Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty: The EPCAT II Trial

Wednesday, June 6, 2018, 2:00PM ET

**Guest Author:** David R. Anderson, MD

**Presenter:** Sara Vazquez, PharmD

**Moderators:** Tracy Minichiello, MD and Mike Streiff, MD
Presenters

David R. Anderson, MD, FRCPC, FACP
Faculty of Medicine Dean, Professor
Dalhousie University
Halifax, Nova Scotia, Canada

Sara Vazquez, PharmD
Clinical Pharmacist
University of Utah Health
Salt Lake City, UT

Michael Streiff, MD
Associate Professor of Medicine
Johns Hopkins University
Medical Director, AMS & Outpatient Clinics & Staff Physician
Johns Hopkins Comprehensive Hemophilia Treatment Center
Baltimore, MD

Tracy Minichiello, MD
Professor of Medicine
Chief Anticoagulation & Thrombosis Service
UCSF/San Francisco VA Medical Center
San Francisco, CA
Disclosures for Sara Vazquez

• None
Background

- Orthopedic surgery patients are at high risk for VTE

Background

• However...much has changed in orthopedic surgery since initial VTE incidence data was reported:
  • Advancements in surgical technique
  • Increased use of regional anesthesia
  • Earlier post-op ambulation
  • Improvements in PT/rehab strategies
  • Earlier hospital discharge
  • Advent of the DOACs as prophylaxis options

### Background

**RECORD 4 trial** (TKA)

<table>
<thead>
<tr>
<th>Study Regimens</th>
<th>N=3148</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban 10 mg po daily x 12 days</td>
<td>6.9%*</td>
</tr>
<tr>
<td>Enoxaparin 30 mg SC BID x 12 days</td>
<td>10.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Composite Efficacy: any DVT, nonfatal PE, death from any cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.9%*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptomatic VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.7%</td>
</tr>
</tbody>
</table>

Background

PEP trial (HFS)

N=13,356

Study Regimens

- ASA 160 mg daily x 35 days
- Placebo x 35 days

Symptomatic DVT or PE

- 1.6%
- 2.5%

Bleeding (systemic complications)

- 3.2%
- 2.3%

Background

**ACCP 2012**
- All grade 1B
  - LMWH (Grade 2C for preference over other agents)
  - Fondaparinux
  - DOAC (apixaban, rivaroxaban, dabigatran)
  - UFH
  - VKA
  - ASA

**AAOS 2011**
- No specific agents listed or given preference

EPCAT II Study Design

Rivaroxaban 10 mg po daily
Started at least 6 hours after wound closure on POD 0 or on POD 1

Addition of mechanical compression therapy to either regimen was optional

Rivaroxaban 10 mg po daily
9 more days for TKA
30 more days for THA

ASA 81 mg po daily
9 more days for TKA
30 more days for THA

90-day outcomes

Design, Setting, and Sponsorship

• Design
  • Randomized, double-blind trial

• Setting
  • 15 university-affiliated health centers in Canada

• Sponsorship
  • Canadian Institutes of Health Research

Inclusion/Exclusion Criteria

Inclusion Criteria
• Patients undergoing elective unilateral primary or revision TKA or THA

Exclusion Criteria
• Hip or lower limb fracture in the previous 3 months
• Metastatic cancer

Permitted continuance of long-term ASA at a dose of < 100 mg/d in addition to the assigned study regimen
Discouraged but did not prohibit use of NSAIDs

Outcomes

**Efficacy**
- Symptomatic VTE (proximal DVT or PE)
- Death, MI, Stroke, Wound infection

**Safety**
- Major Bleeding or CRNMB

Statistical Analysis

• Non-inferiority (for primary efficacy outcome)-criteria not specified
• Estimated rate of VTE in rivaroxaban group 1.0%
• Sample size needed to provide 90% power to demonstrate non-inferiority of ASA to rivaroxaban: 1696 patients per group
• Intention-to-treat analysis

