Venous Thromboembolism Prophylaxis after Major Elective Orthopedic Surgery

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Objectives

• Summarize the evidence for using direct oral anticoagulant (DOAC)
• Summarize the evidence for using aspirin (ASA)
• Summarize the evidence for the hybrid strategy
Disclosures

Grants from Servier and Bayer for expanding the Thrombosis Clinic at St. Paul’s Hospital
Our Patient

John is a 65 year old man with HTN, T2DM and OSA who had an uncomplicated elective right knee arthroplasty yesterday. You saw him at the peri-op clinic last week and you are now reassessing him on the ortho ward. What is your recommendation on VTE prophylaxis?
John is a 65 year old man with HTN, T2DM and OSA who had an uncomplicated elective right knee arthroplasty yesterday. You saw him at the peri-op clinic last week and you are now reassessing him on the ortho ward. What is your recommendation on VTE prophylaxis?

A) Low molecular weight heparin prophylactic dose SC for 14 days
B) Rivaroxaban 10mg PO daily for 14 days
C) Apixaban 2.5mg PO BID for 14 days
D) Dabigatran 220mg PO daily (half dose the first day) for 14 days
E) ASA 81mg PO daily for 14 days
F) Rivaroxaban 10mg PO daily for 5 days and then ASA 81mg daily for 9 days
G) Let the surgeon decide
## Major Elective Orthopedic Surgery

<table>
<thead>
<tr>
<th></th>
<th>2009 - 2010</th>
<th>2014 - 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Hip Arthroplasty (THA)</strong></td>
<td>42713</td>
<td>51272</td>
</tr>
<tr>
<td><strong>Total Knee Arthroplasty (TKA)</strong></td>
<td>51066</td>
<td>61412</td>
</tr>
</tbody>
</table>

20% increase in 5 years

Canadian Joint Replacement Registry
Nonfatal, Symptomatic VTE after Major Orthopedic Surgery

ACCP Guideline 9th ED CHEST 2012
ACCP Guideline 8th ED (2008)

Recommends the routine use of one of the following anticoagulant after elective hip or knee replacement (all Grade 1A)

- Low molecular weight heparin (LMWH)
- Fondaparinux
- Vitamin K antagonist (VKA) with target INR 2-3

Recommends against the use of aspirin (Grade 1A)
Health Canada Approval of DOAC

- Rivaroxaban 10mg PO daily (2008)
- Apixaban 2.5mg PO BID (2011)
- Dabigatran 220mg PO daily with half dose the first day (2014)
ACCP Guideline 9th ED (2012)

Recommends use of one of the following for a minimum of 10 to 14 days rather than no prophylaxis (all Grade 1B)

- LMWH (preferred)
- Fondaparinux
- Rivaroxaban, Apixaban, Dabigatran
- Low dose unfractionated heparin
- VKA
- Aspirin
Evidence for Rivaroxaban

RECORD 1 (NEJM 2008)
• Rivaroxaban vs enoxaparin for 35 days after THA

RECORD 2 (LANCET 2008)
• Extended rivaroxaban vs short term enoxaparin after THA

RECORD 3 (NEJM 2008)
• Rivaroxaban vs enoxaparin for 14 days after TKA

RECORD 4 (LANCET 2009)
• Rivaroxaban vs enoxaparin (BID dose) for 14 days after TKA

Rivaroxaban was superior in all 4 studies
Evidence for Rivaroxaban

A

Cumulative event rate (%)

Time to event relative to surgery (days)

Enoxaparin

101 events

Rivaroxaban

50 events

Turpie et al. Blood Coagulation, Fibrinolysis and Cellular Haemostasis 2011
Evidence for Apixaban

ADVANCE 1 (NEJM 2009)
• Apixaban vs enoxaparin (BID) for 10-14 days after TKA

ADVANCE 2 (LANCET 2010)
• Apixaban vs enoxaparin (daily) for 10 -14 days after TKA

