DOAC DO’S and DON’T’S

Thomas DeLoughery, MD MACP FAWM
Oregon Health & Sciences University

@bloodman
DISCLOSURE

Relevant Financial Relationship(s)
Speaker’s Bureau – none
Goals

• Drugs
• Diseases
• Dilemmas
• Do’s and Don’ts
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
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 underdosing DOACs lead to more thrombosis/stroke without change in bleeding
- Only dose adjust if indicated!
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
<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>
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</tbody>
</table>
# 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>
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<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>Dabig150</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
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>
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</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
Only “load” for acute VTE
Vitamin K Antagonist

Dabigatran
- LMWH
- 5 days
- Dabigatran 150 mg BID

Rivaroxaban
- Must take with food
- 15 mg BID
- 21 days
- 20 mg daily
- 10 mg daily

Apixaban
- 10 mg BID
- 7 days
- 5 mg BID
- 2.5 mg BID

Edoxaban
- LMWH
- 5 days
- Edoxaban 60 mg daily (CrCl 30-50, <60 kg: 30 mg 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
Low Dose DOAC

• Two trials
  – Rivaroxaban 20mg vs 10mg
  – Apixaban 5mg vs 2.5 mg
• Start 6-12 months after VTE
• No difference in VTE or bleeding
  – Trend toward reduce major bleeding
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
Direct Oral Anticoagulants

• Potential to be game changer
• Low dose for long term therapy good option
• But
  – Patients still need close follow-up
  – Still need to management anticoagulants
Dilemmas!
Who Must Stay on Warfarin

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

- DOACs weight base
- Obesity
  - Atrial fibrillation: 140 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>
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<tbody>
<tr>
<td>Bleeding</td>
<td>1.02</td>
<td>0.73-1.43</td>
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<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>
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</table>

N = 25,031 in 10 RCT

JAGS 62:857, 2014
Thrombophilia

• Hereditary
  – No concerns

• Antiphospholipid Syndrome
  – Not for triple positive
  – Not for arterial disease
TRAPS
Randomized controlled trial of Rivaroxaban vs Warfarin in APS

High-risk APS patients
- LA positive
- aCL positive
- aB2GPI positive

Rivaroxaban N=59

Warfarin N=61

Events on Rivaroxaban: 19%

Events on Warfarin: 3%

Stopped early for excess of events on Rivaroxaban
Pregnancy

• NO!
  – Will cross placenta
  – Secreted in breast milk

• LMWH remains anticoagulants of choice
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
Monitoring

- Designed not to need monitoring
  - Many reference labs (UW) offer levels
- When to consider
  - Compliance
  - Drug failure
  - Renal diseases
  - Extremes of weight
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: Dialysis

• Medicare dialysis patients
• Use of apixaban 5mg bid vs warf
  – Less bleeding
  – Less stroke
  – Less mortality
• Circulation. 2018;138:1519–1529
DOAC in Liver Disease

• Increasing data on safety in liver disease
  – Easier to use
  – Less bleeding

• Drug of choice
  – Apixaban ok in Childs B

• Exception Child C
  – Case by case basis
“Break-Through” Clots

• DOACs are not perfect
• Neither are patients…
“Break-Through” Clots

1. Is it a breakthrough clot?
   – New PE in first week ~ 5%
   – DVT can grow on therapy
   – New: new vessel or limb involved
   – PE after 2 weeks
“Break-Through” Clots

2. Was patient taking med?
   - Ideal: levels sent
   - Ok: INR/PTT check
   - Check DOAC dose
   - Ask patient
   - Check pharmacy
“Break-Through” Clots

3. Treatment
  – LWMH
    • If breakthrough LMWH raise dose 25%
  – Warfarin
    • Compliance concerns
Surgery/Procedures

• Increasing data
• Need to know
  – Drug
  – Procedure
  – Renal function
## DOACs and Surgery

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<th>Drug</th>
<th>Surgery</th>
<th>CrCl</th>
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<th>-1</th>
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<td>Major</td>
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<td>Hold</td>
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<tr>
<td></td>
<td>Minor</td>
<td></td>
<td>Hold</td>
<td>Hold</td>
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<tr>
<td>Dabig</td>
<td>Major</td>
<td>&gt;50</td>
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<td>Hold</td>
<td>Hold</td>
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<tr>
<td>Rivarox</td>
<td>Major</td>
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<td>Hold</td>
<td>Hold</td>
<td>Hold</td>
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<td></td>
<td>Minor</td>
<td></td>
<td>Hold</td>
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<td>Hold</td>
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</table>
Residual Preoperative DOAC Levels

Proportion of high bleed risk patients with DOAC level <50 ng/mL = 98.9% (823/832)

- 93.1% <30 ng/mL
- 85.3% <30 ng/mL
- 98.9% <30 ng/mL

Bar chart showing distributions of DOAC levels by different drugs: api-LOW, api-HIGH, dabi-LOW, dabi-HIGH, riva-LOW, riva-HIGH.
PAUSE Trial

• Major bleeding: 0.9-1.85%
  – BRIDGE Trial/Meta: 1.3%/2.7%
• Arterial Thrombosis: 0.2-0.6%
  – BRIDGE Trial/Meta: 0.4%/0.9%
DOACs: Post Surgery

