Managing Patients after an Anticoagulant-related Major Bleed

Do you restart anticoagulants?
If yes, when to restart?
If yes, how to minimize risk for re-bleeding?

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# Lifetime Disclosures and Potential COIs

<table>
<thead>
<tr>
<th>Research Support*</th>
<th>CIHR, HSFC, Boehringer-Ingelheim</th>
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</thead>
<tbody>
<tr>
<td>Employee</td>
<td>Up-to-Date, Merck Manual</td>
</tr>
<tr>
<td>Consultant or Advisory Board*</td>
<td>Actelion, AGEN, Astra-Zeneca, Bayer, Biotie, BMS-Pfizer, Daiichi-Sankyo, Portola, Boehringer-Ingelheim, Cytori, Janssen, Leo, Medicines Co.</td>
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<tr>
<td>Stockholder</td>
<td>None</td>
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<td>Speakers Bureau</td>
<td>None</td>
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<tr>
<td>Speaker’s Fees*</td>
<td>Bayer, Boehringer-Ingelheim, BMS-Pfizer, Leo Pharma, Pfizer, Sanofi</td>
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*Funds from these sources deposited into university-based research accounts or SJHH Foundation. **Last 3 years**
Learning Objectives

- Provide a quick background to bleed management.
- In patients who develop an anticoagulant-related major bleed (GI or ICH), to provide a 4-point approach to patient management:
  1. Should we restart anticoagulant after bleed: yes or no?
  2. When to resume anticoagulation: ≤1, 2-4, >4 weeks?
  3. Do we change anticoagulant to minimize bleed risk?
  4. What else can we do to minimize bleed risk?
Types of Gastrointestinal Bleeding

- Peptic ulcer
- Angiodysplasia
- Gastric antral vascular ectasia
Types of Intracranial Hemorrhage (ICH)

- subdural
- lobar intracerebral
- deep intracerebral
How to reverse warfarin (...and DOACs)?

• Clotting factor replacements
  – FFP: large volume (4 U = 1L saline), time to thaw, variable clotting factor levels, need to cross-match blood
  – 4-factor PCCs: factors 2,7,9,10 (VKAs, oral Xa inhibitors)
  – activated PCC (FEIBA): factors 2,9,10 + activated 7 (dabigatran)

**RE-VERSE AD Trial**

**Primary endpoint:** reversal of dabigatran activity

- **Group A:** uncontrolled bleeding + dabigatran-treated
- **Group B:** emergency surgery/procedure + dabigatran-treated

**Multiple safety endpoints**

- N = 300
- 0 – 15 min
- 90 days follow-up
- 0 – 24 hrs
  - Hospital arrival
  - Pre-1st dose
  - Pre-2nd dose
  - ~20 min
  - 1 h
  - 2 h
  - 4 h
  - 12 h
  - 24 h
  - 30 d
  - 90 d

**How to reverse dabigatran**

- 5 g idarucizumab (two separate infusions of 2.5 g)

Reversal of Dabigatran (dilute Thrombin Time-dTT)

Bleeding
Group A
N = 298

Urgent Surgery/Proc.
Group B
N = 196

How to reverse rivarox/apix/edox-aban

Acute major bleeding ≤18 hrs of last drug dose

andexanet IV bolus + 2-hr infusion

- Patients on apixaban or >7 hrs from last rivaroxaban dose
  - bolus 400 mg
  - infusion 480 mg @4 mg/min

- Pts on enoxaparin, edoxaban or ≤7 hrs from last rivaroxaban dose
  - bolus 800 mg
  - infusion 960 mg @8 mg/min

Effect of andexanet on anti-Xa activity of rivaroxaban (n= 26)

