Update on Regional Anesthesia in Patients on Anticoagulation

Sandra L. Kopp MD
Associate Professor of Anesthesiology
Mayo Clinic, Rochester MN
I have nothing to disclose.

In accordance with ACCP guidelines, for each of the antithrombotic agents, it is recommended that clinicians follow the FDA-approved dosing guidelines.
Goals and Objectives

1. Assess the bleeding risk factors for patients undergoing neuraxial anesthesia

2. Review the pharmacology and physiology of direct acting oral anticoagulants

3. Highlight the new ASRA 4th practice advisory guidelines for these medications
Monday Morning: 1st Case

- 78 yo female for THA
- PMH
  - Atrial fibrillation
  - Chronic kidney disease
    - CrCl 40 ml/min
  - Severe COPD
- Medications
  - Aspirin 81 mg QD
  - Dabigatran 150 mg PO BID (last dose Friday)
  - Atenolol 50 mg po BID
  - Inhalers, herbals, vitamins
Monday Morning: 1st Case

- Standard of care in my hospital
  - Posterior lumbar plexus block (psoas)
  - Spinal vs General

- What will you do??
  - Order lab work?
  - Cancel the case?
  - Proceed with posterior lumbar plexus block?
  - Proceed with spinal?
Bleeding Risk Factors

- Increased age
- Female gender
- Spinal canal pathology
- Renal and/or hepatic disfunction
- Regional technique
  - Spinal < epidural; single inj < catheter, lumbar < thoracic < cervical
  - Traumatic puncture
- Intensity of anticoagulant effect
  - Concomitant aspirin therapy
  - Length of therapy

Moen et al. Anesthesiology 2004
Neurologic Complications after Central Neuraxial Blockade in Sweden

- Retrospective review
  - 1,260,000 spinals
  - 450,000 epidurals (200,000 OB)
    - Permanent nerve damage in 85
    - 14 had preexisting spinal stenosis
      - 1 was diagnosed preop
    - Incidence of cauda equina & spinal hematoma increased with age

Preexisting spinal canal pathology may be a “neglected risk factor”
Regional Anesthetic Management of the Patient on Warfarin

Chronic preoperative anticoagulation

Adequate levels of II, VII, IX, and X may not be present until INR is normal

Stop warfarin 4-5 days before procedure

INR must be normalized

*Differs from INR ≤ 1.4 by ESA
Regional Anesthetic Management of the Patient on Warfarin

- In general, patients receiving 2.5mg-5mg warfarin will not have significant hemostatic alterations for 48 hrs after initiation of therapy.
- In patients receiving an initial dose of warfarin before surgery, we suggest that the INR should be checked 24 hrs after the preoperative dose.
- In patients receiving low-dose warfarin therapy during epidural analgesia, we suggest that the INR be monitored on a daily basis.

*ESA does not recommend warfarin in combination with neuraxial catheters*
Catheter Management on Warfarin

- Epidural may be maintained with an INR < 1.5 during initiation of therapy
  - Clotting factor activity > 40%
- INR > 1.5 and < 3
  - Catheters may be maintained with caution based on INR and duration of therapy
    - 48 hr levels of VII and IX will be depressed

<table>
<thead>
<tr>
<th>Factor</th>
<th>Half-Life, hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VII</td>
<td>6–8</td>
</tr>
<tr>
<td>Factor IX</td>
<td>24</td>
</tr>
<tr>
<td>Factor X</td>
<td>25–60</td>
</tr>
<tr>
<td>Factor II</td>
<td>50–80</td>
</tr>
</tbody>
</table>
Plexus & Peripheral Blockade

- 670 continuous lumbar plexus blocks
  - On warfarin, catheter removed on POD 2
    - 36% with INR > 1.5
    - Local bleeding in 1 patient (INR 3.0)

- Case reports of bleeding
  - All neurodeficits resolved within 6-12 months
    - Expandable peripheral site may be protective
    - Blood loss may be the most serious complication

- Treat deep blocks similarly to neuraxial blocks (1C)

Horlocker et al. RAPM 2010
Unfractionated Heparin

- Subcutaneous heparin
  - 5000 U twice or three times daily, there is no contraindication
  - Place needle/catheter a minimum of 4 hrs (ideally 6 hrs) after SQ dose
  - Post procedure dose may be administered immediately after needle/cath insertion or removal
  - Consider a platelet count in patients treated for more than 4 days

Horlocker et al. RAPM 2010
National Partnership for Maternal Safety: Consensus Bundle on Venous Thromboembolism

