DVT Prophylaxis: 2020 Update
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Conflicts of Interest Disclosure

- No relevant conflicts of interest to disclose related to this program and presentation
- Specifically:
  - No commercial support or sponsorship
  - No discussion of off-label usage of drugs or devices/equipment
  - Book chapter contents are not specifically related to this presentation
  - No royalties accepted
Goals

- Increase awareness of the 10 AAOS guidelines related to VTE prophylaxis in patients undergoing elective hip/knee arthroplasty
- Enhance understanding of new anticoagulation therapies
Learning Objectives

- Review the 10 AAOS guidelines related to VTE prophylaxis in patient undergoing elective hip/knee arthroplasty
- Review site of action of the currently available anticoagulant Rxs
- Name the anticoagulant Rxs that have reversal agents
AAOS Recommendations
Prevention of VTE in Patients Undergoing Elective Hip/Knee Arthroplasty

- 850-page document
- Highlight 10 recommendations from AAOS and strength of the recommendation
AAOS Recommendation 1: Screening for Post-Op DVT (Strong)

- Do not order routine post-op duplex U/S to screen for DVT
- Do not order routine screening venogram
- Do not order routine D-dimer to screen for VTE
AAOS Recommendation 2: Screening for VTE Risks (Limited)

- Consider asking about prior history of VTE (DVT/PE)
- Other than personal h/o VTE – the importance of other risk factors is not clear
- Cited studies
  - Pederson (n = 68K); RR = 8.1
  - Warwick (n = 1,520 [6695 THR and 8325 TKR]); HR = 4.92


AAOS Recommendation 3
Screening for Bleeding Risks (Consensus)

- Ask about bleeding disorders (e.g. hemophilia) and active liver disease which may predispose the patient to increased risk of bleeding.
  - Low cost
  - Minimal risk to the patient
  - Current standard of practice of most orthopaedists
AAOS Recommendation 4: Stoppage of Antiplatelet Rx (Moderate)

- Discontinue antiplatelet agents (e.g. ASA and Clopidogrel) before elective hip/knee arthroplasty
- ASA – trials range from stopping 1-2 weeks before elective surgery
- Clopidogrel – trials range from stopping 3-5 days before elective surgery
AAOS Recommendation 5: VTE Prophylaxis Standard Risk (Moderate)

- Use pharmacologic and/or mechanical devices for VTE prophylaxis in patients who are at standard risk (i.e., risk incurred from the surgery itself) for VTE or bleeding
AAOS Recommendation 6: VTE Prophylaxis – High Risk (Consensus)

Use pharmacologic AND mechanical compressive devices for VTE prophylaxis in patients who have a h/o prior VTE
AAOS Recommendation 7
VTE Prophylaxis – High Bleeding Risk (Consensus)

Use mechanical compressive devices for VTE prophylaxis in patients who have a bleeding disorder (e.g., hemophilia) and/or active liver disease
AAOS Recommendation 8: Mobilization for VTE Prophylaxis (Consensus)

- Early mobilization after hip/knee arthroplasty
  - Low cost
  - Beneficial
  - Standard of current practice
AAOS Recommendation 9: Anesthesia Type (Consensus)

- Neuraxial anesthesia – to prevent blood loss (no effect of VTE risks)
AAOS Recommendation 10
IVC Filters (Inconclusive)

- No recommendation for OR against IVC filters for:
  - Patients with contraindication to chemoprophylaxis
  - Residual VTE
IVC Filters
Two Types– Permanent and Retrievable

