Managing Anticoagulation in the Hospitalized Patient

TRACY MINICHIHELLO, MD
CHIEF, ANTICOAGULATION & THROMBOSIS SERVICE-SAN FRANCISCO VAMC
PROFESSOR OF MEDICINE
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Objectives
- Know when to restart anticoagulation after a bleed
- Appreciate limitations in data for DOACs at extremes of weight
- Understand place of reduced dosing of DOACs in AFIB
- Develop approach to patient bleeding on DOAC
- Review evidence on dual therapy with DOAC in PCI

Financial Disclosures-NONE

THESE SHOULD BE AT YOUR FINGERTIPS

2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Patients with Atrial Fibrillation

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

76 y/o man with CAD (NSTEMI 2006), AFIB CHADS-Vasc=4 on warfarin and ASA is admitted with UGIB. INR is 3.0. He requires 3u PRBCs, vit K and FFP. EGD shows peptic ulcer disease. He is started on high dose PPI therapy, bx for H Pylori done. When should his anticoagulation be restarted?

a) Never  
b) In two weeks  
c) In three months  
d) Let the primary provider deal with this one
What To Do After the Bleed

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“Two weeks may provide the best balance among GI bleed recurrence, thromboembolism and mortality”

AC FORUM Clinical Guidance
Antithrombotic Therapy for VTE

“IN THE EVENT OF GI BLEED WE SUGGEST WAITING AT LEAST 7 DAYS WITHOUT EVIDENCE OF ACTIVE BLEEDING AND AFTER ENDOSCOPIC TX BEFORE REINITIATING AC”
Resumption of DOACs

Anticoagulation FULLY therapeutic within 1-2 hours
Only dabigatran has a reversal agent

Considerations After GIB on AC

- Reassess risk benefit of anticoagulation
  secondary prevention of VTE therapy, low CHADS-vasc
- Assess risk of rebleeding from source
  identifiable source, treatable lesion?
- Take steps to decrease risk of bleeding related
to AC regimen
- Reconsider need for antiplatelet therapy
  if warfarin was INR in range, is control good?
  spurious elevation in INR or poor TTR→DOAC
  increase INR monitoring→home POC INR?
- If ongoing strong indication for AC determine
  best time to restart therapy in
  multidisciplinary meeting with proceduralist -
  Remember DOAC immediately active
What To Do After the Bleed

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DOACs in Extremes of Weight

A 56 year old obese man, BMI 42, weight 155 kg presents with bilateral lower extremity swelling and SOB. D-Dimer is elevated CTa shows multiple bilateral segmental PE. What anticoagulant regimen do you recommend?

a) Rivaroxaban 15 mg BID x21 days then 20 mg daily  
b) Apixaban 10 mg BID x 7 days then 5 mg BID  
c) Enoxaparin bridging to warfarin  
d) Admission for IV heparin bridging to warfarin

DOACs in Extremes of Weight


- Systematic review of 6 trials of DOACs vs warfarin n VTE
  - Proportion of patients classified as high body weight 15-28%
  - Variability may be related to definition (ie > 90kg vs 100kg)
  - Very little information on extreme body weight (eg < 40 kg, > 150 kg

DOACS AND EXTREMES OF WEIGHT

DOACs in Obesity

**Recommendations and Guidelines**

Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH

- Reduced exposure, lower peaks, shorter t1/2

- Recommend standard dosing if BMI < 40 and weight < 120 kg.
- Suggest DOACS not be used if BMI > 40 or weight > 120 kg
- If DOACs used in BMI > 40 or weight > 120 kg suggest drug specific peak and trough level. If level within expected range continue DOAC; if below suggest warfarin.

**Martin et al. Journal of Thrombosis and Haemostasis, 2016 14: 1308–1313**

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**DOAC Dose Reduction**

78 year old man with HTN CHF CKD is found to be in AFIB. His creatinine is 1.6. He weighs 61 kgs. He has a remote history of GI bleeding. What dose of apixaban do you recommend?

