Aspirin as Venous Thromboprophylaxis

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### Disclosures (past 2 years)

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
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<tbody>
<tr>
<td>Investments</td>
<td>None</td>
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<tr>
<td>Research grants</td>
<td>None</td>
</tr>
<tr>
<td>Program support</td>
<td>Bayer Healthcare, Sanofi</td>
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<tr>
<td>Advisory boards, consultancies</td>
<td>Bayer Healthcare, Covidien, Jansen, Pfizer, Sanofi</td>
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<tr>
<td>Honoraria for education</td>
<td>Bayer Healthcare, Leo Pharma, Sanofi</td>
</tr>
<tr>
<td>Humor in my presentations</td>
<td>I wish there was more!</td>
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</tbody>
</table>
Objectives

To review recent evidence for the use of aspirin to prevent VTE:

- Aspirin as a thromboprophylaxis agent
- Evidence for aspirin as primary venous thromboprophylaxis
- Recommendations
- Aspirin to prevent recurrent VTE
The main studies I will review are:

- POISE-2
- EPCAT-1, EPCAT-2
- PEPPER
- WARFASA, ASPIRE, EINSTEIN CHOICE
Aspirin

- 1897: ASA discovered by Felix Hoffmann, a chemist with Friedrich Bayer & Co. *(their 1st major product)*
- 1899: marketed under the trade name “aspirin” for pain, fever, inflammation
- 1962: aspirin shown to inhibit platelets
- 1994: Antiplatelet Trialists’ Collaboration
- 2000: PEP Trial
- 2013, 2017: EPCAT trials
Aspirin as Thromboprophylaxis

Rationale

- Platelet activation has a major role in both arterial and venous thrombosis


How does aspirin prevent VTE?

- Platelet activation has a major role in thrombosis [Davi – NEJM 2007;357:2482; Heestermans – Blood 2016;127:2630]


Aspirin and Venous Thrombosis

Advantages of Aspirin as Thromboprophylaxis

1. Demonstrated antithrombotic effect
2. Few side effects
3. Easy to use (including post-discharge)
4. Low cost (<10 ¢/tablet)
Adverse Effects of Aspirin

1. Bleeding (low absolute rates):
   - GI bleeding $\uparrow$ 60-70% - dose-related + risk greatest early - case fatality rates 5-10% - PPIs $\downarrow$ GIB $\geq$50%$^1$
   - Major bleeding $\uparrow$ 60-70%$^1$
   - Bleeding requiring transfusion $\uparrow$ 21% in hip fracture$^2$
   - Hemorrhagic stroke – rare (0.03%/yr)$^3$

2. Allergy

2. PEP Trial – Lancet 2000;355:1295
POI SE-2 Trial

- Aspirin vs placebo in 10,100 noncardiac surgery patients from 135 centers in 23 countries
- Aspirin 200 mg 2-4 hr preop → 100 mg daily x 30 d
- No routine screening for asymptomatic DVT

<table>
<thead>
<tr>
<th>Outcomes at 30 days</th>
<th>Placebo (n=5,012)</th>
<th>Aspirin (n=4,998)</th>
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</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
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<tr>
<td>VTE</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Severe PE</td>
<td></td>
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<td></td>
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<tr>
<td>Major bleeding</td>
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Devereaux – NEJM 2014;370:1494
Eikelboom – Anesthesiology 2016:125(6):1121
POI SE-2 Trial

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<tbody>
<tr>
<td>Death</td>
<td>60 (1.2%)</td>
<td>65 (1.3%)</td>
<td>1.05 [0.74-1.49]</td>
</tr>
<tr>
<td>VTE</td>
<td>60 (1.2%)</td>
<td>53 (1.1%)</td>
<td>0.89 [0.61-1.28]</td>
</tr>
<tr>
<td>Severe PE</td>
<td>13 (0.3%)</td>
<td>9 (0.2%)</td>
<td>0.69 [0.30-1.62]</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>256 (5.1%)</td>
<td>312 (6.3%)</td>
<td>1.22 [1.04-1.44]</td>
</tr>
</tbody>
</table>

- Aspirin did not reduce VTE (or any vascular events) but increased bleeding

Devereaux – NEJM 2014;370:1494
Eikelboom – Anesthesiology 2016:125(6):1121
VTE in Major Orthopedic Surgery (MOS)

- MOS is “high risk” for VTE
- Thromboprophylaxis is standard of care
- Sympt. VTE without prophylaxis unknown
- Sympt. VTE with prophylaxis: 0.5-2.5%
- Clinical practice has changed past 20 yrs
- Perception by some of ↑ bleeding, wound complications with LMWH, DOACs
- Most VTE present after discharge
Aspirin in Major Orthopedic Surgery

- Aspirin 600 mg BID reduced DVT in THA
  [Harris – NEJM 1977;297:1246]

- Antiplatelet Trialists showed a 23% reduction in VTE in 1,761 major orthopedic patients

