DISCLOSURE

Current Relevant Financial Relationship(s)
None
• A potpourri of cases raising interesting issues...
#1

- Seeing a 85 YO patient for iron deficiency
- You notice she has afib and is on just 2.5mg bid of apixaban because “fall risk” and “being old”
## 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>
<tr>
<td>VTE/Fatal PE*</td>
<td>0.55</td>
<td>0.38 – 0.82</td>
</tr>
</tbody>
</table>

*N = 25,031 in 10 RCT  
*N = 3,665  
Anticoagulation and Falls

• Most commonly cited reason not to anticoagulated older patients

• But what is the data?
Falls: Man-Son-Hing

• Elaborate decision analysis by Man-Son-Hang demonstrate that the average patient would have to fall 295 times in one year for warfarin to be too dangerous to use.

• Retrospective review of hospital falls show only 1 SDH in 2500 falls
Gage Study AJM 118:612

• Patients at risk of falling and Afib had:
  – Higher incidence of ICH (2.8% vs 1.1%/yr)
  – Higher risk of stroke (13.7% vs 6.9%/yr)
  – More stroke risk factors
Gage

• Warfarin use in patients at risk of falls
  – Did not increase ICH rates
  – Did increase 30 day mortality (52% vs 33%)

• Warfarin for patients with CHADS2 > 2 reduced bad outcomes by 25%
Donze

- Prospective study of 515 patients on warfarin
  - 60% at high risk of falls
- No higher risk of bleeding
- 0.6%/yr bleeds after falls
Bond

• 2635 falls in 1861 inpatients
• Major bleeding
  – Warfarin vs nothing
    • 6% vs 11%; p = 0.01
    • No difference with INR 3-5 vs normal
  – Aspirin vs nothing
    • OR 1.45% (1.1 - 1.8)
  – Clopidogrel vs nothing
    • OR 2.2 (1.1 - 4.8)
Even patients at very high risk of ICH/falls benefit from anticoagulation in AF

*Drugs & Aging* 38, 713–723 (2021)
Falls: Bottom Line

- Excess bleeding due to falls is **markedly overstated**
- Patients at risk of falls are those at risk of stroke
- Risk: benefit heavily in favor of treatment esp with DOACs
- Risk of falls is **never** an excuse to deny patients anticoagulation
• eConsult
• Patient had FVL – can they be on a DOAC?
Thrombophilia

• Hereditary
  – No concerns

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

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

Rivaroxaban N=59
Events on Rivaroxaban: 19%

Warfarin N=61
Events on Warfarin: 3%

1.5 years

Stopped early for excess of events on Rivaroxaban
#3

- eConsult
- Patient with DVT
- Can they change to a DOAC?
- Weighs 145 KG
Weight

• Is there a weight limit?
• Is this the same VTE and AF?
• What about bariatric surgery?
Weight

• DOACs weight base

• Obesity
  – Atrial fibrillation: 140 kg
    • Check level if over 140 kg
  – Venous disease: ???

• Like with LMWH monitoring levels will allow greater use
DOAC – Obesity

• New guidance no issues with rivaroxaban or apixaban (VTE)

• Bariatric
  – Gastric banding: Apixaban
    • Other check levels
  – Gastrectomy: Apixaban
    • Other check levels
  – RYGB: ?
    • Check levels
#4

- Patient with new PE
- ED calls you because they are on dialysis
Renal: Standard Heparin

- Surprisingly little data!
- Some UFH renally cleared
- Limited data that aPTT underestimates heparin levels
- Increases risk of bleeding 3 fold
Renal: Low Molecular Weight Heparin

- Renal clearance
- Need to dose adjust
  - Therapy: 1 mg/kg qDay
  - Prophylaxis: 20-30 mg/day
- If dosed right **NO** difference in bleeding compared to UFH
UFH and LMWH

- N = 624 with CrCl <60ml
- UFH major bleeding
  - 26.3/1000 patient days
- Enoxaparin major bleeding
  - 20.7/1000 patient days
  - Dose NOT renally adjusted!

## UFH and LMWH

<table>
<thead>
<tr>
<th></th>
<th>Mild (40-60)</th>
<th>Mod (20-40)</th>
<th>Severe (&lt;20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>16.9</td>
<td>41.8</td>
<td>30.7</td>
</tr>
<tr>
<td>LMWH</td>
<td>12.4</td>
<td>22.5</td>
<td>33.2</td>
</tr>
</tbody>
</table>

Major bleeding /1000 patients days

But...

