Do’s and Don’t of DOACs

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• Clinical pathways
Goals

- Drugs
- Diseases
- Dilemmas
- Do’s and Don’s

Why DOACs?

- No food interactions
- Very few drug interactions
- No monitoring
- Equal to better effectiveness
- Safer
The Drugs

• Anti-thrombin
  – Dabigatran

• Anti-Xa
  – Rivaroxaban
  – Apixaban
  – Edoxaban
  – (Betrixaban)

Dabigatran

• Oral Thrombin Inhibitor
• Bioavailability: 6.5%
• Onset of action: 2-3 hours
• Half-life: 12-14 hours
• Renal excretion: 80%
• Drug interactions: p-glycoprotein
Dabigatran

- Atrial fibrillation: More effective than warfarin
- Venous thrombosis prevention: As effective as LMWH
- Venous thrombosis treatment: As effective as warfarin

Side Effects

- No difference in liver function tests
- Increase in dyspepsia ~ 15%
  - May be improved by PPI
  - May be improved by food
- 1.3x increase risk of MI – outweighed by benefit
Dabigatran

• 150 and 75 mg dose approved by FDA
  – Weirdly not 110mg

• Dosing
  – CrCl > 30 mL/ml – 150mg BID
    • Caution with < 50 mL/ml in older patients
  – CrCl 15-30mL/ml 75 mg BID
  – CrCl < 15 not indicated

Dabigatran: Bottom Line

• Superior to warfarin in stroke prevention
• Effective in venous thrombosis treatment
• GI side effects 15%
• 1.3x increase risk of MI
• CrCl > 50
• Affects aPTT
Rivaroxaban

- Oral Xa Inhibitor
- Bioavailability: 80-100%
- Onset of action: 2.5-4 hours
- Half-life: 5-9 hours
- Renal excretion: ~66%
- Drug interactions: CYP 3A4+P-GP

Rivaroxaban

- Atrial fibrillation: As effective as warfarin
- Venous thrombosis prevention: More effective than LMWH
- Venous thrombosis treatment: As effective and safer than LMWH/warfarin
Rivaroxaban

- Approved 10mg daily for VTE prophylaxis in TKR and THR
- Approved 20mg daily for afib
  - 15mg if CrCl 15-50mL/m
  - Contraindicated < 15mL/m
- Approved for VTE
  - 15mg BID x 3 weeks
  - 20mg daily
  - 10mg chronic

Rivaroxaban: Bottom Line

- Effective in stroke prevention
- Superior in prevention of VTE
- Safer in treatment of VTE
- CrCl > 15 (15mg < 50)
- Once a day drug
  - BID x 3 weeks in acute VTE
- INR sensitive
Apixaban

- Oral Xa Inhibitor
- Bioavailability: 66%
- Onset of action: 1-3 hours
- Half-life: 8-15 hours
- Renal excretion: 25%
- Drug interactions: CYP 3A4 + P-GP

Apixaban

- Atrial fibrillation: More effective and safer than warfarin
- Venous thrombosis prevention: More effective than LMWH
- Venous thrombosis treatment: As effective and safer than LMWH/warfarin
Apixaban

• Approved 2.5 mg for VTE prophylaxis in TKR and THR
• Approved 5 mg BID for afib
  – 2.5mg if 2/3
    • Age > 80
    • Cr > 1.5
    • Weight < 60 kg
• Approved for VTE
  – 10 mg BID x 7 days
  – 5 mg BID
  – > 6 months 2.5 mg BID

Use Right Dose!

• Increasing data that under dosing DOACs lead to more thrombosis/stroke without change in bleeding
• Only dose adjust if indicated!
  – Apixiban 2 of 3
    • Age > 80
    • Creat > 1.5
    • Weight < 60
Apixaban: Bottom Line

- Superior in stroke prevention with less bleeding
- Superior in prevention of VTE
- Safer in therapy of VTE
- BID drug
- Does not affect INR/PTT

Edoxaban

- Oral Xa Inhibitor
- Bioavailability: 45%
- Onset of action: 1-1.5 hours
- Half-life: 9-11 hours
- Renal excretion: 33%
- Drug interactions: CYP 3A4
  - Multiple other pathways
Edoxaban: Bottom Line

- Effective in stroke prevention
- Safer in treatment of VTE
- Approved for CrCl < 95
- Once a day drug
- INR to monitor

The Diseases

- Joint replacement
- Atrial fibrillation
- Venous Thromboembolism
Joint Replacement

