Aspirin for use as VTE Prophylaxis in Orthopedic Surgery Patients

Pharmacotherapy Rounds
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Objectives:
1. Describe the difference in pathophysiology between venous and arterial thrombosis.
2. Discuss trials reviewing aspirin for DVT/PE prophylaxis in orthopedic surgery patients.
3. Based on available evidence, discuss the efficacy and safety profile for aspirin as used for DVT/PE prophylaxis in orthopedic surgery patients.
4. Compare different guidelines for prevention of DVT/PE in orthopedic surgery patients.
Pathophysiology of Thrombosis

I. Arterial Thrombosis

a. High-flow, high-pressure environment
b. Arterial thrombosis is generally a result of underlying vascular abnormalities, such as atherosclerotic vascular disease, which affects medium and large sized arteries. These include the aorta, femoral, coronary, carotid, cerebral, and renal arteries.
c. Arterial thrombus is a response to endothelial cell injury, when circulating platelets interact with the damaged subendothelium and result in clot formation.
d. Aortic clots are sometimes referred to as "white clots" because they are composed of fibrin and platelets.
e. Thrombotic stroke occurs when thrombosis occurs in the cerebral arteries.
f. Myocardial infarction occurs when atherosclerotic plaques rupture and are exposed to thrombogenic factors.

II. Venous Thrombosis

a. Low-flow, low-pressure environment
b. Venous clots are sometimes referred to as "red clots" because they are composed of fibrin and red blood cells.
c. Most commonly occurs in the veins of the lower extremities, however the upper extremities may also be affected.
   i. Superficial vein thrombosis may result in pain, erythema, tenderness and heat at clot site.
   1. The extent of the clot may be determined by palpation.
   2. These clots rarely embolize.
   ii. Deep vein thrombosis (DVT) may result in swelling, erythema, heat, and tenderness.
d. Virchow's Triad
   i. Damage to the vessel wall
      1. Post-surgical state (especially knee replacement or hip surgery)
      2. Previous DVT or PE
      3. Atherosclerosis
      4. Valvular disease or replacement
   ii. Venous stasis
      1. Immobility or bed rest
      2. Paralysis
      3. Atrial fibrillation
      4. Left ventricular dysfunction
      5. Venous obstruction
   iii. Hypercoagulable state
      1. Pregnancy or estrogen therapy
      2. Malignancy
      3. Factor V Leiden
      4. Protein C or S deficiency.
e. Once formed, clots may:
   i. Spontaneously lyse
   ii. Propagate into other vessels
   iii. Embolize
III. Pulmonary Embolism

a. Overview
   i. When thrombi is released into venous circulation, they may distribute bilaterally to the lungs in 65% of cases, with lower lobes affected most often.
   ii. The thrombi occlude the large or medium-sized pulmonary arteries, with less than 35% affecting the smaller pulmonary arteries.
   iii. Acute pulmonary emboli begin lysing immediately upon reaching the lungs and smaller thrombi may completely lyse within several weeks. As lysis occurs, pulmonary circulation improves and symptoms resolve.
   iv. Large thrombi may result in death within hours or even minutes.

b. Clinical presentation
   i. Dyspnea
   ii. Chest pain
   iii. Tachypnea (> 20 breaths/minute)
   iv. Tachycardia (> 100 beats/minute)
   v. Cough
   vi. Hemoptysis

IV. Diagnosis:

a. D-dimer test:
   i. Measurement of cross-linked fibrin degradation products.
   ii. Elevated D-dimer levels are present in almost all patients with VTE, active cardiopulmonary disease, malignancy or recent surgery or trauma.
   iii. Has a negative predictive value.
      1. If number is low, a clot may be ruled out.
      2. If number is high, a clot may or may not be present.
   iv. Therefore, the D-dimer test is most useful in excluding VTE.
      1. D-dimer level < 500 ng/mL on ELISA testing has a negative predictive value of 95%.

b. Deep Vein Thrombosis
   i. Noninvasive tests
      1. Duplex scanning
         a. Doppler ultrasonography – audibly detects venous flow changes.
         b. B-mode compression ultrasound – provides a 2-D image; lack of compressibility is considered diagnostic for DVT.
      2. Doppler ultrasonography alone.
   ii. Invasive tests
      1. Contrast venography (gold standard)
         a. Radiographic visualization of the involved vessels with injection of radiopaque material.

   c. Pulmonary Embolism
   i. Ventilation perfusion (V/Q) lung scan
      1. Perfusion evaluated by radiolabeled albumin.
      2. Ventilation evaluated by inhalation of radiolabeled particles.
      3. V/Q mismatch indicates possible PE.
ii. Spiral CT pulmonary arteriography (commonly used)
   1. Less invasive than V/Q scan
iii. Pulmonary angiography (gold standard)
   1. Invasive procedure
   2. Injection of radiocontrast dye into the pulmonary artery
iv. Ancillary tests
   1. Arterial blood gas (check for acid-base imbalance and hypoxemia)
   2. EKG
   3. CXR (rule out other pulmonary causes)