Mary E. D’Alton, MD, Alexander M. Friedman, MD, Richard M. Smiley, MD, PhD, Douglas M. Montgomery, MD, Michael J. Paidas, MD, Robyn D’Oria, MA, RNC, APN, Jennifer L. Frost, MD, MPH, Afshan B. Hameed, MD, Deborah Karsnitz, CNM, DNP, Barbara S. Levy, MD, and Steven L. Clark, MD

Obstetric venous thromboembolism is a leading cause of severe maternal morbidity and mortality. Maternal death from thromboembolism is amenable to prevention, and thromboprophylaxis is the most readily implementable means of systematically reducing the maternal death rate. Observational data support the benefit of risk-factor-based prophylaxis in reducing obstetric thromboembolism. This bundle, developed by a multidisciplinary working group and published by the National Partnership for Maternal Safety under the guidance of the Council on Patient Safety in Women’s Health Care, supports routine thromboembolism risk assessment for obstetric patients, with appropriate use of pharmacologic and mechanical thromboprophylaxis. Safety bundles outline critical clinical practices that should be implemented in every maternity unit. The safety bundle is organized into four domains: Readiness, Recognition, Response, and Reporting and Systems Learning. Although the bundle components may be adapted to meet the resources available in individual facilities, standardization within an institution is strongly encouraged. (Anesth Analg 2016;123:942–9)
VTE in Pregnancy

- High resource countries
  - 14.9% of maternal deaths related to VTE
  - Thromboprophylaxis

- NPMS
  - Patient safety bundle
    - Evidence-based recommendations for practice
    - NOT a new guideline
    - Selection of existing guidelines

*Khan et al. Lancet 2006*
The NPMS working group recommends thromboprophylaxis with daily LMW heparin or twice-daily unfractionated heparin for all antepartum patients hospitalized for at least 72 hours who are not at high risk for bleeding or imminent childbirth.

Multidisciplinary group worked for months to develop plan for neuraxial anesthesia

- Place needle/catheter a minimum of 4 hrs (ideally 6 hrs) after SQ dose
Preoperative LMWH Dosing

- **Prophylactic (low dose)**
  - Needle placement 10-12 hours after last dose

- **Therapeutic (high dose)**
  - Needle placement 24 hours after last dose
Postoperative LMWH

- TWICE daily dosing
  - Initiate no earlier than 12 hours postop
  - Indwelling catheter should be removed before first dose
  - First dose 4 hours after catheter removal

Antiplatelet or oral anticoagulants in addition to LMWH increases risk of hematoma
Postoperative LMWH

- **ONCE daily dosing**
  - *Initiate 12 hours after needle/catheter placement*
    - 2nd dose 24 hours later
  - *Indwelling catheter should be removed 12 hrs after the last dose*
  - *Administration of LMWH should be delayed 4 hrs after catheter removal*

Ensure there are no other hemostasis altering medications
Thrombin Inhibitors (Desirudin, Lepirudin, Bivalirudin, and Argatroban)

- No change to current recommendations
  - In patients receiving thrombin inhibitors, we recommend against the performance of neuraxial techniques

*ESA recommends a delay of 8-10 hrs (or longer) between administration and needle/catheter placement and 2-4 h between catheter removal and subsequent dosing
Fondaparinux

- **Preoperative**
  - Prophylaxis (2.5 mg dose)
    - Delay needle/catheter placement for 36-42 hrs
  - Treatment (5.0mg)
    - Avoid neuraxial technique due to extreme required delay

- **Postoperative (No change in recommendations)**
  - Until further clinical experience is available, performance of neuraxial techniques should occur under conditions used in clinical trials (single-needle pass, atraumatic needle placement, avoidance of indwelling neuraxial catheters)

*ESA allows maintenance of catheters with 6-12 h admin post catheter removal*
Antiplatelet Medications

- Time interval between discontinuation and neuraxial blockade is:
  - Ticlopidine 10 days
  - Clopidogrel 5-7 days
    - If a neuraxial block is indicated between 5 and 7 days of discontinuation normalization of platelet function should be documented
  - Prasugrel 7 days (ideally 10 days)
  - Ticagrelor 5 days
New Oral Anticoagulants

APIXABAN
EDOXABAN
DABIGATRAN
RIVAROXABAN
Blood coagulation *in vivo*

**Primary hemostasis**
- platelets
  - TF (tissue factor)
  - TF-VIIa
  - Xa
  - X
  - fibrinogen → fibrin
  - stabilised, cross-linked fibrin clot

