USE OF THE DIRECT ORAL ANTICOAGULANTS IN CLINICAL PRACTICE

Gail Pokorney, MD
AKAFP Winter Update
March 12, 2016
NO DISCLOSURES
OBJECTIVES

Review the efficacy and safety of the direct oral anticoagulants (DOACs) in the treatment of venous thromboembolism (VTE) and atrial fibrillation (A-fib)

Provide guidance on which patients are (and are not) good candidates for DOAC therapy

Discuss monitoring and reversal of the DOACs
VENOUS THROMBOEMBOLISM (VTE)

Includes deep vein thrombosis (DVT) and pulmonary embolism (PE)

Can be provoked or unprovoked, which in turn determines duration of anticoagulation
- 3 months for provoked VTE
- 3 months to indefinite therapy for unprovoked VTE

Goals of anticoagulation:
- Prevent thrombus extension or embolization
- Prevent VTE recurrence

ATRIAL FIBRILLATION (A-FIB)

Increases the risk of stroke and thromboembolism

Presence of additional stroke risk factors determines the need for oral anticoagulation

- CHA\textsubscript{2}DS\textsubscript{2}-VASc is now the preferred risk stratification scheme

Goal of anticoagulation: prevent embolic events

Friberg et al. Eur Heart J. 2012;33(12):1500-10
WARFARIN: THE GOOD

Effective recurrent VTE prevention following acute VTE
- 90% relative reduction compared with no or inadequate treatment

Effective stroke prevention in A-fib
- 64% relative reduction compared with controls

Low cost

Familiarity

Documentation of compliance

Antidote

WARFARIN: THE BAD

Slow onset of action

Variable INRs
- Genetic variation
- Drug and food interactions

Monitoring burden
WARFARIN: THE UGLY

Requires heparin bridging for acute VTE treatment

Under-use in atrial fibrillation

INR is within target range <65% of the time
  • Time outside the therapeutic window is highly correlated with worse outcomes

Bleeding is a major problem

Antidote may not be effective in clinical practice

Oldgren. Circulation. 2014;129:1568-76
WARFARIN: THE UGLY, CONT.

Risk of major bleeding in patients anticoagulated with warfarin ranges from 0.4% – 7.2% per year
- 65,000 patients treated annually in US ERs for warfarin-related hemorrhage
- Risk of ICH in warfarin-treated A-fib patients is 0.8% per year

Case-fatality rate after warfarin-associated major bleeding: 13.4%
- This is despite IV vitamin K and FFP readily available!

3% rate of death or disability for bleeding outside the brain vs 76% for bleeding inside the brain

Bottom Line:
Major bleeding can be deadly, and warfarin reversal is imperfect, so it is important to avoid anticoagulation-related bleeding, especially ICH

DIRECT ORAL ANTICOAGULANTS (DOACS)

Dabigatran (Pradaxa)
Rivaroxaban (Xarelto)
Apixaban (Eliquis)
Edoxaban (Savaysa)

All agents are FDA-approved for treatment of venous thromboembolism and stroke prevention in non-valvular atrial fibrillation
CLOTTING CASCADE

DOACs

clot

Warfarin
# DOACS VS WARFARIN: PHARMACOLOGIC PROPERTIES

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>VKORC1</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>OD</td>
<td>BID</td>
<td>OD (BID)</td>
<td>BID</td>
<td>OD</td>
</tr>
<tr>
<td><strong>Time-to-peak effect</strong></td>
<td>4-5 d</td>
<td>1-3 h</td>
<td>2-4 h</td>
<td>1-2 h</td>
<td>1-2 h</td>
</tr>
<tr>
<td><strong>Half-life (h)</strong></td>
<td>40</td>
<td>14-17</td>
<td>7-11</td>
<td>8-14</td>
<td>5-11</td>
</tr>
<tr>
<td><strong>Renal clearance as unchanged drug (%)</strong></td>
<td>None</td>
<td>80</td>
<td>33</td>
<td>27</td>
<td>50</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>Multiple</td>
<td>P-gp</td>
<td>3A4/P-gp</td>
<td>3A4/P-gp</td>
<td>P-gp</td>
</tr>
</tbody>
</table>

OBJECTIVES

Review the efficacy and safety of the direct oral anticoagulants (DOACs) in the treatment of venous thromboembolism (VTE) and atrial fibrillation (A-fib)

Provide guidance on which patients are (and are not) good candidates for DOAC therapy

