Let’s Be Proactive About DOACS!

A Review of the Updates

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I have nothing to disclose concerning possible financial or personal relationships with commercial entities (or their competitors) that may be referenced in this presentation.
Objectives

- Integrate a systematic approach to DOAC prescribing into clinical practice

- Review current and available information regarding DOAC use in special populations

- Apply knowledge of the primary and secondary literature to clinical practice
Prescribing Checklist

- Indication
- Body Weight – Extremes of weight?
- Renal Function
- Medication Reconciliation – Drug/Drug interactions
- Liver Function
- Affordability
• Indication
# DOACs Available

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Betrixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>FDA Indication</strong></td>
<td>NVAF</td>
<td>VTE</td>
<td>NVAF</td>
<td>NVAF</td>
<td>NVAF</td>
</tr>
<tr>
<td></td>
<td>VTE</td>
<td>- Treatment</td>
<td>VTE</td>
<td>VTE</td>
<td>VTE</td>
</tr>
<tr>
<td></td>
<td>- Prophylaxis</td>
<td></td>
<td>- Treatment</td>
<td>- Secondary prevention</td>
<td>- Prophylaxis</td>
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<td></td>
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<td></td>
<td>Prophylaxis</td>
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<td></td>
<td>Prophylaxis</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>CAD/PAD</td>
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</tr>
</tbody>
</table>

- NVAF: Non-valvular atrial fibrillation
- VTE: Venous thromboembolism
- Prophylaxis: Prevention
- CAD/PAD: Coronary artery disease/Pulmonary arterial disease
New Indications

Rivaroxaban

- CAD or PAD: 2.5mg BID with Aspirin
- VTE Px in Acutely Ill: 10mg Daily
• Body Weight
Recommend
Appropriate standard dosing of DOACS in patients with BMI $\leq 40\, \text{kg}\, \text{m}^{-2}$ and weight $\leq 120\, \text{kg}$

Suggest
DOACS should not be used in patients with BMI $>40\, \text{kg}\, \text{m}^{-2}$ or weight $>120\, \text{kg}$

If
DOACS are used in a patient with BMI $>40\, \text{kg}\, \text{m}^{-2}$ or weight $>120\, \text{kg}$ → check drug specific levels

Use of Direct Oral Anticoagulants in Morbidly Obese Patients

**Pharmacokinetic/Pharmacodynamic Studies**

<table>
<thead>
<tr>
<th>Rivaroxaban 10mg</th>
<th>Apixaban 10mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC/Cmax ↔</td>
<td>AUC/Cmax ↑ low bodyweight</td>
</tr>
<tr>
<td>Cmax</td>
<td>high bodyweight</td>
</tr>
<tr>
<td>Factor Xa inhibition similar</td>
<td></td>
</tr>
<tr>
<td>AUC/Cmax ¶ low bodyweight</td>
<td></td>
</tr>
<tr>
<td>PK/PD changes are drug specific!</td>
<td></td>
</tr>
</tbody>
</table>

How do changes in PK/PD profile alter clinical efficacy and safety?

- linearly related to drug concentration
- inversely related to weight

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Safety and Efficacy Information

What information is available?

• RCT data from phase III trials

• Under represented

ISTH Guidance Statement!
So, what is new??

### Study 1
- Stratified by BMI
- No significant interaction between the study intervention and BMI in the composite outcome of stroke/SE
- Apixaban was associated with significantly lower occurrence of major bleeding
  - BMI cohorts: 18.5-25 and 25-30

### Study 2
- Stratified by weight
- A nonsignificant interaction between the 3 weight cohorts for the composite event of stroke or SE
- There was a significant interaction between the 3 cohorts for major bleeding
  - Apixaban significantly lower occurrence for lower weight cohorts

Studies 1 and 2 limited by post hoc nature!

Retrospective Cohort Studies in Patients with Atrial Fibrilliation:

- Compared efficacy and safety of apixaban, dabigatran, or rivaroxaban and warfarin in morbidly obese adults with AF
- No significant difference in occurrence of stroke or transient ischemic attack between DOACs or warfarin
- No significant difference in major bleeding event rate

Limitations – many!
- Underpowered to compare each DOAC to warfarin
- Systemic embolism not included – underestimation of events?