1. Apixaban 5 mg BID
2. Apixaban 2.5 mg BID
3. How about we start anticoagulation tomorrow when it is no longer my shift?
U.S. FDA Labeling Guidelines for DOAC Dose Reduction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dose</th>
<th>Usual dose</th>
<th>AF VTE Treatment/Recurrent VTE Prevention</th>
<th>Orthopedic Surgery VTE Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>150 mg BID</td>
<td>150 mg BID</td>
<td>1 x 75 mg BID if CrCl 15-30 mL/min, none</td>
<td>1.75 mg BID None 75 mg BID None</td>
</tr>
<tr>
<td></td>
<td>15 mg once daily</td>
<td>15 mg once daily if CrCl 15-30 mL/min, none</td>
<td>15 mg BID None 75 mg BID None</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>20 mg once daily</td>
<td>15 mg once daily if CrCl 15-50 mL/min, none</td>
<td>20 mg once daily None 15 mg once daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 mg once daily</td>
<td>15 mg once daily if CrCl 15-50 mL/min, none</td>
<td>10 mg once daily None</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>5 mg BID</td>
<td>5 mg BID</td>
<td>1 x 2.5 mg BID if at least two of the following:</td>
<td>None 2.5 mg BID None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A. Age ≥ 80 years  B. Weight ≤ 60 kg  C. SCr ≥ 1.5</td>
<td>2.5 mg BID after first 6 months 2.5 mg BID if taking strong dual p-gp/CYP3A4 inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.5 mg BID if taking strong dual p-gp/CYP3A4 inhibitors</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>60 mg once daily</td>
<td>30 mg once daily if CrCl 15-50 mL/min, none</td>
<td>None 30 mg once daily</td>
<td></td>
</tr>
</tbody>
</table>

**DOAC Dose Reduction**

- A DOAC dose reduction contrary to FDA labeling was made in > 50% patients-apixaban had highest rate of discrepancy
- History of prior bleeding may have influenced reduction-25% had prior bleed
- Rate of TE was similar to no therapy (10% apix, 5% dabig, 3.6% rivaroxaban)
- Despite lower doses of DOAC there was a high rate of bleeding-20%, ? Due to concomitant antiplatelet therapy (80% on those with bleeds on antiplatelet)


**Evaluation of Dose-Reduced Direct Oral Anticoagulant Therapy**

**ORIGINAL INVESTIGATIONS**

**Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes**

Steinberg BA et al. JACC 2016;68:2597-2604
Patients with AFIB & isolated advanced age, low body weight, or renal dysfunction have higher risk of stroke/SE & major bleeding but show consistent benefits with 5 mg twice daily apixaban vs warfarin compared with patients without these characteristics.

DOAC Dose Reduction

78 year old man with HTN CHF CKD is found to be in AFIB. His creatinine is 1.6. He weighs 61 kgs. He has a remote history of GI bleeding. What dose of apixaban do you recommend?

1. Apixaban 5 mg BID
2. Apixaban 2.5 mg BID
3. How about we start anticoagulation tomorrow when it is no longer my shift?

Reducing the Hospital Burden of HIT

- Not uncommon
  - HIT occurs in 5% of those exposed to UFH
  - Risk reduced 10 fold with LMWH
- High morbidity and mortality
  - Thromboembolic complications 20-50%
  - Expensive
Avoid Heparin Protocol

- Systematic replacement of most IV and SQ UFH with SQ LMWH in prophylactic or therapeutic doses (remaining uses of UFH were for hemodialysis, intraoperative use for cardiovascular surgery, ACS)
- Replacement of heparinized saline in arterial and central venous lines with saline flushes
- Modification of order sets to exclude UFH options
- Removal of UFH stores from most nursing units.

“Reducing the Hospital Burden of HIT”

CLINICAL TRIALS AND OBSERVATIONS
Reducing the hospital burden of heparin-induced thrombocytopenia: impact of an avoid-heparin program

Kelly E. McGowan, JoY Makled, Arterias Diamentoudou, Claudia Bocci, Peter Hampel, Yisa Selby, and William Dworkin

Department of Medicine, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, Department of Medicine, University of Toronto, Toronto, ON, Canada, Department of Pharmacy, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, and Sunnybrook Health Sciences Centre, Department of Clinical Pathology, and Toronto Genetix Safety, University of Toronto, Toronto, ON, Canada.

Key Points
- Use of LMWH is associated with a lower risk of HIT and HIT compared with use of UFH.
- The Avoid-Heparin Initiative resulted in a dramatic reduction in the burden of hospital-based thrombosis.

Avoid Heparin Protocol

~40% reduction in suspected HIT
~80% reduction in HIT
~80% reduction in HIT related costs

Bleeding on DOAC

A 65 year old man with AFIB CHADS-Vasc=5 on rivaroxaban for stroke prevention presents with melena, BP 120/80, HR 99, HCT 30 (baseline 40), PT 18. INR 2.5. How do you manage his anticoagulation?