Discuss monitoring and reversal of the DOACs
# DOACS VS WARFARIN FOR ACUTE VTE: PHASE 3 TRIALS

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial</strong></td>
<td>RE-COVER I &amp; II</td>
<td>EINSTEIN</td>
<td>AMPLIFY</td>
<td>Hokusai-VTE</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>VTE</td>
<td>DVT</td>
<td>PE</td>
<td>VTE</td>
</tr>
<tr>
<td><strong>Index event PE ± DVT (%)</strong></td>
<td>31</td>
<td>0.7</td>
<td>100</td>
<td>34</td>
</tr>
<tr>
<td><strong>Bridge with heparin/LMWH</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Treatment protocol</strong></td>
<td>150 mg BID</td>
<td>15 mg BID for 3 wk; then 20 mg OD</td>
<td>10 mg BID for 7 d; then 5 mg BID</td>
<td>60 mg OD</td>
</tr>
<tr>
<td><strong>Duration (mo)</strong></td>
<td>6</td>
<td>3, 6, 12</td>
<td>6</td>
<td>3-12</td>
</tr>
</tbody>
</table>

DOACs vs Warfarin in VTE: Efficacy

First recurrent VTE or VTE-related death in Phase 3 trials

DOACS VS WARFARIN IN VTE: SAFETY

Major Bleeding in Phase 3 trials

DOACS VS WARFARIN IN VTE: SAFETY

Intracranial, fatal, major GI, and clinically relevant nonmajor bleeding in Phase 3 trials

<table>
<thead>
<tr>
<th></th>
<th>Pooled DOAC (n/N)</th>
<th>Pooled VKA (n/N)</th>
<th>Risk ratio (95% CI)</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial bleeding</td>
<td>15/13477 (0.1%)</td>
<td>43/13841 (0.3%)</td>
<td></td>
<td>0.37 (0.21-0.68)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>7/13477 (0.1%)</td>
<td>22/13481 (0.2%)</td>
<td></td>
<td>0.36 (0.15-0.84)</td>
<td>0.02</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>63/13477 (0.5%)</td>
<td>78/13481 (0.6%)</td>
<td></td>
<td>0.78 (0.47-1.31)</td>
<td>0.35</td>
</tr>
<tr>
<td>CRNM bleeding</td>
<td>854/13477 (6.3%)</td>
<td>1103/13481 (8.0%)</td>
<td></td>
<td>0.73 (0.58-0.93)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

DOACS VS WARFARIN FOR VTE: BOTTOM LINE ON EFFICACY

DOACs are non-inferior to warfarin with respect to overall efficacy in treatment of acute symptomatic VTE

- Effect consistent across subgroups: PE, DVT only, wt >100kg, moderate renal insufficiency, age >75

DOACs are associated with a significant (nearly 40%) relative reduction in major bleeding compared with warfarin

- Reductions in the most feared complications of anticoagulant treatment:
  - Fatal bleeding
  - Intracranial bleeding

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Recommended Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE or DVT of leg, no cancer</td>
<td>Dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist therapy (Grade 2B)</td>
</tr>
<tr>
<td></td>
<td>DOACs suggested as an alternative to conventional therapy for VTE treatment in patients who meet appropriate selection criteria</td>
</tr>
</tbody>
</table>
If anticoagulant therapy is stopped in patients with unprovoked VTE, the risk of recurrence is at least 10% at 1 year and 30% at 5 years.

ASA reduces recurrent VTE risk by 32% compared with placebo in patients who have been treated for their acute event.

Oral anticoagulants reduce recurrent VTE risk by 80-90% compared with placebo.
- Dabigatran is non-inferior to warfarin for extended VTE treatment and is associated with less bleeding.
- Prophylactic (2.5mg) dosing of apixaban is equally effective as therapeutic dosing compared to placebo.