Retrospective Cohort Studies in Patients with Atrial Fibrillation:

• Study compared the use of apixaban or rivaroxaban to warfarin in morbidly obese patients with AF OR VTE – analyzed separately

• No significant difference in occurrence of stroke between apixaban, rivaroxaban, and warfarin
  • SE not included in efficacy outcome

• No significant difference in major bleeding rate between apixaban, rivaroxaban, or warfarin

• Strengths – only morbid obese patient enrollment with BMI >50kg/m² evaluation

• Limitations – small, non diverse sample size; TTR warfarin not reported

Venous Thromboembolism Treatment

Very limited data!!

- Efficacy outcome for VTE cohort → incidence of recurrent VTE

- Baseline age for VTE rivaroxaban group was significantly younger than warfarin and similar to apixaban

- No significant difference in occurrence of recurrent VTE or major bleeding risk among 3 cohorts

- VTE risk factor identification was not included

Summary and Clinical Application

• Influences of BMI/weight on DOACs PK/PD properties and outcomes are agent specific

• Clear complications with DOAC use in morbidly obese patients not exposed

• Limited randomized prospective data available for guidance of optimal DOAC selection in morbidly obese patients

• Information available for AF > >VTE

Summary and Clinical Application

Use this available information to integrate shared decision making with patient upon selection of anticoagulation therapy.
• Renal Function
Renal Function

Indication

Standard Dose

Renal Adjustment
13. For patients with AF who have a CHA₂DS₂-VASc score of 2 or greater in men or 3 or greater in women and who have end-stage chronic kidney disease (CKD; creatinine clearance [CrCl] <15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or apixaban for oral anticoagulation (S4.1.1-26, S4.1.1-29, S4.1.1-30).

**MODIFIED:** New evidence has been added. LOE was updated from B to B-NR. (Section 4.1. in the 2014 AF Guideline)
Pharmacokinetics, Pharmacodynamics, and Safety of Apixaban in Subjects with End-Stage Renal Disease on Hemodialysis

Results and Application

- Single dose apixaban 5mg study
- 16 healthy subject → 8 patients with ESRD on HD
- **Increased exposure** of apixaban in patients with ESRD on HD expected
- Results suggest apixaban can be used with **no dose modification** in patients with ESRD on HD
- Note: safety and efficacy in ESRD on HD NOT STUDIED!

### Geometric Mean Ratio (90%CI) Estimated From the Statistical Analysis Models

<table>
<thead>
<tr>
<th>Comparison</th>
<th>$C_{\text{max}}$ (ng/mL)</th>
<th>AUC$_{inf}$ (ng · h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with ESRD period 1 vs healthy subjects</td>
<td>0.79 (0.62–1.01)</td>
<td>1.17 (0.88–1.54)</td>
</tr>
<tr>
<td>Subjects with ESRD period 2 vs healthy subjects</td>
<td>0.90 (0.70–1.17)</td>
<td>1.36 (1.07–1.73)</td>
</tr>
<tr>
<td>Subjects with ESRD period 1 vs period 2</td>
<td>0.87 (0.72–1.05)</td>
<td>0.86 (0.71–1.04)</td>
</tr>
</tbody>
</table>

AUC$_{inf}$, area under the plasma concentration versus time curve extended to infinity; CI, confidence interval; CL$_D$, hemodialysis clearance; CL$_R$, renal clearance; CL/F, apparent oral clearance; $C_{\text{max}}$, maximum plasma concentration; CV, coefficient of variation; ESRD, end-stage renal disease; Fu, fraction (percent) unbound; Geo, geometric; N/A, not applicable; period 1, hemodialysis started 2 hours after apixaban administration (on dialysis); period 2, apixaban administered immediately after hemodialysis (off dialysis); SD, standard deviation; $T_{\text{el}}$, elimination half-life; $T_{\text{max}}$, time to maximum concentration; %DR, percentage dialysate recovery.