<table>
<thead>
<tr>
<th>Drug</th>
<th>Thrombosis</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>Better</td>
<td>Equal</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Equal</td>
<td>Equal</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Better</td>
<td>Equal</td>
</tr>
</tbody>
</table>

Prophylaxis

- All three agents effective and approved
  - Oral and cheaper!
- Rivaroxaban x 5 days then aspirin 81 mg daily effective
## Atrial Fibrillation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stroke</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>Better</td>
<td>Safer</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Better</td>
<td>Equal</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Equal</td>
<td>Safer</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Equal</td>
<td>Equal</td>
</tr>
</tbody>
</table>

Warfarin ~ $4/month  
DOAC ~ $300/month

## ICH – Atrial Fibrillation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stroke Events/100 years</th>
<th>Stroke RR (95% CI)</th>
<th>Intracranial Hemorrhage Events/100 years</th>
<th>Intracranial Hemorrhage RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>1.19</td>
<td>0.79 (0.65-0.95)</td>
<td>0.33</td>
<td>0.42 (0.30-0.58)</td>
</tr>
<tr>
<td>Dabig 110</td>
<td>1.53</td>
<td>0.91 (0.74-1.11)</td>
<td>0.23</td>
<td>0.31 (0.20-0.47)</td>
</tr>
<tr>
<td>Dabig 150</td>
<td>1.11</td>
<td>0.66 (0.53-0.82)</td>
<td>0.30</td>
<td>0.40 (0.27-0.60)</td>
</tr>
<tr>
<td>Edox 60</td>
<td>1.69</td>
<td>0.88 (0.75-1.03)</td>
<td>0.39</td>
<td>0.47 (0.34-0.63)</td>
</tr>
<tr>
<td>Edox 30</td>
<td>1.97</td>
<td>1.13 (0.97-1.31)</td>
<td>0.26</td>
<td>0.30 (0.21-0.53)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1.76</td>
<td>0.79 (0.66-0.96)</td>
<td>0.49</td>
<td>0.67 (0.47-0.94)</td>
</tr>
</tbody>
</table>

Potential for 10-12,000 less ICH in USA
What is “NVAF”

• Valvular atrial fibrillation is afib in the presence of severe or rheumatic mitral stenosis
• All other patients entered on trials (~20-25%)

Atrial Fibrillation

• Dabigatran
  – Reduced ischemic stroke
• Apixaban
  – More effective than warfarin
  – Better in patients at risk for bleeding
• Edoxaban
  – Only for impaired renal function
• Rivaroxaban
  – Effective
  – Once a day
DOACs and VTE

- Robust randomized trial data for all new anticoagulants
- Now recommend over warfarin by new Chest Guidelines

Venous Thrombosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Heparin First?</th>
<th>Thrombosis</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>No*</td>
<td>Equal</td>
<td>Safer</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Yes</td>
<td>Equal</td>
<td>Equal</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Yes</td>
<td>Equal</td>
<td>Safer</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>No*</td>
<td>Equal</td>
<td>Safer</td>
</tr>
</tbody>
</table>

*Apixaban 10mg bid x 7 days then 5mg BID
*Rivaroxaban 15mg bid x 21 days then 20mg daily
### DOAC in VTE

- **Recurrent VTE:** 0.90 (0.77-1.06)
- **Major bleeding:** 0.74 (0.59-0.85)
- **ICH:** 0.37 (0.21-0.68)
- **Fatal bleeding:** 0.36 (0.15-0.84)


Lower Dose DOACs?

• Older data for lower doses in chronic therapy of VTE
  – LMWH
  – Ximelagatran
  – Did not work for warfarin

Results

• 2 trials N = 5847
• Full vs Low dose
  – rVTE 1.12 (0.67-1.87)
  – Bleeding 0.74 (0.50 -1.05)
• Low vs placebo/Aspirin
  – rVTE 0.26 (0.14-0.45)
  – Bleeding 1.19 (0.81-1.77)

J Thromb Haemo 16:1288, 2018
Low Dose DOAC

• Idiopathic or recurrent VTE
• After 6-12 months of therapy
• Not!
  – Cancer
  – APLA
  – Visceral thrombosis

Current Role of DOAC in DVT

• Initial therapy
  – Rivaroxaban, apixaban no heparin
• Long term therapy
  – Safer and easier
  – Uncomplicated thrombosis step down after 6-12 months
DOAC VTE Stepped Care

