Perioperative Management of Direct Oral Anticoagulants

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No Disclosures
Objectives

- Understand the pharmacokinetics of direct oral anticoagulants (DOACs) & their implications in perioperative/periprocedural management
- Determine the timing of DOACs interruption, bridging, & resumption
- Manage peri/postop bleeding complications associated with DOACs
Your End Goals

1. Be able to manage patients on direct oral anticoagulants (DOACs) undergoing surgeries or procedures

2. Be able to determine when to hold and when to restart DOACs based on the types of the procedures and patients’ characteristics
DOACs & Periop

- “An ongoing challenge . . . due to the lack of good clinical studies”
  
  Faraoni et al. Critical Care 2015

- “Most data are based on expert’s opinions”
  
  Dincq et al. Biomed Research International

“Of 54 recommendations included in the 30 statements, 20 were strong and none was based on high quality evidence highlighting the need for further research”

Kearon et al CHEST 2016
Keys In Managing DOACs

- Types of DOACs & their pharmacokinetic characteristics
- Interruption
- Preop bridging
- Resumption & postop bridging
- Emergent procedures
- Postoperative bleeding complications
Clotting Cascade

Intrinsic pathway:
- XII
- XIIa
- XI
- Xla
- IX
- IXa

Extrinsic pathway:
- VIIa*
- Tissue factor
- Prothrombin (II)
- Xa
- Thrombin (IIa)
- Dabigatran

VKAs:
- Rivaroxaban
- Apixaban
- Edoxaban

Fibrinogen
- Fibrin
<table>
<thead>
<tr>
<th></th>
<th>VKA</th>
<th>UFH</th>
<th>LMWH</th>
<th>DOACs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>Oral</td>
<td>Parenteral iv or sq</td>
<td>Parenteral iv or sq</td>
<td>Oral</td>
</tr>
<tr>
<td>Onset of action</td>
<td>3-5d</td>
<td>1-2h</td>
<td>1-2h</td>
<td>1-3h</td>
</tr>
<tr>
<td>Half-life</td>
<td>24-36h</td>
<td>40-80min</td>
<td>4-7h</td>
<td>9-17h</td>
</tr>
<tr>
<td>Predictable anticoagulant effect</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Types of DOACs & their pharmacokinetic characteristics

**Interruption**
- Preop bridging
- Resumption & postop bridging
- Emergent procedures
- Postoperative bleeding complications
Mr. Doacs is a 52yo M with h/o CHF, HTN, TIA, Afib, DVT (2yrs ago), CKD3 (CrCl 45%) on dabigatran presents with DOE, found to have R sided pleural effusion.

VSS. Thoracentesis is being considered

What to do with dabigatran prior to the procedure

A. Perform thoracentesis immediately
B. Hold 1d
C. Hold 2d
D. Hold 3d
E. Hold at least 5d since his HAS-BLED score is high
F. Hold 15d
Survey-Low Risk Procedure
Survey-High Risk Procedure

![Bar Chart](chart.png)

- **Dabigatran**
- **Apixaban**
- **Rivaroxaban**

**Number of responders (n)**

- Y-axis: Number of responders (n)
- X-axis: Time (0 to 16)

The chart shows the distribution of responders over time for different treatments.
DOACs Interruption—Minimal Procedures

No clinically important bleeding risk:
- Teeth cleaning or uncomplicated extractions, cataract, glaucoma, EGD without biopsy, Skin biopsy, abscess incision

Perform the procedure at trough concentration (12 or 24hrs after the last intake)
DOACs Interruption

Minor procedures:
- EGD w/ biopsy, Prostate/bladder biopsy, thoracentesis, EP study, PPM or ICD implantation
- Last dose of DOACs 24hrs before the elective procedure

Major procedures:
- Liver/kidney biopsy, spinal or epidural anaesthesia, brain surgery, thoracic/abd/orthopedic surgery
- Last dose of DOACs 48hrs before the elective procedure
** Interruption **

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban–edoxaban–rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>No important bleeding risk and/or adequate local haemostasis possible:</strong>&lt;br&gt;<strong>perform at trough level (i.e. ≥12 or 24 h after last intake)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Low risk</strong></td>
<td>CrCl ≥ 80 mL/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 24 h</td>
<td>Low risk ≥ 24 h</td>
</tr>
<tr>
<td></td>
<td>CrCl 50–80 mL/min</td>
<td>≥ 48 h</td>
</tr>
<tr>
<td></td>
<td>≥ 36 h</td>
<td>High risk ≥ 48 h</td>
</tr>
<tr>
<td></td>
<td>CrCl 30–50 mL/min</td>
<td>≥ 72 h</td>
</tr>
<tr>
<td></td>
<td>≥ 48 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl 15–30 mL/min</td>
<td>≥ 96 h</td>
</tr>
<tr>
<td></td>
<td>Not indicated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl &lt; 15 mL/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not indicated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>There is no need for bridging with LMWH/UFH</td>
<td></td>
</tr>
</tbody>
</table>

No official indication for use
Keys In Managing DOACs

- Types of DOACs & their pharmacokinetic characteristics
- Interruption
- Preop bridging
- Resumption & postop bridging
- Emergent procedures
- Postoperative bleeding complications
Mr. Doacs is a 52yo M with h/o CHF, HTN, TIA, Afib, DVT (2yrs ago), CKD3 (CrCl 45%) on dabigatran presents with DOE, found to have R sided pleural effusion.