Table 1. Characteristics of the Patients at Baseline, According to Surgical Subgroup.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Hip Arthroplasty</th>
<th>Total Knee Arthroplasty</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rivaroxaban (N = 902)</td>
<td>Aspirin (N = 902)</td>
<td>Rivaroxaban (N = 1,017)</td>
</tr>
<tr>
<td>Age — yr</td>
<td>60.9±11.0</td>
<td>61.3±11.1</td>
<td>64.7±8.4</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>480 (53.2)</td>
<td>486 (53.9)</td>
<td>353 (43.3)</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>29.4±5.8</td>
<td>29.4±6.0</td>
<td>32.7±6.8</td>
</tr>
<tr>
<td>Risk factors — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous venous thromboembolism</td>
<td>22 (2.4)</td>
<td>20 (2.2)</td>
<td>22 (2.7)</td>
</tr>
<tr>
<td>Previous surgery</td>
<td>28 (3.1)</td>
<td>30 (3.3)</td>
<td>18 (2.2)</td>
</tr>
<tr>
<td>Cancer</td>
<td>19 (2.1)</td>
<td>17 (1.9)</td>
<td>19 (2.3)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>86 (9.5)</td>
<td>83 (9.2)</td>
<td>71 (8.7)</td>
</tr>
<tr>
<td>Hemoglobin — g/liter</td>
<td>140±4±12.5</td>
<td>140±2±13.0</td>
<td>138±2±12.8</td>
</tr>
<tr>
<td>Mean platelet count per mm³</td>
<td>241±200</td>
<td>238±700</td>
<td>240±700</td>
</tr>
<tr>
<td>Type of Surgery — no. (%)</td>
<td>802 (89.9)</td>
<td>809 (90.7)</td>
<td>770 (94.5)</td>
</tr>
<tr>
<td>Revision</td>
<td>64 (7.1)</td>
<td>52 (5.8)</td>
<td>44 (5.4)</td>
</tr>
<tr>
<td>Resurfacing</td>
<td>35 (3.9)</td>
<td>41 (4.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.1)</td>
<td>0 (0.1)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Use of tranexamic acid — no./total no. (%)</td>
<td>478/808</td>
<td>470/901</td>
<td>465/812</td>
</tr>
<tr>
<td>Postoperative-mechanical compression — no./total no. (%)</td>
<td>93/155</td>
<td>60.0 (60.0)</td>
<td>94/162 (58.0)</td>
</tr>
<tr>
<td>Pneumatic compression</td>
<td>93/155 (60.0)</td>
<td>60/62 (58.0)</td>
<td>50/129 (42.0)</td>
</tr>
<tr>
<td>Graduated stockings</td>
<td>45/155 (29.0)</td>
<td>50/162 (32.2)</td>
<td>62/129 (51.2)</td>
</tr>
<tr>
<td>Both</td>
<td>17/155 (11.0)</td>
<td>15/162 (9.3)</td>
<td>7/119 (5.9)</td>
</tr>
<tr>
<td>Anesthetic — no. (%)</td>
<td>263 (29.2)</td>
<td>288 (31.9)</td>
<td>214 (26.3)</td>
</tr>
<tr>
<td>Regional</td>
<td>628 (69.6)</td>
<td>605 (67.1)</td>
<td>597 (73.3)</td>
</tr>
<tr>
<td>Both</td>
<td>11 (1.2)</td>
<td>9 (1.0)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Time in operating room — hr</td>
<td>1±0±0.6</td>
<td>1±0±0.6</td>
<td>1±0±0.5</td>
</tr>
<tr>
<td>Estimated blood loss — ml</td>
<td>3±0±270</td>
<td>374±295</td>
<td>227±174</td>
</tr>
<tr>
<td>Length of hospital stay — days</td>
<td>3±3±1.6</td>
<td>3±4±1.9</td>
<td>3±6±1.6</td>
</tr>
<tr>
<td>Surgical approach — no. (%)</td>
<td>425 (47.1)</td>
<td>421 (46.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Posterior</td>
<td>386 (42.8)</td>
<td>391 (43.9)</td>
<td>NA</td>
</tr>
<tr>
<td>Anterolateral</td>
<td>49 (5.4)</td>
<td>50 (5.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Anterior</td>
<td>42 (4.7)</td>
<td>40 (4.4)</td>
<td>NA</td>
</tr>
<tr>
<td>Anterior longitudinal mline</td>
<td>NA</td>
<td>NA</td>
<td>815 (100)</td>
</tr>
<tr>
<td>Prosthesis — no. (%)</td>
<td>57 (6.3)</td>
<td>49 (5.4)</td>
<td>742 (91.0)</td>
</tr>
<tr>
<td>Hybrid</td>
<td>56 (6.2)</td>
<td>55 (6.1)</td>
<td>47 (5.8)</td>
</tr>
<tr>
<td>Noncemented</td>
<td>788 (87.5)</td>
<td>798 (88.5)</td>
<td>25 (3.1)</td>
</tr>
</tbody>
</table>

* Plus-minus values are means ±SD. None of the between-group comparisons were significant at baseline. NA denotes not applicable.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

~16% in each group used compression therapy.
Results-Outcomes

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.

All bleeding events were surgical site bleeding and most within the first 10 days.
Results-Patients on Long-Term ASA

- 25% of patients in each group were ALSO on long-term ASA

![Table 4. Subgroup Analysis of Primary Outcomes, According to Use of Long-Term Aspirin Therapy.](image)

* P<0.001 for noninferiority.
† This category includes major and clinically relevant nonmajor bleeding.

Results - Mechanical Compression

N=3424 patients randomized

Rivaroxaban
n=1717

Compression
n=274 (16%)  
0 VTE

No compression
n=1443  
2 VTE

ASA
n=1707

Compression
n=276 (16%)  
2 VTE

No compression
n=1431  
9 VTE

Study Strengths/Limitations

Adequately powered
Only analyzed symptomatic events in the primary outcome
External validity (practical use of long-term ASA, only including symptomatic events, varying use of compression)

Few patients with prior VTE included
Cannot provide conclusions on ideal regimen POD 0-5
Since most bleeding events occurred in 1st 10 days, hard to attribute which regimen caused bleeding
PEPPER trial

- **NCT02810704**
- Currently recruiting
- Open label
- THA or TKA

Outcomes: DVT/PE, all-cause mortality, Bleeding (major, CRNMB, wound-related), specific joint function, patient well-being

Sponsor: Medical University of South Carolina