<table>
<thead>
<tr>
<th>Time</th>
<th>Median</th>
<th>Percent Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>277.0</td>
<td>-89 (-58 to -94)</td>
</tr>
<tr>
<td>End of Bolus</td>
<td>16.8</td>
<td>-86 (-55 to -93)</td>
</tr>
<tr>
<td>End of Infusion</td>
<td>30.6</td>
<td>-39 (-27 to -45)</td>
</tr>
<tr>
<td>4 Hr</td>
<td>177.7</td>
<td>-49 (-43 to -57)</td>
</tr>
<tr>
<td>8 Hr</td>
<td>127.1</td>
<td>-64 (-51 to -70)</td>
</tr>
<tr>
<td>12 Hr</td>
<td>97.9</td>
<td></td>
</tr>
</tbody>
</table>
Effect of andexanet on anti-Xa activity of apixaban (n=20)

<table>
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<tr>
<th>Time</th>
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<th>Percent Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>149.7</td>
<td>-93 (-87 to -94)</td>
</tr>
<tr>
<td>End of Bolus</td>
<td>10.3</td>
<td>-92 (-85 to -94)</td>
</tr>
<tr>
<td>End of Infusion</td>
<td>12.5</td>
<td>-30 (-23 to -46)</td>
</tr>
<tr>
<td>4 Hr</td>
<td>103.0</td>
<td>-28 (-19 to -38)</td>
</tr>
<tr>
<td>8 Hr</td>
<td>107.1</td>
<td>-31 (-27 to -41)</td>
</tr>
<tr>
<td>12 Hr</td>
<td>100.2</td>
<td>-30 (-27 to -41)</td>
</tr>
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Learning Objectives

• In patients who develop an anticoagulant-related major bleed (GI or ICH), to provide a 4-point approach to patient management:

(1) Should we restart anticoagulant after bleed: yes or no?
(2) When to resume anticoagulation: ≤1, 2-4, >4 weeks?
(3) Do we change anticoagulant to minimize bleed risk?
(4) What else can we do to minimize bleed risk?
After a GI bleed, resuming anticoagulants will increase the risk for recurrent bleeding

A. True
B. False
Restarting anticoagulants after a GI bleed is associated with an increased risk for death.

A. True
B. False
Outcomes Post-GI Bleed: Restarting vs. not restarting anticoagulants

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication for anticoagulation</th>
<th>Anticoagulant</th>
<th>Follow-up period</th>
<th>Adjusted HR-TE (95% CI)</th>
<th>Adjusted HR-recurrent GIB (95% CI)</th>
<th>Adjusted HR all-cause mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witt 2012, N = 442</td>
<td>AF, VTE, MVR, Other</td>
<td>Warfarin</td>
<td>90 d</td>
<td>0.05 (0.01-0.58)</td>
<td>1.32 (0.50-3.57)</td>
<td>0.31 (0.15-0.62)</td>
</tr>
<tr>
<td>Qureshi 2014, N = 1329</td>
<td>AF</td>
<td>Warfarin</td>
<td>1-y (TE) 90-d (GIB)</td>
<td>0.71 (0.54-0.93)</td>
<td>1.18 (0.94-1.10)</td>
<td>0.67 (0.56-0.81)</td>
</tr>
<tr>
<td>Staerk 2015, N = 3409</td>
<td>AF</td>
<td>Single OAC*</td>
<td>5-y</td>
<td>0.41 (0.31-0.54)</td>
<td>1.22 (0.84-1.77)</td>
<td>0.39 (0.34-0.46)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single antiplatelet†</td>
<td></td>
<td>0.76 (0.61-0.95)</td>
<td>1.19 (0.82-1.74)</td>
<td>0.76 (0.68-0.86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OAC + antiplatelet*</td>
<td></td>
<td>0.54 (0.36-0.82)</td>
<td>1.34 (0.79-2.28)</td>
<td>0.41 (0.32-0.52)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dual antiplatelet‡</td>
<td></td>
<td>0.79 (0.34-1.84)</td>
<td>0.58 (0.08-4.30)</td>
<td>0.88 (0.57-1.36)</td>
</tr>
<tr>
<td>Sengupta 2015, N = 197</td>
<td>Various</td>
<td>Warfarin</td>
<td>90 d</td>
<td>0.12 (0.006-0.81)</td>
<td>2.17 (0.86-6.67)</td>
<td>0.63 (0.22-1.89)</td>
</tr>
</tbody>
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Witt DM. Hematology Am Soc Hematology Educ Program 2016:620
## Outcomes Post-Intracranial Bleed: Restarting vs. not restarting anticoagulants