ADVANCE 3 (NEJM 2010)
• Apixaban vs enoxaparin (daily) for 35 days after THA

Pre-specified stat criteria for non-inferiority were not met
Apixaban was superior
Evidence of Dabigatran

RE-MODEL (JTH 2007)
• Dabigatran vs enoxaparin (daily) for 6-10 days after TKA

RE-NOVATE I (LANCET 2007)
• Dabigatran vs enoxaparin (daily) for 28-35 days after THA

RE-MOBILIZE (J Arthroplasty 2009)
• Dabigatran vs enoxaparin (BID) for 12-15 days after TKA

RE-NOVATE II (Thromb Haemost 2011)
• Dabigatran vs enoxaparin (daily) for 28-35 days after THA

Dabigatran was non-inferior

Failed to show non-inferiority

Dabigatran was non-inferior
What about Aspirin?
Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial

Pulmonary Embolism Prevention (PEP) Trial Collaborative Group*
## Table 2 Comparison of patients on aspirin in the arthroplasty studies with the number and rates of VTE

<table>
<thead>
<tr>
<th>Study author</th>
<th>Dose of aspirin</th>
<th>Length of treatment</th>
<th>Number of patients on aspirin</th>
<th>Number of patients who suffered from symptomatic DVT</th>
<th>Rate of symptomatic DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raphael et al, 2014&lt;sup&gt;15&lt;/sup&gt;</td>
<td>325 mg BD</td>
<td>Unknown</td>
<td>2,800</td>
<td>8</td>
<td>0.29%</td>
</tr>
<tr>
<td>Jiang et al, 2014&lt;sup&gt;16&lt;/sup&gt;</td>
<td>?</td>
<td>?</td>
<td>60</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>Zou et al, 2014&lt;sup&gt;17&lt;/sup&gt;</td>
<td>100 mg/d</td>
<td>14 d</td>
<td>110</td>
<td>2</td>
<td>1.81%</td>
</tr>
<tr>
<td>Na et al, 2015&lt;sup&gt;18&lt;/sup&gt;</td>
<td>100 mg/d</td>
<td>14 d</td>
<td>282</td>
<td>0</td>
<td>0.00%</td>
</tr>
<tr>
<td>Pow and Vale, 2015&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Unknown</td>
<td>Minimum 10–14 d</td>
<td>125</td>
<td>4</td>
<td>3.20%</td>
</tr>
<tr>
<td>Ogonda et al, 2016&lt;sup&gt;21&lt;/sup&gt;</td>
<td>150 mg OD</td>
<td>6 wk</td>
<td>11,459</td>
<td>37</td>
<td>0.32%</td>
</tr>
<tr>
<td>Yhim et al, 2017&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Unknown</td>
<td>On average for 9 d</td>
<td>28,176</td>
<td>232</td>
<td>0.82%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>—</td>
<td>—</td>
<td><strong>43,012</strong></td>
<td><strong>283</strong></td>
<td><strong>0.66%</strong></td>
</tr>
</tbody>
</table>

Abbreviations: BD, twice a day; DVT, deep vein thrombosis; OD, once daily; VTE, venous thromboembolism.
The Hybrid Strategy

Aspirin

Anticoagulant
Aspirin Versus Low-Molecular-Weight Heparin for Extended Venous Thromboembolism Prophylaxis After Total Hip Arthroplasty
A Randomized Trial

David R. Anderson, MD; Michael J. Dunbar, MD; Eric R. Bohm, MD; Etienne Belzile, MD; Susan R. Kahn, MD; David Zukor, MD; William Fisher, MD; Wade Gofton, MD; Peter Gross, MD; Stephane Pelet, MD; Mark Crowther, MD; Steven MacDonald, MD; Paul Kim, MD; Susan Pleasance, BScN; Nicki Davis, BSc; Pantelis Andreou, PhD; Philip Wells, MD; Michael Kovacs, MD; Marc A. Rodger, MD; Tim Ramsay, PhD; Marc Carrier, MD; and Pascal-Andre Vendittoli, MD
EPCAT I