• Study in CrCl 30-50 with 4x risk of bleeding
  – Especially bridging therapy
• Rec:
  – Caution with bridging therapy
  – Dose decrease for long term
    • 0.8 mg/kg q 12
    • Follow levels
• Arch Int Med 2012 Dec 10;172(22):1713-8.
Warfarin

• CYP 2CP decreased by 30%
• Risk of bleeding 3 fold increased
• Increased incidence of erratic INR’s
  – Supplement vitamin K
  – DOACs?
DOAC: Renal Disease

- Renal Function
  - All renally cleared:
    - Apixaban – dose reduced to 2.5 mg bid if
      - Creatinine > 1.5 + 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
Use Right Dose!

- Increasing data that underdosing DOACs lead to more thrombosis/stroke without change in bleeding risk
- Only dose adjust if indicated!
## Wrong Dosing

<table>
<thead>
<tr>
<th></th>
<th>Stroke/Systemic Embolism HR (95% CI)</th>
<th>Bleeding HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Off-Label UNDER-dose</strong></td>
<td>1.22 (1.05-1.42) ↑ 22%</td>
<td>No difference</td>
</tr>
<tr>
<td><strong>Off-Label OVER-dose</strong></td>
<td>1.26 (1.11-1.43) ↑ 26%</td>
<td>1.30 (1.04-1.62) ↑ 30%</td>
</tr>
</tbody>
</table>

*J Am Heart Assoc 2022;11(6):e024402*
A

Crude cumulative incidence (%)

Days after stroke

VKA INR <2
VKA INR 2-3
VKA INR >3

Numbers at risk

424
449
106
393
436
102
372
423
95
357
416
93
358
419
92

log-rank p value <0.01

B

Crude cumulative incidence (%)

Days after stroke

Underdosed DOAC
Appropriate DOAC
Overdosed DOAC

Numbers at risk

259
670
194
197
542
176
186
520
167
176
155
184
497

log-rank p value <0.01
#5

- While you are talking to the ED they have a patient with a new portal vein thrombosis
- “Too risky to anticoagulated liver disease right?”
Portland Portal Vein Protocol
Portal Vein: Cirrhosis

• Incidental
  – SMV negative – no treat
  – SMV involved - treat

• Symptomatic – treat
Noncirrhotics: Symptomatic

- Provoked
  - Surgery
  - Infection, etc.
    - Treatment: 3 months
    - Work-up: not recommended

- Unprovoked
  - PNH, MPS, APLA
  - Indefinite anticoagulation
2017 Meta-Analysis

- 8 studies with 353 patients
- Recanalization
  - 71% vs 42%
- Complete recanalization
  - 53% vs 33%
- PVT progression
  - 9% vs 33%
- Bleeding
  - 11% vs 11%
- Gastro 153:480, 2017
2021 Update: DOAC & PVT

• DOAC vs Warfarin
  – Increased PVT recanalization – RR = 1.67
  – Decreased progression – RR = 0.14

• Anticoagulation in PVT
  – Increased PVT recanalization – OR 4.29
  – Decreased progression – OR 0.26
  – Bleeding slightly up – OR 1.16

Dig Liver Dis 2022 Jan;54(1):56-62
Hepatol Int 2021 Dec;15(6):1356-1375
DOAC in PVT

- Increasing data on safety in liver disease
  - Easier to use
  - Less bleeding
- Drug of choice: apixaban
- Exception Child C
  - Case by case basis
#6

• Questioned emailed from a podcast listener

• “What do we do about breakthrough clots”
“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

   - Olson SR, RPTH 2019
“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
#7

- Asked to see patient with GI bleed on warfarin
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 14-28 days
- RCT underway
#8

- Long time patient of yours wants her enoxaparin refilled to bridge before her colonoscopy
Anticoagulation and Surgery

- Millions of people on anticoagulation
- ~10% yearly need procedures
- Common issue is peri-operative management
Approaches to Warfarin Anticoagulation and Procedures

- Continue agents
- Stop drug
- Bridging therapy
Continue Warfarin

- Recommended approach for low risk procedures
  - Dental extractions
  - Cataracts
  - Simple endoscopy/colonoscopy
  - Pacemaker/ICD placement
  - Hip/Knee arthroplasty