# DOACS VS WARFARIN FOR A-FIB: PHASE 3 TRIALS

<table>
<thead>
<tr>
<th>Drug</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
<th>ENGAGE-AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug dosing</td>
<td>150 mg twice a day</td>
<td>110 mg twice a day</td>
<td>20 mg once a day</td>
<td>5 mg twice a day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60 mg once a day</td>
</tr>
</tbody>
</table>

DOACS VS WARFARIN IN A-FIB: EFFICACY

Stroke or systemic embolism in Phase 3 trials

<table>
<thead>
<tr>
<th>Study</th>
<th>NOAC (events)</th>
<th>Warfarin (events)</th>
<th>RR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY5</td>
<td>134/6076</td>
<td>199/6022</td>
<td>0.66 (0.53-0.82)</td>
<td>0.0001</td>
</tr>
<tr>
<td>ROCKET AF6</td>
<td>269/7081</td>
<td>306/7090</td>
<td>0.88 (0.75-1.03)</td>
<td>0.12</td>
</tr>
<tr>
<td>ARISTOTLE7</td>
<td>212/9120</td>
<td>265/9081</td>
<td>0.80 (0.67-0.95)</td>
<td>0.012</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48g</td>
<td>296/7035</td>
<td>337/7036</td>
<td>0.88 (0.75-1.02)</td>
<td>0.10</td>
</tr>
<tr>
<td>Combined (random)</td>
<td>911/29312</td>
<td>1107/29229</td>
<td>0.81 (0.73-0.91)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Favours NOAC

Favours warfarin

DOACS VS WARFARIN IN A-FIB: SAFETY

Major bleeding in Phase 3 trials

<table>
<thead>
<tr>
<th></th>
<th>NOAC (events)</th>
<th>Warfarin (events)</th>
<th>RR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY²</td>
<td>375/6076</td>
<td>397/6022</td>
<td>0.94 (0.82-1.07)</td>
<td>0.34</td>
</tr>
<tr>
<td>ROCKET AF³</td>
<td>395/7111</td>
<td>386/7125</td>
<td>1.03 (0.90-1.18)</td>
<td>0.72</td>
</tr>
<tr>
<td>ARISTOTLE³</td>
<td>327/9088</td>
<td>462/9052</td>
<td>0.71 (0.61-0.81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48³</td>
<td>444/7012</td>
<td>557/7012</td>
<td>0.80 (0.71-0.90)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Combined (random)</td>
<td>1541/29287</td>
<td>1802/29211</td>
<td>0.86 (0.73-1.00)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

DOACS VS WARFARIN IN A-FIB: EFFICACY AND SAFETY

Secondary efficacy and safety outcomes in Phase 3 trials

<table>
<thead>
<tr>
<th></th>
<th>Pooled NOAC (events)</th>
<th>Pooled warfarin (events)</th>
<th>RR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>665/29292</td>
<td>724/29221</td>
<td>0.92 (0.83-1.02)</td>
<td>0.10</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>130/29292</td>
<td>263/29221</td>
<td>0.49 (0.38-0.54)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>413/29292</td>
<td>432/29221</td>
<td>0.97 (0.78-1.20)</td>
<td>0.77</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2022/29292</td>
<td>2245/29221</td>
<td>0.90 (0.85-0.95)</td>
<td>0.0003</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>204/29287</td>
<td>425/29211</td>
<td>0.48 (0.39-0.59)</td>
<td>-0.0001</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>751/29287</td>
<td>591/29211</td>
<td>1.25 (1.01-1.55)</td>
<td>0.043</td>
</tr>
</tbody>
</table>
DOACS VS WARFARIN FOR A-FIB: BOTTOM LINE ON EFFICACY

Stroke and systemic embolic events are significantly reduced in patients receiving DOACs

- Effect consistent across subgroups: age, gender, diabetes, renal function, CHADS2 score, prior stroke/TIA, INR consistency

DOACS VS WARFARIN FOR A-FIB: BOTTOM LINE ON SAFETY

DOACs have a favorable safety profile compared with warfarin

- Significant reduction in intracranial hemorrhage (by 50%)
- Significant reduction in all-cause mortality (by 10%)
<table>
<thead>
<tr>
<th>Risk</th>
<th>Recommended Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESC 2012</strong></td>
<td><strong>AHA/ACC/HRS 2014</strong></td>
</tr>
<tr>
<td>No risk factors ( \text{CHA}_2\text{DS}_2)-VASc=0</td>
<td>No antithrombotic therapy</td>
</tr>
<tr>
<td></td>
<td>No antithrombotic therapy</td>
</tr>
<tr>
<td>CHA(_2)DS(_2)-VASc=1</td>
<td>DOAC &gt; VKA (IIaA)</td>
</tr>
<tr>
<td></td>
<td>None or OAC or ASA</td>
</tr>
<tr>
<td>CHA(_2)DS(_2)-VASc(\geq2)</td>
<td>DOAC &gt; VKA (IA)</td>
</tr>
<tr>
<td></td>
<td>DOAC or VKA</td>
</tr>
<tr>
<td>Mechanical prosthetic valve</td>
<td>VKA: INR 2.0-3.0 (AVR)</td>
</tr>
<tr>
<td></td>
<td>VKA: INR 2.5-3.5 (MVR)</td>
</tr>
</tbody>
</table>