**Secondary hemostasis**
- activated platelets
  - VII
  - IX
  - (αTHR) IXa
  - (αTHR) Xa
  - X
  - (APC) Va
  - (APC) VIIIa
  - VIII
  - (αTHR) XIa
  - XI
  - (αTHR) THROMBIN
Mechanism of Action of Direct Thrombin Inhibitors as Compared with Heparin

Mechanism of Action of Direct Thrombin Inhibitors as Compared with Heparin

Efficacy of DOAC compared to warfarin in Non-Valvular A-fib

- Meta-analysis 71,683 patients in 4 studies
  - Higher-dose DOACs associated with reductions
    - All stroke (19%, p<0.0001)
    - Ischemic stroke (8%, p=0.10)
    - Intracranial hemorrhage (52%, p<0.0001)
    - All-cause mortality (10%, p<0.001)
  - Increase in major GI bleeding (25%, p=0.04)

*Ruff CT. et al. Lancet March 2014*
Recommendations from our Cardiology Colleagues

- **Canadian Cardiovascular Society**
  - “…we suggest…that…most patients should receive dabigatran, rivaroxaban, or apixaban in preference to warfarin…”

- **European Society of Cardiology**
  - “One of the new OACs, either a DTI or fXa inhibitor should be considered rather than dose-adjusted VKA…for most patients (IIaA)”

- **AHA**
  - “Warfarin, dabigatran, apixaban, and rivaroxaban are…indicated for the prevention of …stroke in…non-valvular a-fib.”

Skanes AC et al. Can J Cardiol 2012  
Camm AJ et al. Eur Heart J 2012  
Furie KL et al. Stroke 2012
DOACs vs Warfarin: Caveats

- Advantages disappear with very good INR control
- Trial experience not the same as real world
- Short half-life—avoid missing doses
- Can’t assess patient adherence with test
- No antidote—reversibility may be difficult
- Not studied on certain populations
- Cost: warfarin $50/yr, DOACs $1200/yr

Ansell J. Circ 2012
# Pharmacokinetic Properties of New Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td>150 mg BID**</td>
<td>10 mg/day</td>
<td>2.5 mg BID</td>
<td>60 mg QD</td>
</tr>
<tr>
<td><strong>Onset of action</strong></td>
<td>1.5-3 hrs</td>
<td>2-4 hrs</td>
<td>3 hrs</td>
<td>1-3 hrs</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>14-17 hrs</td>
<td>5-9 hrs</td>
<td>8-15 hrs</td>
<td>10-14 hrs</td>
</tr>
<tr>
<td><strong>Elderly</strong></td>
<td>11-13 hrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>80% renal</td>
<td>66% renal</td>
<td>25% renal</td>
<td>50% renal</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>20% fecal</td>
<td>33% fecal</td>
<td>75% biliary/fecal</td>
<td>50% biliary</td>
</tr>
<tr>
<td><strong>Detection of effect</strong></td>
<td>TT, ECT</td>
<td>Anti-Xa assay</td>
<td>Anti-Xa assay</td>
<td>Anti-Xa assay</td>
</tr>
<tr>
<td><strong>Dialyzable</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Limited clinical experience</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Surgical Procedures at High Risk for Bleeding

- Open Heart Surgery
- Abdominal/Vascular Surgery
  - Neurosurgery
- Major Cancer Surgery
- Urologic Procedures

Problem: Many procedures with *low-moderate* bleeding risk use *neuraxial anesthesia*!
New Oral Anticoagulants

<table>
<thead>
<tr>
<th>Drug</th>
<th>T1/2</th>
<th>Renal Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>DABIGATRAN</td>
<td>12-17</td>
<td>80%</td>
</tr>
<tr>
<td>RIVAROXABAN</td>
<td>11-13</td>
<td>60%</td>
</tr>
<tr>
<td>APIXABAN</td>
<td>10-15</td>
<td>33%</td>
</tr>
<tr>
<td>EDOXABAN</td>
<td>10-14</td>
<td>55%</td>
</tr>
</tbody>
</table>

- Needle/catheter placement: discontinue 5 half lives prior (treatment/a-fib dose)
- Catheter removal: delay for 2 half lives (prophylactic dose)
- First dose after catheter removal: 8 hours minus time to maximum anticoagulant effect

ASRA 4th Practice Advisory
ASRA Spring Meeting, April 2014
Dabigatran (Pradaxa)