Acute
A 10mg BID x 7 Days
R 15 mg bid x 21 days

6-12 Months
A 5.0 mg BID x 6-12 M
R 20 mg qD x 6-12 M

> 6-12 Months
A 2.5 mg BID
R 10 mg qD

Dilemmas!
Who Must Stay on Warfarin

- Mechanical valves
- Weight < 50kg or > 140ish kg

Weight

- DOACs weight base
- Obesity
  - Atrial fibrillation: 120 kg
    - Increasing data for up to BMI 40
  - Venous disease: 140 kg
    - Chronic 160 kg
- Like with LMWH monitoring levels will allow greater use
Who Should get DOACs

- Venous thrombosis
- Older patients (> 75)
- Renal insufficiency
- Prior stroke or TIA
- Risk of bleeding
  – Apixaban

DOAC in Patients > 75

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>OR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>1.02</td>
<td>0.73-1.43</td>
</tr>
<tr>
<td>Stroke/embolism</td>
<td>0.65</td>
<td>0.48-0.87</td>
</tr>
<tr>
<td>VTE/Fatal PE</td>
<td>0.45</td>
<td>0.27-0.77</td>
</tr>
</tbody>
</table>

N = 25,031 in 10 RCT

JAGS 62:857, 2014
**DOAC > 75**

- Higher risk of thrombosis leads to higher benefit
- Lack of diet and drug interactions beneficial

**Thrombophilia**

- Hereditary
  - No concerns
- Antiphospholipid Syndrome
  - Inferior to warfarin in “triple positive patients”
History of GI Bleed

• Both rivaroxaban (1.5 HR) and dabigatran (1.6 HR) increase risk of bleeding but not apixaban (0.9 HR)
• Remember patients with GIB have better outcomes if placed back on anticoagulation

DOACs in Cancer

• Advantages
  – Few drug no food interactions
  – Short half-life
  – Not a shot
• Warfarin inferior to LMWH
  – Increase thrombosis
• Less than 33% of cancer patients on LMWH
### Edoxaban Cancer

<table>
<thead>
<tr>
<th></th>
<th>Edoxaban (522)</th>
<th>LMWH (524)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>67 (12.8%)</td>
<td>71 (13.5%)</td>
</tr>
<tr>
<td>rVTE</td>
<td>41 (7.9%)</td>
<td>59 (11.3%)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>36 (6.9%)</td>
<td>21 (4.0%)</td>
</tr>
</tbody>
</table>

Bleeding increase in GI cancers
10% dalteparin drop out due to shots


### Rivaroxaban Cancer

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (203)</th>
<th>LMWH (203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rVTE</td>
<td>8 (4%)</td>
<td>22 (11%)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>6 (3%)</td>
<td>9 (4%)</td>
</tr>
<tr>
<td>Relevant Bleeding</td>
<td>36 (17%)</td>
<td>11 (5.0%)</td>
</tr>
</tbody>
</table>

Bleeding increased in upper GI cancers

J Clin Oncol. 2018 Jul 10;36(20):2017-2023
**Apixaban Cancer**

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (145)</th>
<th>LMWH (203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rVTE</td>
<td>5 (3.4%)</td>
<td>20 (14.1%)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>0 (0%)</td>
<td>3 (2.1%)</td>
</tr>
<tr>
<td>Relevant Bleeding</td>
<td>9 (6.2%)</td>
<td>9 (6.2%)</td>
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</tbody>
</table>

ASH 2018

**DOAC in Cancer Patients**

- DOAC used in majority of patients
- 3 RCT showing equivalence/superiority with LMWH
  - GI bleeding concern with GI tumors
    - Rivaroxaban/edoxaban
  - Apixaban maybe prefer in patients at risk of GI bleeding
Cancer

• DOACs now front line
• Reserve LMWH for break through thrombosis
• GI bleeding issue
  – Less with apixaban?

Renal Disease

• Renal Function
  – All renally cleared:
    • Apixaban – dose reduced to 2.5 mg bid if
      – Creatinine > 1.5 plus age over 80 or weight < 60kg
      – Increasing dialysis data
    • Dabigatran – not for CrCl < 50
    • Rivaroxaban – 15mg CrCl 49-15
      – 10mg for dialysis
    • Edoxaban – 30mg/day if CrCl 15-50
**Apixaban: Renal Disease**

- GRF < 50 mL/min
  - Stroke: 0.61 (0.39-0.94)
  - Mortality: 0.78 (0.63-0.96)
  - Bleeding: 0.48 (0.37-0.64)


**Apixaban: Dialysis**

- Increasing use
  - Start at 5 mg bid and check levels
- Indications
  - Unstable INR
  - Calciphylaxis
- Monitoring levels
- RCT underway vs warfarin
Monitoring

• Designed not to need monitoring
  – Many reference labs offer levels
    • University of Washington