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<th>Anticoagulant</th>
<th>Follow-up period</th>
<th>HR-TE (95% CI)</th>
<th>HR-recurrent ICH (95% CI)</th>
<th>HR all-cause mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuramatsu 2015, N = 719¹⁷</td>
<td>AF, VTE, MVR, Other</td>
<td>VKA</td>
<td>1-y</td>
<td></td>
<td>NR*</td>
<td>0.26 (0.13-0.53)‡</td>
</tr>
<tr>
<td>Witt 2015, N = 160¹⁸</td>
<td>AF, VTE, MVR, Other</td>
<td>Warfarin</td>
<td>1-y</td>
<td>0.28 (0.06-1.27)§</td>
<td>0.47 (0.10-2.30)§</td>
<td>0.76 (0.30-1.89)¶</td>
</tr>
<tr>
<td>Nielsen 2015, N = 1752¹⁹</td>
<td>AF</td>
<td>VKA, DOAC</td>
<td>1-y</td>
<td>0.59 (0.33-1.03)¶</td>
<td>0.91 (0.56-1.49)¶</td>
<td>0.55 (0.37-0.82)¶</td>
</tr>
<tr>
<td></td>
<td>Antiplatelet therapy</td>
<td></td>
<td></td>
<td>0.98 (0.65-1.49)¶</td>
<td>0.60 (0.37-1.03)¶</td>
<td>0.90 (0.67-1.21)¶</td>
</tr>
</tbody>
</table>

Witt DM. Hematology Am Soc Hematology Educ Program 2016:620
After a ICH, resuming anticoagulants will increase the risk for recurrent bleeding

A. True
B. False
Restarting anticoagulants after an ICH is associated with an increased risk for death

A. True
B. False
Outcomes Post-Intracranial Bleed: Restarting vs. not restarting anticoagulants

- Retrospective, multicenter cohort study in Germany (2006-12)
- 1,176 patients with ICH
- 719 patients had VKA resumption

Karamatsu JB, et al. JAMA 2015;313:824
Restarting vs. not restarting VKAs after ICH: Effect on ischemic and bleeding events

Restarting vs. not restarting VKAs after ICH: Effect on mortality

Restarting vs. Not restarting VKA after ICH: Effect on Recurrent ICH

**eTable 8.** Propensity-matched analysis of event and incidence rates in A-fib patients – new ischemic stroke *versus* recurrent ICH.

<table>
<thead>
<tr>
<th>Patients with atrial fibrillation</th>
<th>No. of Patients</th>
<th>No. of events (%)</th>
<th>( P ) Value</th>
<th>Incidence rate per 100 patient years (95%CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>New cerebral Infarction</td>
<td>261</td>
<td>20 (7.7%)</td>
<td></td>
<td>8.7 (3.8-12.6)</td>
<td></td>
</tr>
<tr>
<td>According to treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAC resumption</td>
<td>108</td>
<td>4 (3.7%)</td>
<td>0.04</td>
<td>3.9 (1.9-5.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>No OAC resumption</td>
<td>153</td>
<td>16 (10.5%)</td>
<td></td>
<td>12.7 (6.5-19.1)</td>
<td></td>
</tr>
<tr>
<td>Recurrent ICH</td>
<td>261</td>
<td>9 (3.4%)</td>
<td></td>
<td>3.9 (1.4-6.5)</td>
<td></td>
</tr>
<tr>
<td>According to treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAC resumption</td>
<td>108</td>
<td>4 (3.7%)</td>
<td>0.55</td>
<td>3.9 (1.9-5.8)</td>
<td>0.92</td>
</tr>
<tr>
<td>No OAC resumption</td>
<td>153</td>
<td>5 (3.3%)</td>
<td></td>
<td>3.9 (2.2-5.7)</td>
<td></td>
</tr>
</tbody>
</table>