- Discontinue at least 5 days prior
- Consider checking TT or ECT if < 5 days
  - Result must be “no activity” to assure safe performance
- Remove deep peripheral/plexus or neuraxial catheters 6 hrs prior to first postoperative dose
  - No indwelling catheters
- Unanticipated administration with indwelling catheter
  - Hold dabigatran for 34-36 hrs (2 drug half-lives in a renal insufficient patient) then remove catheter

ASRA 4th Practice Advisory
ASRA Spring Meeting, April 2014
Direct Xa Inhibitors

- Rivaroxaban (*Xarelto*)
  - Discontinue at least 3 days prior
  - Consider checking anti-Xa level if < 3 days
    - Result must be “no activity” to assure safe performance
  - Remove deep peripheral/plexus or neuraxial catheters 6 hrs *prior* to first (postoperative) dose
    - No indwelling catheters
  - Unanticipated administration with indwelling catheter- hold rivaroxaban for 22-26 hrs (2 drug half-lives in a renal insufficient patient) then remove

*ASRA 4th Practice Advisory
ASRA Spring Meeting, April 2014*
Direct Xa Inhibitors

- Apixaban (Eliquis)
  - Discontinue at least **3 days** prior
  - Consider checking anti-Xa level if < 3 days
    - Result must be “no activity” to assure safe performance
  - Remove deep peripheral/plexus or neuraxial catheters 6 hours *prior* to first (postoperative) dose
    - No indwelling catheters
  - Unanticipated administration with indwelling catheter- hold rivaroxaban for 20-28 hrs (2 drug half-lives in a renal insufficient patient) then remove
Direct Xa Inhibitors

- Edoxaban (Savaysa)
  - Discontinue at least 3 days prior
  - Consider checking anti-Xa level if < 3 days
    - Result must be “no activity” to assure safe performance
  - Remove deep peripheral/plexus or neuraxial catheters 6 hours prior to first (postoperative) dose
    - No indwelling catheters
  - Unanticipated administration with indwelling catheter - hold rivaroxaban for 26-30 hrs (2 drug half-lives in a renal insufficient patient) then remove
  - Not for use if CrCl > 95 ml/min

ASRA 4th Practice Advisory
ASRA Spring Meeting, April 2014
<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitive to deficiency of</th>
<th>Dabigatran</th>
<th>Rivaroxaban Apixaban Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin time (PT/INR)</td>
<td>I, II, V, VII, X</td>
<td>Too sensitive</td>
<td>May show some linearity with selective reagents.</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (APTT)</td>
<td>I, II, V, VIII, IX, X,XI, XII,</td>
<td>Somewhat sensitive, increases in non-linear fashion. May underestimate high levels</td>
<td>Prolongs dose dependently but is less sensitive than the PT</td>
</tr>
<tr>
<td>Thrombin time (TT)</td>
<td>I, (IIa)</td>
<td>Standard TT is oversensitive, dilute TT or HEMOCLOT appears suitable option</td>
<td>Insensitive</td>
</tr>
<tr>
<td>Chromogenic Anti-Xa assay</td>
<td>Xa</td>
<td>Insensitive</td>
<td>Standard assay is too sensitive. Modified anti-Xa appears suitable</td>
</tr>
<tr>
<td>Ecarin Clotting Time (ECT)</td>
<td>II (activated)</td>
<td>Sensitive. Appears to be a reasonable option</td>
<td>Insensitive</td>
</tr>
<tr>
<td>dRVVT assay (Russell Viper Venom Time)</td>
<td>I, II, V, X</td>
<td>Sensitive but requires more extensive evaluation</td>
<td>Sensitive but requires more extensive evaluation</td>
</tr>
</tbody>
</table>
### Specific Antidotes

<table>
<thead>
<tr>
<th></th>
<th><strong>Idraracixamab</strong>&lt;br&gt; <strong>Praxbind</strong></th>
<th><strong>Andexanet alpha</strong></th>
<th><strong>PER977</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td>Humanized Fab fragment</td>
<td>Human rXa variant</td>
<td>Synthetic small molecule</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>Dabigatran</td>
<td>fXa inhibitors</td>
<td>Universal</td>
</tr>
<tr>
<td><strong>Binding</strong></td>
<td>Non-competitive&lt;br&gt;High Affinity</td>
<td>Competitive</td>
<td>?</td>
</tr>
<tr>
<td><strong>Clinical studies</strong></td>
<td>Rapid complete reversal</td>
<td>Rapid, near complete reversal</td>
<td>?</td>
</tr>
</tbody>
</table>