Safe and Effective Use of Novel Oral Anticoagulants for Atrial Fibrillation: What You Need to Know

*Slide credit: Granger and Pokorney 2014.*
ANTICOAGULATION FOR WARFARIN-INELIGIBLE PATIENTS WITH A-FIB

AVERROES trial: double-blind RCT of ASA vs apixaban in A-fib patients at increased risk of stroke but unsuitable for warfarin

55% reduction in stroke risk with apixaban compared with aspirin
  ▪ Similar risk of major bleeding, including ICH
  ▪ Only issue is cost

Bottom Line:
Think twice about using aspirin for stroke prevention for A-fib!

APIXABAN VS ASPIRIN IN A-FIB

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Review the efficacy and safety of the direct oral anticoagulants (DOACs) in the treatment of venous thromboembolism (VTE) and atrial fibrillation (A-fib)

Provide guidance on which patients are (and are not) good candidates for DOAC therapy

Discuss monitoring and reversal of the DOACs
CLINICAL SCENARIOS

Would you prescribe a DOAC to the following patients?

• 34yF smoker on OCPs with acute LLE DVT after a long plane flight
• 55yM with hemodynamically stable acute PE
• 68yF with new-onset A-fib and CrCl 45cc/min
• 80yM with chronic A-fib and a hx of mechanical AVR
• 60yM with pancreatic cancer and post-op RLE DVT
• 70yF with paroxysmal A-fib and a hx of bleeding ulcer
DOACS: ADVANTAGES

Effective treatment for acute VTE and stroke prevention in A-fib

Improved safety profile

Relatively few drug and food interactions relative to warfarin

Predictable pharmacological effects
  • Fixed doses
  • Routine monitoring not required

Fast onset of activity

Short half-life

Potentially more cost-effective from health system perspective

DOACS: DISADVANTAGES

No reliable, readily available measurement assay
No routine monitoring of whether drugs are being taken
Short half-life
No antidote to FXa inhibitors
Potentially higher drug acquisition costs for patients
Fewer studies and approved indications
Disease-state interactions do exist

DOAC CONTRAINDICATIONS

Avoid DOACs in the following patient groups:
- Active cancer (no comparison vs LMWH)
- High-risk thrombophilic conditions (APLS, HIT)
- Extensive DVT or massive PE (advanced treatment required)
- Hepatic dysfunction (acute or chronic hepatitis, cirrhosis, ALT >3x ULN)
- Body weight extremes (<50kg, >120kg or BMI >35)
- Pregnancy
- Breastfeeding
- Pediatric population (age <18)

Bottom Line:
Await evidence of efficacy before routinely recommending DOACs in unstudied scenarios!

Yeh et al. Blood 2014;124(7):1020-1028
RENAL IMPAIRMENT

Clinical trials excluded patients with CrCl <25-30cc/min

Dose appropriately for renal function

- Rivaroxaban in A-fib: 15mg/d with CrCl 30-49cc/min
- Apixaban in A-fib: 2.5mg bid with two of three – age >80, weight <60kg, Cr >1.5
- Edoxaban in A-fib and VTE: 30 mg for CrCl 30–49cc/min, weight ≤60 kg, or strong P-gp inhibitor
- Dabigatran in A-fib: 110mg bid for CrCl 30-49cc/min

Very important to monitor renal function regularly

Bottom Line:
Xa inhibitors are the DOAC of choice in mild-moderate renal insufficiency.
Do not use DOACs in patients with CrCl <30cc/min.