- Works best if INR < 3.0
Stop all Drugs

• Approach associated with least risk of bleeding but (in theory) highest risk of thrombosis
• Warfarin and antiplatelet agents must be stopped 5-7 days before procedure
• Can take 2-5 days to get INR back up
• Best approach for patients not at high risk of thrombosis
Holding Anticoagulation

![Graph showing INR levels and Warfarin dosage over days for DVT prophylaxis. The graph indicates the timing for holding anticoagulation.](image)
Bridging
Bridging

• Covering the patient with LMWH while off warfarin
• Increasing data
  – Increases risk of bleeding
  – No decrease in thrombosis
• Shift away from aggressive bridging
Stop Warfarin

Start LMWH

Stop LMWH ~24 hour before

-5 -4 -3 -2 -1 0 1 2 3

Restart Warfarin

Restarting LMWH

Simple procedure – after procedure

Complex – Prophylactic 24-48 hrs
- Therapeutic 48 hrs or more
Bridging Therapy

INR

DAYS

-5 -4 -3 -2 -1 OR 1 2 3 4 5 6

Warfarin

1.5

Full-dose LMWH

↓ ↓ ↓ ↓ ↓

P F F F F F

LMWH

Warfarin
But Does Bridging Work?
2012 Meta-Analysis

- N = 12,278 patients in 34 studies
- Bleeding 5.4 (3.00-9.74)
- Major bleeding 3.6 (1.52-8.50)
- Thrombosis 0.8 (0.42-1.54)

- Circulation 126:1630, 2012
FIGURE 1 Rates of Periprocedural Thromboembolism and Bleeding

A

<table>
<thead>
<tr>
<th>Event Rate</th>
<th>Thromboembolism</th>
<th>Major Bleeding</th>
<th>Any Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Bridged</td>
<td>0.52%</td>
<td>1.18%</td>
<td>2.80%</td>
</tr>
<tr>
<td>Bridged</td>
<td>0.94%</td>
<td>3.52%</td>
<td>11.83%</td>
</tr>
</tbody>
</table>

B

<table>
<thead>
<tr>
<th>Event Rate</th>
<th>Thromboembolism</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>A fib</td>
<td>0.65%</td>
<td>2.26%</td>
</tr>
<tr>
<td>VTE</td>
<td>0.76%</td>
<td>1.14%</td>
</tr>
<tr>
<td>Mechanical Valves</td>
<td>1.13%</td>
<td>3.32%</td>
</tr>
</tbody>
</table>
Bridge Trial

• N = 1884
• Atrial fibrillation CHAD2 ≥ 1
• Excluded:
  – Mechanical valves
  – Stroke, arterial or venous thrombosis last 12 weeks
• NEJM 373:823, 2015
## Bridge Trial

<table>
<thead>
<tr>
<th>Condition</th>
<th>No Bridge</th>
<th>Bridge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial Thrombosis</td>
<td>4 (0.4)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>0 (0)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>MI</td>
<td>7 (0.8)</td>
<td>14 (1.6)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>12 (1.3)</td>
<td>29 (3.2)</td>
</tr>
</tbody>
</table>
Bottom Line

• Bridging associated with harm and no reduction in thrombosis
• Only highest risk patients should be bridged
Who to Bridge: Valves

- Valves
  - Mitral valve replacement
  - Multiple valves
  - Non-bileaflet aortic valve
  - Bileaflet AVR with other risk factors
Who to Bridge: Atrial Fibrillation

• Atrial fibrillation
  – Mechanical valves
  – Recent (< 12 weeks) stroke, arterial or venous thrombosis
  – Rheumatic Valvular disease
  – CHADS 5-6??
Who to Bridge: Venous Thrombosis

• Venous Thrombosis
  – Thrombus within 3 months
    • One month IVC filter?
  – Cancer and thrombosis
  – Virulent thrombophilia
## Indication for Warfarin

<table>
<thead>
<tr>
<th>Bridge?</th>
<th>Mechanical Valve</th>
<th>Atrial Fibrillation</th>
<th>Venous Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>Mitral</td>
<td>Mechanical or rheumatic valve</td>
<td>VTE last 3 months</td>
</tr>
<tr>
<td></td>
<td>Older valve</td>
<td>Recent event</td>
<td>Severe thrombophilia</td>
</tr>
<tr>
<td></td>
<td>Non-Bileaflet Aortic</td>
<td></td>
<td>Cancer</td>
</tr>
<tr>
<td></td>
<td>Bileaflet Aortic + stroke risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>Bileaflet Valve and NO stroke risk factors</td>
<td>All other atrial fibrillation</td>
<td>VTE &gt; 3 months ago, no other major risk factors</td>
</tr>
</tbody>
</table>
Factors Which Increase Risk for Bleeding