*Lauw M et al. Can J Cardiol 2014*
FDA asked the company to “provide additional information primarily related to manufacturing.” In addition, the FDA also “asked for additional data to support inclusion” in the label of two additional anticoagulants, edoxaban and enoxaparin. The FDA also indicated to the company that “it needs to finalize its review of the clinical amendments to Portola’s post-marketing commitments that recently were submitted.”
Reversing Direct Xa Inhibitors

- Control of bleeding by surgery, compression, radiological procedures
- Oral activated charcoal
  - Must be given within few hours
  - Not ideal prior to surgery
- Prothrombin complex concentrate
  - May improve thrombin generation, risks
- FFP
  - Unlikely to overcome fXa or thrombin inhibition
Peripheral Nerve Blocks

- Serious hemorrhagic complications have been reported following plexus/peripheral blocks
  - Approx half had altered hemostasis
  - Cases of major bleeding were after psoas compartment or lumbar sympathetic block
  - In the presence of anticoagulants or antiplatelet agents
  - Neurologic compromise was not always reported

Horlocker et al. RAPM 2010
Femoral Catheters in Patients Taking Rivaroxaban

- 504 patients
  - Preoperative femoral catheter for TKA
    - Continued for 36-48 hours
  - Rivaroxaban 10 mg daily
    - Catheter removed 20 hours after first dose
  - Assessed for hematoma causing neurovascular compromise or ecchymosis formation
    - No neurovascular compromise

Idestrup C, et al. RAPM 2014
## Femoral Catheters in Patients Taking Rivaroxaban

<table>
<thead>
<tr>
<th>Variable</th>
<th>POD 1</th>
<th>POD 2</th>
<th>POD 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematoma with neurovascular compromise, n</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>0.0–0.8</td>
<td>0.0–0.8</td>
<td>0.0–0.8</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ecchymosis, n (size, cm)</td>
<td>7 (1 × 2 to 15 × 6)</td>
<td>56 (1 × 1 to 38 × 9)</td>
<td>61 (1 × 1 to 38 × 9)</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>1.4 (0.4–2.4)</td>
<td>11.1 (8.4–13.9)</td>
<td>12.1 (9.3–15.0)</td>
</tr>
<tr>
<td>Tenderness, n</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>0.0–0.8</td>
<td>0.6 (0–1.3)</td>
<td>0.4 (0–1.0)</td>
</tr>
<tr>
<td>Oozing at site, n</td>
<td>15</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>3.0 (1.5–4.5)</td>
<td>5.2 (3.2–7.1)</td>
<td>0.6 (0–1.3)</td>
</tr>
<tr>
<td>Decreased motor function, n</td>
<td>108</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>21.4 (17.9–25.0)</td>
<td>1.8 (0.6–3.0)</td>
<td>0.2 (0–0.6)</td>
</tr>
<tr>
<td>Decreased sensory function, n</td>
<td>290</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>57.5 (53.2–61.9)</td>
<td>2.2 (0.9–3.5)</td>
<td>0.4 (0–1.0)</td>
</tr>
</tbody>
</table>

Data presented as incidence number (n), percentage (%), and 95% CI (lower confidence limit to upper confidence limit).

*Idestrup C, et al. RAPM 2014*
Plexus/Peripheral Block Recommendations

- Paucity of information in form of case reports
- Difficult to make definitive recommendations
- Bleeding complications are *typically* less serious than neuraxial bleeding
  - Nerve palsy or hematoma
- Dependent on compressibility of the site and structures in the vicinity
**Recommended Time Intervals Before and After Neuraxial Block or Catheter Removal***

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time before puncture/catheter manipulation or removal</th>
<th>Time after puncture/catheter manipulation or removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>5 days</td>
<td>6 hours</td>
</tr>
<tr>
<td>Apixaban</td>
<td>3 days</td>
<td>6 hours</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>3 days</td>
<td>6 hours</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>7-10 days</td>
<td>6 hours</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>5-7 days</td>
<td>6 hours</td>
</tr>
</tbody>
</table>

*Developed at 4th ASRA Practice Advisory for Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy*
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  - Atrial fibrillation
  - Chronic kidney disease
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- What will you do??
  - Order lab work?
  - Cancel the case?
  - Proceed with posterior lumbar plexus block?
  - Proceed with spinal?
QUESTIONS?