HISTORY OF GI BLEEDING

Major GI bleeding events in Phase 3 trials comparing DOACs with warfarin

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>TSOACs Events</th>
<th>VKAs Events</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-MEDY, 2013</td>
<td>5</td>
<td>8</td>
<td>0.62 [0.20, 1.90]</td>
</tr>
<tr>
<td>RE-COVER, 2009</td>
<td>9</td>
<td>5</td>
<td>1.79 [0.60, 5.32]</td>
</tr>
<tr>
<td>RE-COVER II, 2014</td>
<td>6</td>
<td>10</td>
<td>0.60 [0.22, 1.66]</td>
</tr>
<tr>
<td>J-ROCKET AF, 2012</td>
<td>6</td>
<td>12</td>
<td>0.50 [0.19, 1.32]</td>
</tr>
<tr>
<td>AMPLIFY, 2013</td>
<td>7</td>
<td>18</td>
<td>0.39 [0.16, 0.93]</td>
</tr>
<tr>
<td>EINSTEIN-DVT, PE 2010/2012</td>
<td>15</td>
<td>26</td>
<td>0.57 [0.30, 0.98]</td>
</tr>
<tr>
<td>ARISTOTLE, 2011</td>
<td>105</td>
<td>119</td>
<td>0.88 [0.68, 1.14]</td>
</tr>
<tr>
<td>ROCKET AF, 2011</td>
<td>224</td>
<td>154</td>
<td>1.46 [1.19, 1.78]</td>
</tr>
<tr>
<td>RE-LY, 2009</td>
<td>385</td>
<td>148</td>
<td>1.30 [1.07, 1.56]</td>
</tr>
<tr>
<td>ENGAGE-AF-TIMI-48, 2013</td>
<td>361</td>
<td>190</td>
<td>0.95 [0.80, 1.13]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>53753</td>
<td>40650</td>
<td>0.94 [0.75, 1.19]</td>
</tr>
<tr>
<td>Total events</td>
<td>1123</td>
<td>690</td>
<td></td>
</tr>
</tbody>
</table>

Bottom Line: Tricky! Consider apixaban in patients with a history of GI bleed.

Medication adherence is critical with the fast offset of action

**VTE**

Similar efficacy and improved safety of DOACs compared to warfarin in patients age >75

**A-fib**

Compared with younger patients, older patients have a relatively greater risk of bleeding with dabigatran than warfarin

- ESC recommends the lower dose of dabigatran (110mg bid) for patients age >80

Relative risk of bleeding with oral Xa inhibitors versus warfarin is similar in older and younger patients

- With apixaban, patients >75-80 have consistently less bleeding than with warfarin

**Bottom Line:** Apixaban is probably the DOAC of choice in most elderly patients, assuming good compliance.


[Van Es and Buller. *Hematology 2015*. 2015;125-131](#)
APIXABAN VS WARFARIN IN ELDERLY A-FIB PATIENTS

### Event Rate (%/year)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Apixaban</th>
<th>Warfarin</th>
<th>HR (95% CI)</th>
<th>Interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke/Systemic Embolism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 80</td>
<td>1.23</td>
<td>1.55</td>
<td>0.79 (0.65, 0.96)</td>
<td>0.91</td>
</tr>
<tr>
<td>Age ≥ 80</td>
<td>1.53</td>
<td>1.90</td>
<td>0.81 (0.51, 1.29)</td>
<td></td>
</tr>
<tr>
<td>Major Bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 80</td>
<td>1.93</td>
<td>2.78</td>
<td>0.70 (0.60, 0.82)</td>
<td>0.74</td>
</tr>
<tr>
<td>Age ≥ 80</td>
<td>3.55</td>
<td>5.41</td>
<td>0.66 (0.48, 0.90)</td>
<td></td>
</tr>
<tr>
<td>All Bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 80</td>
<td>17.0</td>
<td>24.4</td>
<td>0.71 (0.67, 0.76)</td>
<td>0.83</td>
</tr>
<tr>
<td>Age ≥ 80</td>
<td>26.4</td>
<td>37.4</td>
<td>0.73 (0.64, 0.83)</td>
<td></td>
</tr>
<tr>
<td>Intracranial Bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 80</td>
<td>0.32</td>
<td>0.73</td>
<td>0.43 (0.30, 0.62)</td>
<td>0.67</td>
</tr>
<tr>
<td>Age ≥ 80</td>
<td>0.47</td>
<td>1.32</td>
<td>0.36 (0.17, 0.77)</td>
<td></td>
</tr>
</tbody>
</table>

Halvorsen S, et al.  
Eur Heart 2014
Patients at particularly high risk of thrombo-embolism were excluded from the four large A-fib trials comparing DOACs with warfarin:

- Significant mitral stenosis
- Mechanical valves

Some of the DOAC trials included patients with other valvular abnormalities (mitral insufficiency, aortic valve disease, bioprosthetic valves) with similar benefits demonstrated

**Bottom Line:**
Do not use DOACs in mitral stenosis or mechanical valve patients.
Likely OK to use DOACs with other valve abnormalities – check with cardiology if unsure.