Dabigatran held for 2d prior to thoracentesis

Should Mr. Doacs be bridged with parenteral anticoagulant?

A. YES
B. NO
DOACs: To Bridge or Not To Bridge?

Dresden registry:

<table>
<thead>
<tr>
<th>DOACs</th>
<th>Continued</th>
<th>Interrupted =&gt; Heparin bridging?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Prophylactic</td>
</tr>
<tr>
<td>N (%)</td>
<td>187 (21.7%)</td>
<td>419 (48.6%)</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>63 (7.3%)</td>
</tr>
<tr>
<td></td>
<td>Therapeutic</td>
<td>179 (20.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 (1.7%)</td>
</tr>
</tbody>
</table>

~30% received heparin bridging
With Heparin  
N = 257

Without Heparin  
N = 606

Rates of major cardiovascular events & none clinically relevant bleedings were similar for patients with heparin or without heparin.

Bridging predicted major bleeding (OR 5.9; 95% CI 1.2–20.4) but did not appear to protect patients against thrombotic events.
## RELY Trial Subanalysis

<table>
<thead>
<tr>
<th>Warfarin-treated (n = 1,424)*</th>
<th>Dabigatran-treated (n = 2,709)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bridged (n = 391)</td>
<td>Not Bridged (n = 1,033)</td>
</tr>
<tr>
<td>27.5%</td>
<td></td>
</tr>
<tr>
<td>Bridged (n = 418)</td>
<td>Not Bridged (n = 2,291)</td>
</tr>
<tr>
<td>15.4%</td>
<td></td>
</tr>
</tbody>
</table>
### RELY Trial Subanalysis

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Bridging status</th>
<th>Dabigatran group (2,691)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% (N) patients with events/(N) patients assessed</td>
</tr>
<tr>
<td><strong>Major Bleeding</strong></td>
<td>Bridged</td>
<td>6.5 (27/417)</td>
</tr>
<tr>
<td></td>
<td>Not Bridged</td>
<td>1.8 (42/2,274)</td>
</tr>
<tr>
<td><strong>Stroke &amp; systemic embolism</strong></td>
<td>Bridged</td>
<td>0.5 (2/417)</td>
</tr>
<tr>
<td></td>
<td>Not Bridged</td>
<td>0.3 (6/2,2734)</td>
</tr>
<tr>
<td><strong>Any thromboembolism</strong></td>
<td>Bridged</td>
<td>1.2 (13/417)</td>
</tr>
<tr>
<td></td>
<td>Not Bridged</td>
<td>0.6 (15/2,274)</td>
</tr>
</tbody>
</table>
## RELY Trial Subanalysis

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Bridging status</th>
<th>Warfarin group (N=1,415)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% (N) patients with events/(N) patients assessed</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>Bridged</td>
<td>6.8 (26/383)</td>
</tr>
<tr>
<td></td>
<td>Not Bridged</td>
<td>1.6 (16/1,032)</td>
</tr>
<tr>
<td>Stroke &amp; systemic embolism</td>
<td>Bridged</td>
<td>0.5 (2/383)</td>
</tr>
<tr>
<td></td>
<td>Not Bridged</td>
<td>0.2 (2/1,032)</td>
</tr>
<tr>
<td>Any thromboembolism</td>
<td>Bridged</td>
<td>1.8 (7/383)</td>
</tr>
<tr>
<td></td>
<td>Not Bridged</td>
<td>0.3 (3/1,032)</td>
</tr>
</tbody>
</table>
Use and Outcomes Associated With Bridging During Anticoagulation Interruptions in Patients With Atrial Fibrillation

Findings From the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF)

Benjamin A. Steinberg, MD, MHS; Eric D. Peterson, MD, MPH; Sunghee Kim, PhD; Laine Thomas, PhD; Bernard J. Gersh, MBChB, DPhil; Gregg C. Fonarow, MD; Peter R. Kowey, MD; Kenneth W. Mahaffey, MD; Matthew W. Sherwood, MD, MHS; Paul Chang, MD; Jonathan P. Piccini, MD, MHS; Jack Ansell, MD; on behalf of the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Investigators and Patients*
Vascular Medicine