Patients with THA and dalteparin 5000 units SC daily x 10 days

Randomization

Aspirin 81mg PO daily x 28 days

Dalteparin 5000 units SC daily x 28 days

90-days follow up for symptomatic VTE and bleeding events
Table 2. Primary Outcome Results*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LMWH Recipients (n = 398)</th>
<th>Aspirin Recipients (n = 380)</th>
<th>P Value</th>
<th>Difference (95% CI), percentage points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5 (1.3)</td>
<td>1 (0.3)</td>
<td>0.22†</td>
<td>1.0 (−0.5 to 2.5)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>3 (0.8)</td>
<td>0</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>2 (0.5)</td>
<td>1 (0.3)</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

DVT = deep venous thrombosis; LWMH = low-molecular-weight heparin.
* Values reported are numbers (percentages).
† Aspirin was noninferior (P < 0.001) but not superior to dalteparin.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>LMWH Recipients (n = 400)</th>
<th>Aspirin Recipients (n = 385)</th>
<th>P Value</th>
<th>Difference (95% CI), percentage points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding†</td>
<td>1 (0.3)</td>
<td>0</td>
<td>1.00</td>
<td>0.25 (−4.9 to 1.0)</td>
</tr>
<tr>
<td>Clinically significant nonmajor bleeding†</td>
<td>4 (1.0)</td>
<td>2 (0.5)</td>
<td>0.68</td>
<td>0.48 (−1.0 to 2.0)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>18 (4.5)</td>
<td>8 (2.1)</td>
<td>0.164</td>
<td>2.40 (−0.3 to 5.2)</td>
</tr>
<tr>
<td>Bleeding at operative site</td>
<td>5 (1.3)</td>
<td>4 (1.0)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2 (0.5)</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>3 (0.8)</td>
<td>2 (0.5)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hematuria</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>4 (1.0)</td>
<td>1 (0.3)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1 (0.3)</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Conjunctival</td>
<td>2 (0.5)</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Table 3. Bleeding Results*

Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty

Patients with THA or TKA and Rivaroxaban 10mg PO daily x 5 days

Randomization

Aspirin 81mg PO daily x 9 days for TKA or 30 days for THA
Dalteparin 5000 units SC daily x 9 days for TKA or 30 days for THA

90-days follow up for symptomatic VTE and bleeding events
### Table 2. Primary Effectiveness and Safety Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban (N=1717)</th>
<th>Aspirin (N=1707)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous thromboembolism</td>
<td>12 (0.70)</td>
<td>11 (0.64)</td>
<td>0.84*</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>6 (0.35)</td>
<td>5 (0.29)</td>
<td></td>
</tr>
<tr>
<td>Proximal deep-vein thrombosis</td>
<td>4 (0.23)</td>
<td>4 (0.23)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism and proximal deep-vein thrombosis</td>
<td>2 (0.12)</td>
<td>2 (0.12)</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>5 (0.29)</td>
<td>8 (0.47)</td>
<td>0.42</td>
</tr>
<tr>
<td>Any bleeding†</td>
<td>17 (0.99)</td>
<td>22 (1.29)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

* P<0.001 for noninferiority, as defined by the upper boundary of the 95% confidence interval for the absolute between-group difference.
† This category includes major bleeding and clinically relevant nonmajor bleeding.
Our Patient

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Take Home Message
Take Home Message

Prior DVT or PE?
Cost?
Cancer?
Thrombophilia?
Renal impairment?
Bad liver disease?
Obese?
Extensive bowel surgery?
Compliance with SC injection?
Drug interactions?
Context is everything!

Compliance with SC injection?

Extensive bowel surgery?

Drug interactions?

Cancer?

Obese?

Bad liver disease?

Renal impairment?

Prior DVT or PE?

Thrombophilia?

Cost?