Table 1
Classic, extended, and prophylactic indications for IVC filter placement

<table>
<thead>
<tr>
<th>Patients with documented VTE and classic indications</th>
<th>Patients with documented VTE and expanded indications</th>
<th>Patients without VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraindication to anticoagulation</td>
<td>Iliocaval or large free-floating proximal DVT</td>
<td>Trauma patient with high risk of VTE</td>
</tr>
<tr>
<td>Complication of anticoagulation necessitating cessation</td>
<td>Inability to achieve/maintain adequate anticoagulation</td>
<td>Surgical procedure in a patient at high risk for VTE</td>
</tr>
<tr>
<td>Failure of anticoagulation</td>
<td>Massive PE with residual DVT in a patient at risk for further PE</td>
<td>Medical condition with high risk of VTE</td>
</tr>
<tr>
<td>Propagation/progression of DVT during therapeutic anticoagulation</td>
<td>Chronic venous thromboembolism treated with thromboendarterectomy</td>
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<tr>
<td></td>
<td>Thrombolysis of iliocaval DVT</td>
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<td></td>
<td>VTE with limited cardiopulmonary reserve</td>
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<tr>
<td></td>
<td>Recurrent PE with IVC filter in place (filter failure)</td>
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<td>Poor compliance with anticoagulation</td>
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<tr>
<td></td>
<td>High risk of complication of anticoagulation (e.g., high fall risk)</td>
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</tbody>
</table>

Abbreviations: DVT, deep venous thrombosis; IVC, inferior vena cava; PE, pulmonary embolism; VTE, venous thromboembolism.

Four Major Classes of Anticoagulant Therapies

- VKA
- Heparins (unfractionated and LMWH)
- Direct Thrombin Inhibitors*
- Factor Xa Inhibitors*

*Often referred to as Novel Oral Anticoagulants or Non-Vitamin K Oral Anticoagulants (NOACs) or Direct Oral Anticoagulants (DOACs)
Four Major Classes of Anticoagulant Rxs

- **Direct Thrombin Inhibitors** (Lepirudin, Desirudin, Bivalarudin, Argatroban, Dabigatran)
- **Factor Xa Inhibitors** (Fondaparinux, Rivaroxaban, Apixaban, Edoxaban, Betrixaban)
- **Vitamin K Antagonists**
- **Heparins** (UFH, LMWH: Enoxaparin, Dalteparin, Tinzaparin)
- **Direct Thrombin Inhibitors** (Lepirudin, Desirudin, Bivalarudin, Argatroban, Dabigatran)

Major classes of anticoagulants include warfarin, heparin, Direct thrombin inhibitors, and factors Xa inhibitors. This figure illustrates the sites within the coagulation cascade at which these major classes of anticoagulant exerts its effects.
VTE Prophylaxis
(slide presented at ATS in 2019)

- Commonly used (proven benefit) with hip fractures\(^1\):
  - Heparin
  - LMWH
  - Fondaparinux (Arixtra)
  - Warfarin

- If there is any particular agent you do not want used on your patient – communicate this to the medicine consultant

- IVC Filter use – should be RARE

What about the NOACs/DOACs?

Dabigitran

- RE-NOVATE I (n = 3494) – v. Enoxaparin in THA
- RE-NOVATE II (n = 2055) – v. Enoxaparin in THA
- RE-MODEL (n= 2615) – v. Enoxaparin in TKA

(All 3 trials demonstrated Dabigitran was “non-inferior” for composite of total VTE, major VTE, and all-cause mortality)

- RE-MOBILIZE (n = 2076) – v. Enoxaparin in TKA

(DID NOT demonstrate non-inferiority for Dabigitran in total VTE and death in TKA patients)

What about the NOACs/DOACs?

Rivaroxaban

- RECORD 1 (4541) – v. Enoxaparin in THA
- RECORD 2 (n = 2509) – v. Enoxaparin in THA
- RECORD 3 (n= 2531) – v. Enoxaparin in TKA
- RECORD 4 (n= 3148) – v. Enoxaparin in TKA

(all 4 trials demonstrated Rivaroxaban had superior efficacy for primary outcomes of composite DVT, nonfatal PE, and all-cause mortality)

What about the NOACs/DOACs?