Periprocedural Heparin Bridging in Patients Receiving Vitamin K Antagonists

Systematic Review and Meta-Analysis of Bleeding and Thromboembolic Rates

Deborah Siegal, MD, MSc; Jovana Yudin, MD, BSc; Scott Kaatz, DO, MSc; James D. Douketis, MD, FRCPC; Wendy Lim, MD, MSc, FRCPC; Alex C. Spyropoulos, MD, FCCP, FRCPC
Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

DOACs: To Bridge or Not To Bridge Preoperatively

- Bridging for DOACs with parenteral anticoagulants prior to the procedure generally NOT recommended
- The need to bridge preop?
  - Duration of DOAC interruption (>3d)
  - Significant thrombotic risks
- If bridged:
  - Start heparin when the next dose of DOAC due
  - Hold iv unfractionated heparin 4-6hrs & LMWH 24hrs prior to the procedure
Keys In Managing DOACs

- Types of DOAC & their pharmacokinetic characteristics
- Interruption
- Preop bridging
- **Resumption & postop bridging**
- Emergent procedures
- Postoperative bleeding complications
Mr. Doacs is a 52yo M with h/o CHF, HTN, TIA, Afib, DVT (2yrs ago), CKD3 (CrCl 45%) on dabigatran presents with DOE, found to have R sided pleural effusion.

Underwent thoracentesis successfully. DOE resolved

When should dabigatran be resumed?

A. Immediately
B. 1d
C. 2d
D. 3d
E. 4d
F. 15d
When to Resume DOACs

- Types of procedures, postop clinical setting, hemostasis status

<table>
<thead>
<tr>
<th>Minor Procedure</th>
<th>Low Bleeding Risk</th>
<th>High Bleeding Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-8hrs</td>
<td>24hrs</td>
<td>48hrs</td>
</tr>
</tbody>
</table>
To Bridge or Not To Bridge Postoperatively?

Most: no need to bridge postop

Consider bridging:

- High risk of thrombosis but concerns of bleeding if DOACs restarted esp at full dose
- \( \Rightarrow \) Lower DOACs dose
- Unable to tolerate oral (postop ileus, intractable n/v)
- Possibility of reintervention

\( \Rightarrow \) Bridge with parenteral anticoagulant @ prophylactic dose after hemostasis achieved & defer restarting DOACs 48-72hrs

When ready to transition, restart DOACs

- 0-2hrs BEFORE the time the next dose of LMWH scheduled or at the time iv unfractionated heparin discontinued
Keys In Managing DOACs

- Types of DOAC & their pharmacokinetic characteristics
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- Emergent procedures
- Postoperative bleeding complications
Case Scenario

- Mr. Doacs is a 52yo M with h/o CHF, HTN, TIA, Afib, DVT (2yrs ago), CKD3 (CrCl 45%) on dabigatran presents with DOE, found to have R sided pleural effusion.

- Underwent thoracentesis successfully. DOE resolved

- Dabigatran was resumed => compliant

- 3 months later, he accidentally tripped & fell & broke his R hip

- Ortho team wonders when we can safely bring him to OR & fix his hip
Emergent Procedures

- Discontinue DOACs
- Timing of the last dose
- How emergent?
  - If possible, delay the invasive procedure
  - The benefit of performing a surgery without delay should be balanced with the risk of major hemorrhage
<table>
<thead>
<tr>
<th></th>
<th>Below on-therapy range</th>
<th>On-therapy range</th>
<th>Above on-therapy range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td>TT</td>
<td>Dilute TT, ECT, ECA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>APTT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT</td>
<td></td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>Anti-Xa Activity</td>
<td></td>
<td>APTT</td>
</tr>
<tr>
<td></td>
<td>PT</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>Anti-Xa Activity</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>PT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Intra/Postoperative Bleeding Management

- Limited info: insufficient clinical data on human models
- Prothrombin Complex Concentrate (PCC)
  - Effective in reversing anticoagulant effect, esp in case of massive bleeding
- Activated PCC (FEIBA)
  - More potent, effective, but increased thrombosis risk
  - Life-threatening bleeding
- Activated charcoal esp in patients on dabigatran or apixaban, most effective when last dose taken within 2hrs
- Consider hemodialysis in dabigatran overdose
- Consult hem/onc
Idarucizumab
Take Home Points

- DOAC users undergoing surgeries/procedures are common, so ability to manage these patients is necessary.

- DOACs interruption preoperatively usually from 12-48hrs for most procedures, longer if renal insufficiency or undergoing high bleeding risk procedures.

- Most DOAC users do NOT require bridging prior to or after the procedure.

- In addition to PCC, aPCC, idarucizumab, adexanet, further strategies and development of new reversal agents are needed to treat bleeding complications.