1. hold rivaroxaban and transfuse PRBCs & IV fluids as needed
2. hold rivaroxaban and administer PCC
3. hold rivaroxaban and transfuse FFP and vitamin K
4. Where is that protocol? I know we have one somewhere.
Bleeding on DOAC

- Is drug still present?
  - When was last dose of drug?
  - What is patient’s renal function?
  - Will laboratory data help?
- If present should drug be reversed?

Timing of Last Dose

<table>
<thead>
<tr>
<th>Property</th>
<th>Dabigatran&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Rivaroxaban&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Apixaban&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Edoxaban&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last 1/2 hrs</td>
<td>Crcl &gt; 90</td>
<td>CrCl 90-79</td>
<td>CrCl 30-50</td>
<td>CrCl 15-29</td>
</tr>
<tr>
<td>hrs</td>
<td>14</td>
<td>7-8</td>
<td>5-7</td>
<td>8-9</td>
</tr>
</tbody>
</table>

Renal clearance of absorbed dose:
- 80% for Dabigatran
- 33% for Rivaroxaban
- 27% for Apixaban
- 50% for Edoxaban

Approximate anticoagulation resolution:
- Day 2.5–3.5 after last dose for Dabigatran
- Day 1.5–2 after last dose for Rivaroxaban
- Day 1–2 after last dose for Apixaban
- Day 1.3–2 after last dose for Edoxaban

*Estimated as the time it takes for 5 half-lives to elapse since the last dose.

Interpreting Lab Tests on DOACS

- **Dabigatran**
  - High aPTT clinically significant drug levels
  - Normal PTT rules out supratherapeutic drug levels, does not rule out clinically significant residual AC effect
  - Normal aPTT rules out residual dabigatran
- **Rivaroxaban/apixaban/edoxaban**
  - Elevated PT clinically significant levels (rivaroxaban only)
  - Normal PT does not rule out clinically significant residual AC effect
  - In a pinch can use UFH or LMWH level. If negative it is a reasonable surrogate for excluding above trough drug levels

Managing DOAC Bleeding: EHRA 2015 Recommendations

**MILD BLEEDING**
- Delay/discontinue next dose
- Reconsider concomitant medication, especially antipl Denise

**MODERATE TO SEVERE BLEEDING**
- Mechanical compression
- Endoscopic hemostasis if GI bleed
- Surgical hemostasis
- Fluid replacement (colloids if needed)
- RBC substitution if needed
- FFP (as plasma expander)
- Platelet substitution if platelet count < 50 x 10<sup>9</sup>/L

**LIFE-THREATENING BLEEDING**
- Consider
  - PCC (eg, CoFact®) 50 U/kg, +25 U/kg if indicated
  - aPCC (Feiba®) 50 U/kg, max 200 U/kg/d
  - rFVIIa (NovoSeven®) 90 µg/kg (no data about additional benefit)
  - For dabigatran, administer idarucizumab 5 g IV

**Bleeding on DOAC**

A 65 year old man with AFIB CHADS-Vase=5 on rivaroxaban for stroke prevention presents with melena, BP 120/80, HR 99, HCT 30 (baseline 40), PT 18, INR 1.5. How do you manage his anticoagulation?

1. hold rivaroxaban and transfuse PRBCs & IV fluids as needed
2. hold rivaroxaban and administer PCC
3. hold rivaroxaban and transfuse FFP and vitamin K
4. I knew we should have had a protocol for this. Didn’t she mention at last years conference??

**DUAL Therapy with DOAC**

A 68 yo man with AFIB, DM, HTN on dabigatran, ASA and metoprolol presents with NSTEMI. Cardiac cath shows 90% occlusion in left circumflex, he has PCI with drug eluting stent. You are preparing him for discharge. What antithrombotic regimen should he be discharged on?

1. Triple therapy with dabigatran, clopidigrel and ASA
2. Dual therapy with dabigatran and clopidigrel
3. Dual therapy with clopidigrel and ASA-restart dabigatran after dropping one of the antiplatelet agents
4. Whatever cardiology tells me to do

**DUAL THERAPY WITH DOAC-PCI**

Dabigatran and PCI for ACS or CAD
110 mg dab + PGY12 inhibitor; 150 mg dab + PGY 12 inhibitor or triple therapy with warfarin ASA plus PGY 12 inhibitor
1. endpoint-major and CRNM bleeding
2. endpoint composite of TE death or revascularization
DUAL THERAPY WITH DOAC-PCI

Dual therapy with dabigatran and PGY12 inhibitor resulted in lower risk of bleeding with non inferior Rates of TE when compared to triple therapy.