Phase 2 trial of dabigatran vs warfarin in patients with mechanical AVR or MRV

Trial was terminated prematurely after enrollment of 252 patients because of an excess of thromboembolic and bleeding events among patients in the dabigatran group

- All patients with major bleeding had pericardial bleeding

Bottom Line: A mechanical valve is a strict contraindication to DOAC use.

DABIGATRAN VS WARFARIN IN MECHANICAL VALVES

A  First Thromboembolic Event

B  First Bleeding Event

No. at Risk
Dabigatran  168  156  126  108  73  44  15  7
Warfarin     84   82   66  55  40  22  9  4

No. at Risk
Dabigatran  168  129  103  86  58  32  11  6
Warfarin     84   73   56  50  38  22  11  4

PATIENT SELECTION: SUMMARY

No contraindication to DOAC therapy

Adequate organ function
  ▪ Check renal and liver function!

Disease-state interactions
  ▪ Hx of GI bleeding

No significant drug-drug interactions
  ▪ P-gp or 3A4
  ▪ Antiplatelet agents
  ▪ NSAIDs

Highly likely to be adherent with DOAC therapy
  ▪ Medication dosing
  ▪ Affordability

Patient preference for and willingness to take a DOAC

TO SWITCH OR NOT TO SWITCH?

Consider a switch from warfarin to a DOAC:
- Erratic INR
- Burdensome testing and dose adjustment ("warfarin hate factor")
- DOAC selection criteria met
- Start DOAC once INR drops <2 (dabigatran, apixaban), <2.5 (edoxaban), <3 (rivaroxaban)

Consider continuing warfarin:
- DOAC patient selection criteria not met
- Stable on warfarin with therapeutic INR

TIPS ON DOAC SELECTION

Oral therapy preferred for VTE → apixaban or rivaroxaban

Poor adherence to BID dosing → rivaroxaban or edoxaban

Antidote preferred → dabigatran

History of GI Bleed → apixaban

Age > 75 with A-fib → apixaban
CLINICAL SCENARIOS, AGAIN

Would you prescribe a DOAC to the following patients?

- 34yF smoker on OCPs with acute LLE DVT after a long plane flight
- 55yM with hemodynamically stable acute PE
- 68yF with new-onset A-fib and CrCl 45cc/min
- 80yM with chronic A-fib and a hx of mechanical AVR
- 70yF with chronic A-fib and a hx of bleeding ulcer
- 60yM with pancreatic cancer and post-op RLE DVT
OBJECTIVES

Review the efficacy and safety of the direct oral anticoagulants (DOACs) in the treatment of venous thromboembolism (VTE) and atrial fibrillation (A-fib)

Provide guidance on which patients are (and are not) good candidates for DOAC therapy

Discuss monitoring and reversal of the DOACs
LAB MEASUREMENT

DOACs do not require routine lab monitoring and dose adjustment

Special circumstances:

- Treatment failure
- Assessment of adherence
- Overdose
- Declining renal or hepatic function
- Urgent or emergent invasive procedure
- Hemorrhage

## LAB MEASUREMENT

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Class</th>
<th>Quantification Test</th>
<th>Emergency Scenario Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Anti-IIa</td>
<td>Dilute thrombin time (TT)</td>
<td>PTT</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Anti-Xa</td>
<td>Anti-Xa activity</td>
<td>PT</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Anti-Xa</td>
<td>Anti-Xa activity</td>
<td>PT</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Anti-Xa</td>
<td>Anti-Xa activity</td>
<td>None</td>
</tr>
</tbody>
</table>

The assays most suitable for DOAC quantification are not widely offered and are not typically available on a stat basis.