Apixaban

- ADVANCE 1 (n = 3195) – v. Enoxaparin in TKA
  (Similar efficacy with ; non-inferiority criteria not met because of low number of events)
- ADVANCE 2 (n = 3057) – v. Enoxaparin in TKA
- ADVANCE 3 (n= 3866) – v. Enoxaparin in THA
  (Significant reduction in total VTE and all-cause mortality; no difference in major and clinically relevant nonmajor bleeding)

# Pharmacokinetics of DOACs

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>DOACs</th>
<th>FDA-Approved Indications</th>
<th>t ½ (hours)</th>
<th>Renal Elimination</th>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTI</td>
<td>Dabigatran (Pradaxa)</td>
<td>• VTE treatment; • CVA prophylaxis non-v A Fib</td>
<td>14-17 h</td>
<td>80%</td>
<td>• Renal impairment, recurrent GI bleed</td>
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<td></td>
<td>• P-gp interactions</td>
</tr>
<tr>
<td>Factor Xa Inhibitor</td>
<td>Apixaban (Eliquis)</td>
<td>• VTE treatment; • CVA prophylaxis non-v A Fib</td>
<td>9-12 h</td>
<td>25%</td>
<td>• Caution if Cr Cl &lt; 30 ml/min</td>
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<td></td>
<td>• CYP3A4 interactions</td>
</tr>
<tr>
<td>Factor Xa Inhibitor</td>
<td>Rivaroxaban (Xarelto)</td>
<td>• VTE treatment; • CVA prophylaxis non-v A Fib</td>
<td>5-13 h</td>
<td>30%</td>
<td>• CYP3A4 interactions</td>
</tr>
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<td></td>
<td>• P-gp interactions</td>
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<tr>
<td>Factor Xa Inhibitor</td>
<td>Edoxaban (Savaysa)</td>
<td>• VTE treatment; • CVA prophylaxis non-v A Fib</td>
<td>10-14 h</td>
<td>50%</td>
<td>• P-gp interactions</td>
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</tr>
<tr>
<td>Factor Xa Inhibitor</td>
<td>Betrixaban (Bevyxxa)</td>
<td>• VTE prophylaxis in patients with acute medical illness</td>
<td>20-26 h</td>
<td>&lt; 20%</td>
<td>• CI if hepatic impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• P-gp interactions</td>
</tr>
</tbody>
</table>
# Specific Reversal Agents for NOACs/DOACs

<table>
<thead>
<tr>
<th>Antidote</th>
<th>Brand Name</th>
<th>Mechanism of Action</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idarucizumab</td>
<td>Praxbind®</td>
<td>Monoclonal Ab fragment that binds Dabigatran</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>Andexanet Alfa</td>
<td>AndexXa®</td>
<td>Modified decoy form of FXa that binds FXa inhibitors and ATIII</td>
<td>Rivaroxaban, Apixaban, Edoxaban, LMWH</td>
</tr>
<tr>
<td>Ciraparantag or Aripazine</td>
<td>N/A</td>
<td>Small molecule that binds Heparin, DTI, and FXa inhibitors</td>
<td>Dabigatran, Rivaroxaban, Apixaban, Edoxaban, Heparin</td>
</tr>
<tr>
<td>FXa\textsuperscript{116L}</td>
<td>N/A</td>
<td>Recombinant mutant form of activated coagulation FXa that becomes active when FVa</td>
<td>Dabigatran, Rivaroxaban, Apixaban, Edoxaban</td>
</tr>
</tbody>
</table>

Summary

- Reviewed the 10 AAOS guidelines related to VTE prophylaxis in patient undergoing elective hip/knee arthroplasty
- Many reasonable options exist for VTE, including NOACs/DOACs
- Reviewed site of action of the currently available anticoagulant Rx
- Currently available reversal agents for Dabigatran, Rivaroxaban, Apixaban, and Edoxaban
Questions?

“Chance favors the prepared mind.”
-Louis Pasteur

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