A 68 yo man with AFIB, DM, HTN on dabigatran, ASA and metoprolol presents with NSTEMI. Cardiac cath shows 90% occlusion in left circumflex, he has PCI with drug eluting stent. You are preparing him for discharge. What antithrombotic regimen should be discharged on?

1) Triple therapy with dabigatran, Plavix and ASA
2) Dual therapy with dabigatran and Plavix
3) Dual therapy with Plavix and ASA-restart dabigatran after dropping one of the antiplatelet agents
4) Whatever cardiology tells me to do

Thrombophilia Testing

A 54 year old man presents with sudden onset chest pain and shortness of breath. D-dimer is elevated and CT chest shows bilateral PE. He has no past medical history and denies recent trauma, travel or surgery. Should he have a thrombophilia work up for this unprovoked VTE event?

- Yes
- No
- More coffee, please?
Clinical Characteristics Suggestive of Inherited Thrombophilia in Patients with Venous Thromboembolism (VTE).

Thrombosis at a young age (<50 yr), especially in association with weak provoking factors (minor surgery, combination oral contraceptives, or immobility) or unprovoked VTE

Strong family history of VTE (first-degree family members affected at a young age) Recurrent VTE events, especially at a young age

VTE in unusual sites such as splanchic or cerebral veins†

* The antiphospholipid syndrome must also be considered, but it is not inherited.
† Patients with splanchic-vein VTE should be assessed for myeloproliferative neoplasms and paroxysmal nocturnal hemoglobinuria.

Table 1. Clinical Characteristics Suggestive of Inherited Thrombophilia in Patients with Venous Thromboembolism (VTE).

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis at a young age (&lt;50 yr), especially in association with weak provoking factors (minor surgery, combination oral contraceptives, or immobility) or unprovoked VTE</td>
<td>High</td>
</tr>
<tr>
<td>Strong family history of VTE (first-degree family members affected at a young age)</td>
<td>High</td>
</tr>
<tr>
<td>Recurrent VTE events, especially at a young age</td>
<td>High</td>
</tr>
<tr>
<td>VTE in unusual sites such as splanchic or cerebral veins†</td>
<td>High</td>
</tr>
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Explanation:
- High: Clinical characteristics are common and should be considered in the evaluation of patients with VTE.
- Moderate: Clinical characteristics are less common but may still be relevant in certain cases.
- Low: Clinical characteristics are rare and are unlikely to be the primary cause of VTE.

Table 2. Summary of Recommendations Regarding Testing for Thrombophilia.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No clinical clues at the time of VTE event</td>
<td>Consider testing for factor V Leiden and prothrombin gene mutation.</td>
</tr>
<tr>
<td>Recent or remote symptom duration of less than 7 days</td>
<td>Consider testing for factor V Leiden and prothrombin gene mutation.</td>
</tr>
<tr>
<td>Recent or remote symptom duration of more than 7 days</td>
<td>Consider testing for factor V Leiden and prothrombin gene mutation.</td>
</tr>
<tr>
<td>No personal history of VTE</td>
<td>Consider testing for factor V Leiden and prothrombin gene mutation.</td>
</tr>
<tr>
<td>No personal history of VTE and no personal history of antiphospholipid syndrome</td>
<td>Consider testing for factor V Leiden and prothrombin gene mutation.</td>
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Conclusion:
- Consider testing for factor V Leiden and prothrombin gene mutation in patients with VTE and no personal history of VTE or antiphospholipid syndrome.
Thrombophilia Testing

A 54 year old man presents with sudden onset chest pain and shortness of breath. D-dimer is elevated and CT chest shows bilateral PE. He has no past medical history and denies recent trauma, travel or surgery. Should he have a thrombophilia work up for this unprovoked VTE event?

- Yes
- No
- More coffee, please?

Take Home Points

- After GIB on AC-reconsider risk benefit of therapy; multidisciplinary approach to determining when to restart AC after bleeding event
- Caution using DOACs in morbidly obese pending additional data
- Adhering to FDA labeling for DOACs may provide better outcomes in AFIB patients
- Consider renal function and timing of last dose to determine residual anticoagulant effect in patient bleeding on DOAC. No evidence-based reversal agents with exception of idarucizumab for dabigatran
- Have institutional protocol for reversal of all anticoagulants
- Avoid thrombophilia work up in hospitalized patients

WORKSHOP

- IVC filters
- Incidental PE
- Does this patient need to be bridged?
- Thrombophilia work up
- Management of patient with recurrent VTE despite therapeutic anticoagulation
- Calf vein thrombosis, superficial vein thrombosis, PICC line thrombosis and more

THE END