- Treat like LMWH
- Simple – restart next day
- Complex
  - Prophylactic dose
  - Full dose 48 hours or more
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>
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<tr>
<th></th>
<th>Edoxaban (522)</th>
<th>LMWH (524)</th>
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</thead>
<tbody>
<tr>
<td>Primary Outcome</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 GI cancers

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

<table>
<thead>
<tr>
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<th>Apixaban (145)</th>
<th>LMWH (145)</th>
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</thead>
<tbody>
<tr>
<td>rVTE</td>
<td>5 (3.1%)</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>36 (17%)</td>
<td>11 (5.0%)</td>
</tr>
</tbody>
</table>

Presented at 2018 ASH, in press
Cancer

- 3 RCT: DOAC vs LMWH
- Recurrence: HR 0.48
- Bleeding: HR 1.54 (NS)
  - Mainly GI cancers
- DOAC can/should be use in cancer patients
  - Caution for upper GI cancers
Cancer

- DOACs now front line
- Reserve LMWH for break through thrombosis
- GI bleeding issue
  - Less with apixaban?
ELIQUIS HAS RISK OF UNCONTROLLABLE BLEEDING & HEMORRHAGING

If you or a loved one has taken XARELTO®?
- Internal Bleeding
- Stroke
- Or Death
Call us today!

Xarelto Linked To:
- Bleeding on the Brain
- Internal Bleeding
- Uncontrolled Bleeding
- Stroke
- Death

Have you or a loved one been injured while using Pradaxa®?
You may be entitled to financial compensation!

There is a limited time to file your claim!
DON’T DELAY!
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
Irreversibility = Myth

• Less need to reverse

• **No** difference in outcomes in multiple studies with bleeding
Dabigatran Reversal
Idarucizumab

- 45–64 yr, DE 220 mg + idarucizumab 5 g
- 65–80 yr, DE 220 mg + idarucizumab 5 g
- Mild RI, DE 150 mg + idarucizumab 5 g
- Moderate RI, DE 150 mg + idarucizumab 2 x 2.5 g

DE, dabigatran etexilate; dTT, diluted thrombin time; RI, renal impairment (CL\text{cr}: mild RI ≥ 60–< 90 mL/min; moderate RI ≥ 30–< 60 mL/min); TT, thrombin time.
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
- 30 day thrombosis seen in ~ 5% patients
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
Andexanet - PRT0644445

- “R-antidote”
- Recombinant fXa derivative
  - Catalytically inactive
  - Lacks the Gla-domain
- Reverses both direct and indirect Xa inhibitors
However....

• Short duration
• Thrombosis rate ~ 10%
• Expensive
  – $25-50,000
• Limited availability
Thrombosis

• 18% at start of trial and 10% final
• ~ 50% arterial
• Higher than PCC or Idarucizumab trials (4/6%)
  – Prothrombotic effect?
  – Blocks TFPI
Eligibility Criteria

• 2-3/9 OHSU ICH would have been in trial
• Sicker patients selected out?  
   – MGH 40% death rate
PCC

- Prothrombin Complex Concentrates (4 factor)
- Increasing data on effectiveness
  - Low rates of thrombosis
- Can use before procedures
- Does - 50 units/kg
PCC

• Recent meta-analysis
• Effectiveness 69-77%
• Mortality 14%
• Thrombosis 4%

Bleeding!

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

- Dabigatran
  - Idarucizumab 5 grams
The Future!

- Ciraparantag
  - “broad spectrum” reversal agent
  - Prolonged clinic effect
  - In clinical trials
Anticoagulation: When to Restart after a Bleed

- Very common problem
- Increasing data on subject
- Risk of rebleed varies with site of bleed and presence of anatomic lesions
Risk of Rebleeding

- ICH/SDH: long term risk of recurrence ~2%
  - Higher if cerebral amyloid angiopathy present (deep lobar bleeds)
- Gastrointestinal
  - Higher (10-20%?) especially if lesion present
GI Bleeding

- 9 studies show restarting anticoagulation
  - Associated with less thrombosis
  - Associated with less mortality
  - Minimal increase in the risk of bleeding
  - Apixaban less bleeding

- Restart 7 days

  All GI bleeding patients needs work-up

CNS Bleeding

• Risk of rebleeding 1-2%
• Higher if lobar bleed
  – Cerebral amyloid angiopathy
• Increasing data that is better to restart anticoagulation
## CNS Bleeding

**Meta-analysis 10 studies**

<table>
<thead>
<tr>
<th></th>
<th>Restart</th>
<th>Stop</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>18.7%</td>
<td>32.3%</td>
<td>0.51</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.5%</td>
<td>7.0%</td>
<td>0.56</td>
</tr>
<tr>
<td>New ICH</td>
<td>6.7%</td>
<td>7.7%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Thromb Res. 2017 Dec;160:97-104
Aspirin after ICH

- Not a substitute for anticoagulation
  - No affect on stroke rates
  - Increased risk of bleeding
- Nothing or anticoagulation
CNS Bleeding

- Unless evidence of CAA restart anticoagulation
- Apixaban may be safer
- No concurrent antiplatelet therapy
- Restart 7-14 days
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