- **Pre-procedure**
  - Trough LMWH level too high
    - Need to stop q12 LMWH 24 hours before and q24 maybe 36-48%
    - Too aggressive LMWH in patients with renal disease
- **Post-procedure**
  - Starting therapeutic LMWH too soon!!
    - Need 48 hours or more
- Do not use fondaparinux
Post-Op

• PERIOP-2
• N = 1471
• Randomized (all restarted warfarin)
  – No LMWH after surgery
  – LMWH bridging until INR at goal
• BMJ 2021
Post-Op

• Thrombosis
  – NB: 1.2% B: 1.0%

• Major Bleeding
  – NB: 2% B: 1.3%

• No benefit of post-op aggressive bridging
Post-Op

- Restart warfarin
- Prophylactic LMWH if in hospital
DOACs and Surgery

• Protocol based on drug, renal function and surgery
  • Minor
    – Endoscopy
    – Dermatologic surgery
  • Major
    – Abdomen or thoracic surgery
• NEVER need bridging
## 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>
</tr>
</thead>
<tbody>
<tr>
<td>Apix</td>
<td>Major</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hold</td>
<td>Hold</td>
</tr>
<tr>
<td></td>
<td>Minor</td>
<td></td>
<td></td>
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<td>Hold</td>
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<td>Hold</td>
</tr>
<tr>
<td>Dabig</td>
<td>Major</td>
<td>&gt;50</td>
<td></td>
<td></td>
<td>Hold</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>&lt;50</td>
<td>Hold</td>
<td>Hold</td>
<td>Hold</td>
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<td>Hold</td>
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<tr>
<td></td>
<td>Minor</td>
<td>&gt;50</td>
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<td>Hold</td>
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<td></td>
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<td>&lt;50</td>
<td>Hold</td>
<td>Hold</td>
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<tr>
<td>Rivarox</td>
<td>Major</td>
<td></td>
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<td>Hold</td>
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<tr>
<td></td>
<td>Minor</td>
<td></td>
<td></td>
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<td></td>
<td>Hold</td>
<td>Hold</td>
</tr>
</tbody>
</table>
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
DOACs: Post Surgery

- Treat like LMWH
- Simple – restart next day
- Complex
  - Prophylactic dose
  - Full dose 48 hours or more
## Summary of RCT Results (>80% LMWH)

<table>
<thead>
<tr>
<th>Trial</th>
<th>COVID patient population</th>
<th>Anticoagulant Dose Comparisons (LMWH)</th>
<th>Primary Outcome Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perepu et al.</td>
<td>~2/3 ICU ↑D-dimer</td>
<td>Intermediate vs. prophylactic</td>
<td>No difference</td>
</tr>
<tr>
<td>INSPIRATION</td>
<td>ICU patients</td>
<td>Intermediate vs. prophylactic</td>
<td>No difference</td>
</tr>
<tr>
<td>Multiplatform RCT</td>
<td>ICU stratum</td>
<td>Therapeutic vs prophylactic/interm</td>
<td>Prophylactic-dose better</td>
</tr>
<tr>
<td>Multiplatform RCT</td>
<td>non-ICU stratum</td>
<td>Therapeutic vs prophylactic/interm</td>
<td>Therapeutic-dose better</td>
</tr>
<tr>
<td>ACTION</td>
<td>non-ICU ↑D-dimer</td>
<td>Therapeutic vs prophylactic (DOAC)</td>
<td>No difference</td>
</tr>
<tr>
<td>HEP-COVID</td>
<td>~2/3 non-ICU, ↑D-dimer</td>
<td>Therapeutic vs prophylactic/interm</td>
<td>Therapeutic-dose better</td>
</tr>
<tr>
<td>RAPID</td>
<td>non-ICU ↑D-dimer</td>
<td>Therapeutic vs prophylactic</td>
<td>Therapeutic-dose better</td>
</tr>
</tbody>
</table>
COVID

- Mild – no anticoagulation
- Hospitalization on oxygen – therapeutic LMWH
- ICU – prophylactic LMWH
- Discharge – consider prophylaxis in high risk patients