In an emergency:

- Normal PTT likely excludes excess levels of dabigatran
- Normal TT excludes clinically relevant levels of dabigatran
- Normal PT likely excludes excess levels of rivaroxaban and edoxaban but not apixaban

Cuker and Siegal. *Hematology* 2015. 2015;117-124
MANAGEMENT OF BLEEDING

Ask: Is the DOAC present in significant quantities?
- Anticoag effect will dissipate rapidly after d/c if normal renal function
- Time of last dose allows an estimate of anticoag effect (t1/2 = 12 hrs)
- Lab measurements provide limited information

Ask: Is reversal really necessary?
- Do not panic – supportive care may be the best option
- Reversal agents may not be necessary, even if available

Ask: If reversal is necessary, what is the best strategy?
- Evidence base for any reversal strategy is poor
- Antidote for dabigatran is now available

Verheugt and Granger. Lancet. 2015;386:303-10
MANAGEMENT OF BLEEDING

Patients with bleeding on DOAC therapy

- Minor bleeding
  - Local hemostatic measures
  - Consider anticoagulant withdrawal (balance bleeding vs clotting risks)

- Moderate bleeding
  - Anticoagulant withdrawal
  - Mechanical compression
  - Monitor hemodynamics
  - Surgical intervention
  - Fluid replacement
  - Blood product transfusion

- Severe/life-threatening bleeding
  - Intensive care setting
  - Hemodynamic support
  - Consider PCC
  - For dabigatran:
    - Idarucizumab
    - Hemodialysis

NON-SPECIFIC REVERSAL AGENTS

Prothrombin complex concentrate (PCC)
Activated PCC
Recombinant factor VIIa (rVIIa)

All have been studied for their ability to reverse the anticoagulant effect of DOACs in vitro, in animal models, and in human volunteers

- Evidence is of low quality and shows conflicting results
- Most of these studies do not evaluate relevant clinical outcomes

Studies evaluating clinical outcomes in DOAC-treated patients receiving nonspecific reversal agents for bleeding complications are lacking

Cuker and Siegal. Hematology 2015. 2015;117-124
SPECIFIC REVERSAL AGENTS

Idarucizumab (Praxbind)
- Humanized monoclonal antibody fragment with high affinity for dabigatran
- Received expedited FDA-approval based on the RE-VERSE AD study
- Phase III prospective cohort study evaluating efficacy and safety in 90 dabigatran-treated patients: 51 with serious bleeding, 39 requiring an urgent procedure
- 5g IV idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes in 88-98% of patients
  - In the serious bleeding group: hemostasis restored at a median of 11.4h
  - In the urgent procedure group: normal intra-op hemostasis achieved in 92%
- However: no control group!

Andexanet alfa
- Recombinant factor Xa protein that acts as a decoy and binds the FXa inhibitors
- Effective and safe based on phase III studies in healthy volunteers
- Prospective cohort study in Fxa inhibitor-treated patients is currently enrolling

Cuker and Siegal. Hematology 2015. 2015;117-124
MANAGEMENT OF BLEEDING

Even without specific reversal agents (antidotes):

There is encouraging evidence to suggest that DOAC patients who develop a major bleed require less blood or factor products, have shorter lengths of hospital stay, and potentially have better outcomes compared to patients experiencing warfarin-associated major hemorrhage

PERI-OPERATIVE MANAGEMENT

For procedures with low bleeding risk: hold DOAC for 2-3 half lives (24-48 hours)
  ▪ Procedure planned Friday -> give last dose on Wednesday

For procedures with high bleeding risk: hold DOAC for 5 half lives (48-72 hours)
  ▪ Procedure planned Friday -> give last dose on Tuesday

Resume drug ONLY when ready for full anticoagulant effect

No bridging with parenteral anticoagulant necessary

MONITORING AND REVERSAL: BOTTOM LINE

DOACs do not require routine lab monitoring, which is fortunate, as the assays most suitable for DOAC quantification are not widely available.

In the event of bleeding: DOAC half lives are short, so time is the most effective reversal agent

- If absolutely necessary:
  - Idarucizumab (dabigatran only)
  - PCCs

Antidotes are in development, but this does not need to be a major consideration for a patient who is appropriate for DOAC therapy

- A drug that leads to a lower event rate is better than a drug with an antidote
THE FUTURE OF DOACS

Monitoring system

Use in context of ACS and coronary interventions

Antidotes

Cost reduction
CONCLUSIONS

The Good
DOACs are easy to use, as good as or better than warfarin at preventing recurrent VTE and stroke, and safer than warfarin with respect to the most feared bleeding outcomes (despite antidote limitations!)

The Bad
DOACs are expensive (though likely cost-effective), renally metabolized, and not easily measurable in clinical practice

The Ugly
There are unanswered questions, so it is important to prescribe DOACs only for the populations and conditions for which they have been studied
QUESTIONS?

Terrific Resource:
Anticoagulation Forum
www.acforum.org