- Several studies show that ASA + IPC as effective as warfarin or LMWH

- Both AAOS and ACCP consider aspirin an acceptable option in THA/TKA
  [AAOS – 2011; Falck-Ytter – Chest 2012;141:e278S]
Aspirin as Thromboprophylaxis

Limitations of Evidence:

- Few, small, old RCTs
- Most serious methodological limitations
- Aspirin doses 200-3,000 mg/day
- Variable, sometimes contradictory results
- Many trials negative
- Aspirin often part of multimodal therapy

∴ Evidence supporting aspirin alone is weak
EPCAT I Study

- Double-blind RCT in 12 Canadian centers

THA (N=778) 2007-10

Dalteparin 5,000 U daily x 10 days

R

Continue dalteparin 28 days

Aspirin 81 mg

Follow-up 90 days for sympt VTE and bleeding

EPCAT I Study

- Double-blind RCT in 12 Canadian centers

**THA (N=778) 2007-10**

- Dalteparin 5,000 U daily x 10 days

- Continue dalteparin

- Aspirin 81 mg

- Follow-up 90 days for sympt VTE and bleeding

<table>
<thead>
<tr>
<th>Outcomes Day 10-90</th>
<th>Dalteparin (n=400)</th>
<th>Aspirin (n=386)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic VTE</td>
<td>5 (1.3%)</td>
<td>1 (0.3%)</td>
<td>0.22  0.01 noninf</td>
</tr>
<tr>
<td>Clinically impot bleeding</td>
<td>5 (1.3%)</td>
<td>2 (0.5%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Net event rate</td>
<td>10 (2.5%)</td>
<td>3 (0.8%)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

EPCAT I Study: Limitations

- 82% of THR patients excluded
- Premature study termination (after 36% of projected sample) due to slow recruitment (rivaroxaban approved)
- Lower adherence in LMWH group
- 5% of patients received long-term aspirin

EPCAT II Study

- Double-blind RCT in 15 Canadian centers

THA or TKA (N=3,424)
rivaroxaban 10 mg PO daily until POD 5

Continue rivaroxaban 10 mg PO daily
30 days for THA, 9 days for TKA

Aspirin 81 mg

Follow-up 90 days for sympt VTE and bleeding

Anderson – ISTH 2017:OC 52.2; in press
EPCAT II Study

- Double-blind RCT in 15 Canadian centers

THA or TKA (N=3,424)

rivaroxaban 10 mg PO daily until POD 5

Continue rivaroxaban 10 mg PO daily

30 days for THA, 9 days for TKA

Aspirin 81 mg

Follow-up 90 days for sympt VTE and bleeding

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (n=1,714)</th>
<th>Aspirin (n=1,719)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic VTE</td>
<td>12 (0.7%)</td>
<td>11 (0.6%)</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>noninf</td>
</tr>
<tr>
<td>Clinically impot bleeding</td>
<td>17 (1.0%)</td>
<td>22 (1.3%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>5 (0.3%)</td>
<td>8 (0.5%)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Anderson – ISTH 2017:OC 52.2; in press
Oral Rivaroxaban after THR/TKR

Risk reduction 55%  p<0.001

Risk reduction 50%  p=0.001

P=0.14

Turpie – Thromb Haemost 2011;105:444
Network Meta-Analysis of Thromboprophylaxis Options

- Systematic review of 94 RCTs, 1990-June 2016
- 11 prophylaxis options compared to LWMH
## Network Meta-Analysis of Thromboprophylaxis Options

<table>
<thead>
<tr>
<th>94 RCTs</th>
<th>Odds ratio vs LMWH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All DVT</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>0.5 [0.3-0.9]</td>
</tr>
<tr>
<td>Direct FXa inhibitor</td>
<td>0.5 [0.4-0.6]</td>
</tr>
<tr>
<td>Dir thrombin inhibitor</td>
<td>0.8 [0.6-1.1]</td>
</tr>
<tr>
<td>LMWH BID</td>
<td>0.7 [0.6-0.9]</td>
</tr>
<tr>
<td>LMWH once daily</td>
<td>Reference</td>
</tr>
<tr>
<td>VKA INR 2-3</td>
<td>1.6 [1.1-2.1]</td>
</tr>
<tr>
<td>VKA INR &lt;2</td>
<td>9.5 [2.2-52]</td>
</tr>
<tr>
<td>Heparin</td>
<td>1.3 [0.9-2.0]</td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.8 [0.3-1.9]</td>
</tr>
<tr>
<td>IPC</td>
<td>1.2 [0.8-1.8]</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.9 [2.2-3.8]</td>
</tr>
</tbody>
</table>
Comparative Effectiveness of Thromboprophylaxis in TJA (PEPPER)

- Compare the 3 most common prophylaxis options
- RCT in 24 American centers; N=25,000; 2016-2021

**RCT** in 24 American centers; N=25,000; 2016-2021

- ECASA 81 mg BID
- Warfarin INR 1.7-2.2
- Rivaroxaban 10 mg

Follow-up for 6 months

Outcomes at 6 mos:

- Efficacy: VTE leading to readmission + death
- Safety: bleeding (major, clin-impt, wound-related)
- Joint function, patient well-being

Clinicaltrials.gov:NCT02810704
Aspirin as Thromboprophylaxis

Conclusions

1. Aspirin is somewhat effective in preventing VTE but less effective than anticoagulants.

2. In major orthopedic surgery, aspirin alone is less effective than alternatives.

3. \[ \therefore \] Aspirin alone should not be used.