Karamatsu JB. et al. *JAMA* 2015;313:824
Outcomes Post-Intracranial Bleed: Restarting vs. not restarting anticoagulants

- Nationwide (Danish) linked database

- 2,415 patients (61% male, mean age 77 yrs) with atrial fibrillation who developed VKA-associated ICH

- ICH = hemorrhagic stroke + traumatic bleeding

Restarting vs. not restarting VKA after ICH

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- In patients who develop an anticoagulant-related major bleed (GI or ICH), to provide a 4-point approach to patient management:

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2. When to resume anticoagulation: ≤1, 2-4, >4 weeks?
3. Do we change anticoagulant to minimize bleed risk?
4. What else can we do to minimize bleed risk?
After a GI bleed, when should you resume anticoagulation?

A. within 1 week
B. 1-2 weeks
C. 2-4 weeks
D. 4-8 weeks
After an ICH, when should you resume anticoagulation?

A. within 1 week  
B. 1-2 weeks  
C. 2-4 weeks  
D. 4-8 weeks
What is the optimal timing to resume OAC that minimizes bleeding and TE risk?

<table>
<thead>
<tr>
<th>TE Risk</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF, CHADS &lt; 4</td>
<td>resume earlier</td>
<td>delay</td>
<td>delay</td>
</tr>
<tr>
<td>aortic valve</td>
<td>resume earlier</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mitral valve</td>
<td>resume earlier</td>
<td>delay</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>delay</td>
<td></td>
</tr>
</tbody>
</table>

Bleeding Risk:
- Low
- Moderate
- High
What is the risk for thromboembolism with anticoagulation interruption?

- **High-risk (>10%/yr if NOT anticoagulated)**
  - mechanical mitral valve or older aortic valve
  - AF and CHADS<sub>2</sub>VA<sub>2</sub>SC = 7-9
  - recent (within 3 months) ATE or VTE

- **Moderate-risk (5-10%/yr)**
  - bileaflet aortic valve
  - AF and CHADS<sub>2</sub>VA<sub>2</sub>SC = 5-6

- **Low-risk (<5%/yr)**
  - AF and CHADS<sub>2</sub>VA<sub>2</sub>SC = 1-4

Siegal D, et al. *Circulation* 2012;126:1630
When to resume anticoagulants after an upper GI bleed?

- M-W tear
- EtOH gastritis esophagitis
- Gastric/duodenal ulcer (healed)
- Gastric/duodenal ulcer (bleeding)
- GAVE
- Unresectable neoplasm

Low (empiric bleed risk) high

≤1 week  2-4 weeks  >4 weeks  never?
When to resume anticoagulants after a lower GI bleed?

- Hemorrhoid: ≤1 week
- Diverticulosis: 2-4 weeks
- Angiodysplasia: >4 weeks
- Ulcerative colitis: never?
- C. difficile colitis: (empirc bleed risk)
- Unresectable neoplasm: high
ICH and Recurrent Bleed Risk

• primary ICH > secondary ICH
  - hypertension
  - amyloid

• Lobar (cortex) > deep (basal ganglia, cerebellum, thalamus, internal capsule)
  - trauma
  - AVM
  - neoplasm
  - coagulopathy
When to resume OAC after ICH?

