<tr>
<td>Mean CHA₂DS₂VASc score</td>
<td>5.27 ± 1.77</td>
<td>5.24 ± 1.79</td>
</tr>
<tr>
<td>Antiplatelet (% )</td>
<td>154 (6.6%)</td>
<td>1,712 (7.4%)</td>
</tr>
<tr>
<td>Prior major bleeding (% )</td>
<td>217 (9.2%)</td>
<td>2,319 (10.0%)</td>
</tr>
<tr>
<td>Hemodialysis (%)</td>
<td>2,216 (94.3%)</td>
<td>21,930 (94.6%)</td>
</tr>
</tbody>
</table>

*n=7,053 for main analysis in which apixaban patients were matched in 1:3 ratio to warfarin patients
Note: 44% of patients in the apixaban group were on 5 mg BID

### Results

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (n=2,351)</th>
<th>Warfarin (n=7,053)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/SE</td>
<td>81 (3.4%)</td>
<td>373 (5.3%)</td>
<td>0.88 (0.69-1.12)</td>
<td>0.29</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>129 (5.5%)</td>
<td>715 (10.1%)</td>
<td>0.72 (0.59-0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>155 (6.6%)</td>
<td>710 (10.1%)</td>
<td>0.86 (0.72-1.02)</td>
<td>0.09</td>
</tr>
<tr>
<td>Intracranial bleeding*</td>
<td>21 (0.89%)</td>
<td>111 (1.57%)</td>
<td>0.79 (0.49-1.26)</td>
<td>0.32</td>
</tr>
<tr>
<td>Death</td>
<td>159 (6.8%)</td>
<td>753 (10.7%)</td>
<td>0.85 (0.71-1.01)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*n=2050 and warfarin n= 7050

### Dose Specific Comparisons of Apixaban versus Warfarin

- Both doses of apixaban are associated with a lower major bleeding risk than warfarin
- Only the apixaban 5 mg BID dose was associated with a reduction in thromboembolic events and mortality compared to warfarin

### Author’s Conclusion

- Both doses of apixaban are associated with a lower major bleeding risk than warfarin
- Only the apixaban 5 mg BID dose was associated with a reduction in thromboembolic events and mortality compared to warfarin
Evaluation of Study

Strengths

- Large sample size
- Compared outcomes based upon apixaban dose

Limitations

- Did not evaluate minor bleeding
- Unable to assess appropriateness of 2.5 mg BID dose without patient weight
- Did not look at TTR for VKA group

Summary of Studies

- Did not compare anticoagulation to no anticoagulation
- Risk of bleeding is higher than in patients with normal renal function
- Apixaban is a safe alternative to warfarin for patients on dialysis
- Apixaban 5 mg BID may be more effective than 2.5 mg BID

Comparison of Safety/Efficacy Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Major bleed*</th>
<th>Stroke/SE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARISTOTLE</td>
<td>2.13 vs 3.09 (HR 0.69, p&lt;0.0001)</td>
<td>1.27 vs 1.60 (HR 0.79, p&lt;0.01)</td>
</tr>
<tr>
<td>Stanton et al</td>
<td>9.49 vs 11.57 (p=0.149)</td>
<td>7.5% vs 7.5%</td>
</tr>
<tr>
<td>Reed et al</td>
<td>7 vs 24 (p=0.01)</td>
<td>0% vs 0%</td>
</tr>
<tr>
<td>Siontis et al</td>
<td>19.7 vs 22.9 (HR 0.72, p&lt;0.001)</td>
<td>12.4 vs 11.8 (HR 0.88, p=0.29)</td>
</tr>
</tbody>
</table>

* per 100 patient years

Studies in Progress in Patients with ESRD on Dialysis

- Randomized, controlled trial of apixaban 5 mg BID (or apixaban 2.5 mg BID for select patients) vs warfarin (INR 2-3)
  - Estimated completion date of May 2019

- Randomized, controlled trial of apixaban 2.5 mg BID vs phenprocoumon (INR 2-3)
  - Estimated completion date of April 2019

- Randomized, controlled trial of no anticoagulation vs VKA (INR 2-3)
  - Estimated completion date of January 2023

Question

KJ is a 62 year old male with diabetes, hypertension, and is on dialysis for ESRD. He weighs 80 kg and was recently diagnosed with non-valvular atrial fibrillation. His physician has decided to initiate anticoagulation therapy. Which medication would you recommend?

A. Warfarin titrated to an INR of 2-3
B. Apixaban 2.5 mg BID
C. Apixaban 5 mg BID
D. Aspirin 81 mg daily

Conclusion

- The decision to anticoagulate a patient with atrial fibrillation and ESRD on dialysis is complex and should be individualized
- Apixaban can be considered as an alternative to warfarin for patients with atrial fibrillation and ESRD on dialysis
- Apixaban 5 mg BID might be more efficacious than 2.5 mg BID
Acknowledgements

- Daniel Giddings, PharmD, BCPS
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