$n = 5$ for urine parameters.
Outcomes Associated with Apixaban Use in Patients with End-Stage Kidney Disease and Atrial Fibrillation in the United States

### Outcomes

#### Table 2. Event Rates and Association Estimates From Cox Regression Analyses in Prognostic Score–Matched Cohorts of Apixaban and Warfarin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Overall</th>
<th>Apixaban</th>
<th>Warfarin</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke/systemic embolism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>9404</td>
<td>2351</td>
<td>7053</td>
<td>0.88 (0.69–1.12)</td>
<td>0.29</td>
</tr>
<tr>
<td>No. of events</td>
<td>454</td>
<td>81</td>
<td>373</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event rate per 100 PY</td>
<td>11.9</td>
<td>12.4</td>
<td>11.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Major bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>9404</td>
<td>2351</td>
<td>7053</td>
<td>0.72 (0.59–0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of events</td>
<td>844</td>
<td>129</td>
<td>715</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event rate per 100 PY</td>
<td>22.3</td>
<td>19.7</td>
<td>22.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>9404</td>
<td>2351</td>
<td>7053</td>
<td>0.86 (0.72–1.02)</td>
<td>0.09</td>
</tr>
<tr>
<td>No. of events</td>
<td>865</td>
<td>155</td>
<td>710</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event rate per 100 PY</td>
<td>23.4</td>
<td>23.8</td>
<td>23.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intracranial bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>9400</td>
<td>2350</td>
<td>7050</td>
<td>0.79 (0.49–1.26)</td>
<td>0.32</td>
</tr>
<tr>
<td>No. of events</td>
<td>132</td>
<td>21</td>
<td>111</td>
<td></td>
<td></td>
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<tr>
<td>Event rate per 100 PY</td>
<td>3.4</td>
<td>3.1</td>
<td>3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>9404</td>
<td>2351</td>
<td>7053</td>
<td>0.85 (0.71–1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>No. of events</td>
<td>912</td>
<td>159</td>
<td>753</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event rate per 100 PY</td>
<td>24.7</td>
<td>23.7</td>
<td>24.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HRR indicates hazard ratio; and PY, patient-years. Association estimates are derived from univariable Cox regression analyses with drug exposure (apixaban or warfarin) as the only predictor variable. Hazard ratio <1 favors apixaban.

Apixaban Dosing

Summary and Clinical Application

- Apixaban vs Warfarin
  - Significantly lower major bleeding

- Apixaban 5mg BID vs Apixaban 2.5 mg BID or Warfarin
  - Significantly lower risk of stroke/SE
  - Significantly lower rates of death

LIMITATION
Retrospective Cohort Study

• Medication Reconciliation
  - DDI
# DDI Mechanism

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Betrixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolism</strong></td>
<td>P-gp</td>
<td>P-gp</td>
<td>P-gp</td>
<td>P-gp</td>
<td>P-gp</td>
</tr>
<tr>
<td></td>
<td>CYP3A4</td>
<td></td>
<td></td>
<td>CYP3A4</td>
<td></td>
</tr>
<tr>
<td><strong>Inhibitors</strong></td>
<td>Possible dose adjustment</td>
<td>Possible dose adjustment</td>
<td>Avoid if CrCl &lt;50mL/min</td>
<td>Possible dose adjustment</td>
<td>Avoid</td>
</tr>
<tr>
<td><strong>Inducers</strong></td>
<td>Avoid</td>
<td>Avoid ?</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
</tbody>
</table>
Inducers vs Inhibitors

- Carbamazepine
- Primidone
- Phenytoin
- Phenobarbital
- Rifampin
- St. John’s Wort

- Grapefruit
- Clarithromycin/Erythromycin
- Ketoconazole/Intraconazole/Posaconazole
- Ritonavir
Prescribing Checklist

- Indication
- Body Weight – Extremes of weight?
- Renal Function
- Medication Reconciliation – Drug/Drug interactions
- Liver Function
- Affordability
67yo M, 94kg, with PMH s/o T2DM, HTN, ESRD on HD is diagnosed with atrial fibrillation. CHA₂DS₂-VASc score 3. You decide to initiate anticoagulation; what is the least appropriate option for stroke risk reduction from those listed below?

A) Apixaban 2.5mg BID
B) Warfarin dosed for target INR 2-3
C) Apixaban 5mg BID
67yo M, 94kg, SCr 1.2, with PMH s/o T2DM, HTN, essential tremor is diagnosed with atrial fibrillation. CHA$_2$DS$_2$VASc score 3. The patient is on the following medications: metformin, lisinopril, primidone.

You decide to initiate anticoagulation. What is the most appropriate option for stroke risk reduction if you do not plan to change any existing medications?

A) Rivaroxaban 20mg daily  
B) Warfarin dosed for target INR 2-3  
C) Apixaban 5mg BID
Resources

- Apixaban Package Insert
- Betrixaban Package Insert
- Dabigatran Package Insert
- Edoxaban Package Insert
- Rivaroxaban Package Insert