- Cerebral DVT
- Hemorrhagic transformation
- Subdural/trauma
- Small intra-cerebral deep (basal ganglia)
- Moderate-large intra-cerebral lobar (cortex)
- Amyloid
- Some cancers

- ≤1 week (low risk)
- 2-4 weeks
- >4 weeks
- Never?
Timing of Restarting OAC after GI or IC Bleed

- 2 retrospective, multicenter cohort studies:
  - 207 patients (63% AF, 11% MHV) with upper GI bleed
  - 234 patients (58% AF, 15% MHV) with ICH

  - After GI bleed: 121 (58%) patients restarted VKA at median of 1 week (IQR: 0.2-3.4 weeks)
  - After ICH: 59 (25%) patients restarted VKA at median of 5.6 weeks (IQR: 2.6-17 weeks)

Majeed A, et al. *Stroke* 2010;41:2860
Risk for Recurrent GI Bleed and TE **without** VKA restart

- ↑ risk for bleed: OR = 2.5 (CI: 1.4-4.5)

Risk for Recurrent GI Bleed and TE **with** VKA restart at ~1 week post-bleed

- ↓ risk for TE: OR = 0.19 (CI: 0.07-0.55)
- ↓ risk for death: OR = 0.61 (CI: 0.39-0.94)

Majeed A, et al. T&H; 2017
Post-GI bleed: When to resume anticoagulants?

GI Bleed + TE
GI Bleed
thromboembolism (TE): patients with AF

Post-ICH: When to resume anticoagulants?

Majeed A, et al. *Stroke* 2010;41:2860
Learning Objectives

• In patients who develop an anticoagulant-related major bleed (GI or ICH), to provide a 4-point approach to patient management:

(1) Should we restart anticoagulant after bleed: yes or no?
(2) When to resume anticoagulation: ≤1, 2-4, >4 weeks?
(3) Do we change anticoagulant to minimize bleed risk?
(4) What else can we do to minimize bleed risk?
After a DOAC-related bleed, what should you do about the anticoagulant?

A. switch to warfarin
B. switch DOACs
C. continue the same DOAC but at lower dose
D. continue the same DOAC at same dose
Should we switch anticoagulants...is it safer?

- If taking VKA and develops ICH
  - better INR control, control modifiable risk factors
  - change to DOACs (40-60% RRR for ICH)

- If taking DOAC and develops GI bleed
  - apixaban/edoxaban instead of dabigatran/rivaroxaban

- If taking DOAC and any bleed, is dose correct?
  - dabigatran: 110 mg if >75 yrs
  - rivaroxaban/edoxaban: 15 mg/30 mg if CrCl <50
  - apixaban: 2.5 mg if 2/3 of >80 yrs, <60 kg, creat >133

Abraham NS, et al. Gastroenterology 2017;152:1014
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(4) What else can we do to minimize bleed risk?
After an ICH, what is proven to reduce the risk for re-bleeding?

A. better INR control
B. stopping ASA, NSAIDs
C. better BP control
D. all of the above

25%  25%  25%  25%
Can we reduce the risk for re-bleeding?
Look for reversible risk factors!

• **H-A-S-B-L-E-D** score factors
  – Hypertension
  – Labile INRs
  – Alcohol use
  – Drug use: antiplatelets (ASA, P2Y12, NSAIDs)

• **Other factors**
  – vision and hearing testing
  – walking assist devices
Effect of Good BP Control (<140/90 mmHg) on Recurrent ICH Risk


Figure 2. Estimated Yearly Risk of Recurrent ICH Based on Mean Blood Pressure Measurements During Follow-up

A. Lobar ICH

- Previous lobar ICH

B. Nonlobar ICH

- Previous non-lobar ICH
Take-home Message: do’s and don’ts after the anticoagulant-related bleed

• **Do...**
  – determine cause of bleeding and risk for re-bleeding
  – resume anticoagulation in most patients
  – re-start ≤1 week if self-limiting bleed
  – delay re-start for 2-4 weeks if higher bleed risk

• **Don’t...**
  – forget to address modifiable bleeding risk factors
    • ensure good BP control (target: 130/80 mmHg)
    • stop non-essential antiplatelet drugs (ASA or NSAIDs)