4. Aspirin likely to be noninferior to LMWH or DOACs if combined with SCDs.

5. In major orthopedic surgery, after initial prophylaxis with a DOAC or LMWH, aspirin appears to be noninferior to DOAC or LMWH.
Thromboprophylaxis options in Major Orthopedic Surgery

1. **DOACs**
   - rivaroxaban 10 mg PO QD
   - apixaban 2.5 mg PO BID

2. **LMWH***
   - dalteparin 5,000 U QD
   - enoxaparin 40 mg QD or 30 mg BID
   - tinzaparin 4,500 U QD

*higher dose if wt >100 kg

3. ASA - ?after early use DOAC or LMWH
Thromboprophylaxis for TJA

Rivaroxaban* 10 mg daily x 15-30 days

Rivaroxaban* 10 mg daily x 5-10 days
Aspirin 81 mg daily x 10-25 days

Total prophylaxis 15-30 days

*or apixaban 2.5 mg BID
Aspirin as Thromboprophylaxis: Excellent References

- Karthikeyan – Does acetyl salicylic acid (ASA) have a role in the prevention of venous thromboembolism? Br J Haematol 2009;146:142.


- Anderson D – Extended venous thromboembolism prophylaxis comparing rivaroxaban to aspirin following total hip or knee arthroplasty (EPCAT II). ISTH 2017:OC 52.2.

Aspirin for extended VTE treatment
Aspirin to Prevent Recurrent VTE

Recurrent venous thromboembolism

Hazard ratio, 0.68 (95% CI, 0.52–0.90, P=0.008)

NNT with aspirin x 1 year = 42

WARFASA N=402
ASPIRE N=822

Simes – Circulation 2014;130:1062
# Aspirin to Prevent Recurrent VTE

<table>
<thead>
<tr>
<th>Outcome and Study</th>
<th>Placebo</th>
<th>Aspirin</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>P Value for Heterogeneity</th>
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<tbody>
<tr>
<td>Venous thromboembolism</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ASPIRE</td>
<td>73/411</td>
<td>57/411</td>
<td>0.74 (0.52–1.05)</td>
<td>0.09</td>
<td>0.42</td>
</tr>
<tr>
<td>WARFASA</td>
<td>43/197</td>
<td>28/205</td>
<td>0.58 (0.36–0.93)</td>
<td>0.02</td>
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<tr>
<td>Pooled</td>
<td>116/608</td>
<td>85/616</td>
<td>0.68 (0.51–0.90)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Major vascular events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASPIRE</td>
<td>88/411</td>
<td>62/411</td>
<td>0.66 (0.48–0.92)</td>
<td>0.01</td>
<td>0.96</td>
</tr>
<tr>
<td>WARFASA</td>
<td>48/197</td>
<td>36/205</td>
<td>0.67 (0.43–1.03)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>136/608</td>
<td>98/616</td>
<td>0.66 (0.51–0.86)</td>
<td>0.002</td>
<td></td>
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<tr>
<td>Clinically relevant bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASPIRE</td>
<td>8/411</td>
<td>14/411</td>
<td>1.72 (0.72–4.11)</td>
<td>0.22</td>
<td>0.50</td>
</tr>
<tr>
<td>WARFASA</td>
<td>4/197</td>
<td>4/205</td>
<td>0.98 (0.24–3.96)</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>12/608</td>
<td>18/616</td>
<td>1.47 (0.70–3.08)</td>
<td>0.31</td>
<td></td>
</tr>
</tbody>
</table>

*Brighton – NEJM 2012;367:1979*
Rivaroxaban for Extended VTE Treatment (EINSTEIN CHOICE)

Symptomatic Recurrent VTE

Major Bleeding

MB + CRNMB: ASA 2.0%
  riva 10  2.4%
  riva 20  3.3%

Weitz – NEJM 2017;376(13):1211
Secondary Prevention of VTE

- Patients with unprovoked VTE already treated ≥6 mos

*vs placebo

Aspirin as Thromboprophylaxis

Conclusions

1. Aspirin is less effective than anticoagulants in preventing primary or secondary venous thrombosis

2. In major orthopedic surgery, aspirin alone should not be used

3. Aspirin likely to be noninferior to LMWH or DOACs if combined with SCDs

4. In major orthopedic surgery, after initial prophylaxis with a DOAC or LMWH, aspirin appears to be noninferior to DOAC or LMWH