• When to consider
  – Compliance
  – Drug failure
  – Renal diseases
  – Extremes of weight

DOACs and Surgery

• Protocol based on drug, renal function and surgery

• Minor
  – Dermatologic surgery

• Major
  – Abdomen or thoracic surgery
DOACs and Surgery

<table>
<thead>
<tr>
<th>Drug</th>
<th>Surgery</th>
<th>CrCl</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>Surgery</th>
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<tbody>
<tr>
<td>Apix</td>
<td>Major</td>
<td></td>
<td></td>
<td></td>
<td>Hold</td>
<td>Hold</td>
<td>Hold</td>
</tr>
<tr>
<td>Minor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hold</td>
<td>Hold</td>
<td>Hold</td>
</tr>
<tr>
<td>Dabig</td>
<td>Major</td>
<td>&gt;50</td>
<td>Hold</td>
<td>Hold</td>
<td>Hold</td>
<td>Hold</td>
<td>Hold</td>
</tr>
<tr>
<td>Minor</td>
<td>&gt;50</td>
<td>Hold</td>
<td>Hold</td>
<td>Hold</td>
<td>Hold</td>
<td>Hold</td>
<td>Hold</td>
</tr>
<tr>
<td>Minor</td>
<td>&lt;50</td>
<td>Hold</td>
<td>Hold</td>
<td>Hold</td>
<td>Hold</td>
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<td>Hold</td>
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<tr>
<td>Rivarox</td>
<td>Major</td>
<td></td>
<td></td>
<td></td>
<td>Hold</td>
<td>Hold</td>
<td>Hold</td>
</tr>
<tr>
<td>Minor</td>
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<td>Hold</td>
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DOACs: Post Surgery

- Treat like LMWH
- Simple – restart next day
- Complex
  - Prophylactic dose
  - Full dose 48 hours or more
DOAC: Bleeding

• Analysis of all phase III trials
  – Venous thrombosis therapy
  – Atrial fibrillation
• N = 102,607 patients
• Chai-Adisaksopha Blood. 2014 Oct 9;124(15):2450-8

Results

• Major Bleeding RR = 0.72
  – NNT = 156
• Fatal Bleeding RR = 0.78
  – NNT = 454
• ICH RR = 0.76
  – NNT = 185
• Total Bleeding RR = 0.76
  – NNT = 18
• GI bleeding RR = 0.94
New Antithrombotic Agents

  - Prothrombin Complex Concentrates (PCC) standard
  - FFP not effective for rapid reversal
    - 75% patients dead or disabled after intracranial hemorrhage

Irreversibility = Myth

- Less need to reverse
- **No** difference in outcomes in multiple studies with bleeding
Dabigatran Reversal
Idarucizumab

- Effective in ~ 98% of patients in reversing thrombin and Ecarin time – 24% with no drug on board
- 98% of patients could undergo emergency surgery
- ~ 2% of patients required redosing for bleeding – Up to 20% in clinical practice
Idarucizumab

• Idarucizumab reverses dabigatran
• But need to treat cause of bleeding also
  – 2.5 - 11 hours to stop bleeding after antibody administered
• Allowed emergency surgery
• Should be used for ICH or urgent surgery

Our Protocol

1. Indication: ICH for patient on dabigatran
2. Baseline thrombin time and aPTT
   – Not to screen for use but to assess drug use
3. Five grams administered as 2.5 grams bolus one right after other
4. Consider for emergency surgery if TT/aPTT elevated
Xa Blockers

- Prothrombin Complex concentrates
  - Animal and human studies
- Studies - no difference in warfarin or DOAC ICH patients

Andexanet - PRT064445

- “R-antidote”
- Recombinant fXa derivative
  - Catalytically inactive
  - Lacks the Gla-domain
- Reverses both direct and indirect Xa inhibitors
- Approved but
  - Limited distribution
  - Expensive ($25-50,000/use)
PCC

• Prothrombin Complex Concentrates (4 factor)
• Increasing data on effectiveness
• Does - 50 units/kg
What We Do

- Warfarin and anti-Xa
  - 50 units/kg of 4 factor PCC
  - For warfarin add vitamin K
- Dabigatran
  - Idarucizumab 5grams

DOAC Do’s!

- Use in
  - High risk patients
  - Atrial fibrillation
  - Patients unstable INR
  - First line venous thrombosis/embolism
  - Cancer patients
  - Orthopedic prophylaxis
DOAC Don’ts!

• Don’t use wrong dose
• Don’t use with mechanical valves
• Don’t use in very obese patients