**Thrombosis in Orthopedic Surgery Patients**

I. DVT in Orthopedic Surgery Patients

   a. Approximately 50% of patients untreated for DVT will develop some form of pulmonary embolism (PE)
   b. Without prophylaxis, the incidence of DVT in patients after orthopedic surgery is 50-60%\(^4\)
      i. Total Knee Arthroplasty\(^5\):
         1. Proximal DVTs are reported in 9% of patients in the operative leg
         2. Proximal DVTs are reported in 14% of patients in non-operative leg
      ii. Total Hip Arthroplasty:
         1. Proximal DVTs are reported in 25% of patients in the operative leg
         2. Proximal DVTs are reported in 20% of patients in nonoperative leg
   iii. Diagnosed PEs may occur in 7-11% of this population
   c. With DVT prophylaxis:
      i. Total Knee Arthroplasty:
         1. Fatal PEs are reported in 0.1% of patients\(^6\)
      ii. Total Hip Arthroplasty\(^7\):
         1. Nonfatal PEs are reported in 1.2% of patients
         2. Fatal PEs are reported in 0.4% of patients\(^8\)

**Venous Thrombosis: Who Is at Risk?**

- Age > 40 years (doubles with each decade)
- Prior venous thromboembolism (VTE)
- Conditions resulting in venous stasis:
  - Prolonged immobility (>4 days)
  - Presence of varicose veins
  - Pregnancy and postpartum
  - Obesity
  - Serious illness (heart failure, MI, sepsis)
- Conditions resulting in vessel wall damage:
  - Instrumentation (IV catheterization)
  - Orthopedic, urologic and gynecologic surgeries
  - Major trauma
- Abnormalities in circulating coagulation elements:
  - Antithrombin deficiency
  - Malignancy (especially metastatic)
  - Estrogen and selective estrogen receptor modulator use (raloxifene, tamoxifen)
  - Resistance to activated protein C (Factor V Leiden mutation)
  - Factor VIII and XI excess
  - Antiphospholipid antibodies
  - Protein C
  - Protein S deficiency
  - Prothrombin 20210 gene mutation
### Categories of Individual Risk

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Moderate Risk</th>
<th>High Risk</th>
<th>Highest Risk</th>
</tr>
</thead>
</table>
| Calf vein: <5%  
Proximal DVT: <1%  
Fatal PE: <0.1%  | Calf vein: 10% to 20%  
Proximal DVT: 2% to 4%  
Fatal PE: 0.1% to 0.4%  | Calf vein: 20% to 40%  
Proximal DVT: 4% to 8%  
Fatal PE: 0.4% to 1.0%  | Calf vein: 40% to 80%  
Proximal DVT: 10% to 20%  
Fatal PE: 1% to 5%  |
| • Minor surgery (<30 minutes in patients <40 years of age with no additional risk factors)  
• Minor trauma or medical illness | • Minor surgery: aged 40 to 60 years or 1 risk factor  
• Major general surgery: <40 years, with no additional risk factors | • Major general surgery: aged 40 to 60 years with 1 risk factor  
• Major surgery or illness: >60 years with no risk factors  
• Major medical illness, trauma, burns  
• Minor surgery or illness with prior VTE  
• Lower limb paralysis | • Fracture/surgery involving pelvis, hip, leg  
• Major surgery or illness with prior VTE  
• Major surgery for metastatic cancer  
• Major surgery or trauma with risk factors |

### Thromboprophylactic Mechanism of Aspirin

I. Mechanism of Action of Aspirin

a. Coagulation Pathway\(^9\)
   i. Injury to the tissue results in the release of phospholipids
   ii. Phospholipids increase the level of arachidonic acid in the body
   iii. Arachidonic acid is converted into prostaglandins and thromboxane A\(_2\) via the COX 1 enzyme
   iv. Thromboxane A\(_2\) facilitates platelet activation

b. Cyclooxygenase (COX) Enzymes
   i. COX 1 is present in most cells and is beneficial in homeostatic functions, such as protecting gastric mucosa, and aiding in platelet aggregation
   ii. COX 2 induction is upregulated by inflammatory mediators, leading to further inflammation, pain, swelling and fever

c. Aspirin irreversibly inhibits both COX 1 and COX 2 via acetylation, which results in decreased formation of prostaglandin precursor thromboxane A\(_2\)\(^10\)
   i. COX 1
      1. When low-dose aspirin is administered chronically, it irreversibly inhibits the formation of thromboxane A\(_2\) in platelets to inhibit platelet aggregation and prevent the formation of thrombi
         a. Useful in reducing the incidence of heart attacks
         b. May lead to an increased risk of bleeding
   ii. COX 2
      1. Since aspirin also inhibits the activity of prostaglandin synthase, the production of prostaglandin H\(_2\) is decreased
         a. Anti-inflammatory effects
II. Pharmacokinetics of Aspirin

a. Approximately 80-100% of aspirin is rapidly absorbed in the stomach and small intestine, and is widely and rapidly distributed, resulting in platelet inhibition within an hour of ingestion.
b. The antiplatelet effect continues for 7-10 days, with 50% of platelet functionality returning 5-6 days after ingestion\(^\text{11}\)

III. Benefits of Using Aspirin for VTE Prophylaxis

a. Potential advantages of aspirin over conventional therapy (warfarin, UH, LMWH)\(^\text{12}\)
   i. Lower risk of bleeding
   ii. Ease of administration
   iii. Decreased inconvenience to patient by frequent monitoring of lab values
   iv. Minimal cost
Conflicting Guidelines for Aspirin use in Orthopedic Surgery Patients

I. Summary of Current Guidelines for VTE Prophylaxis\textsuperscript{13,14}

a. Guidelines differ between the CHEST 2008 and American Academy of Orthopaedic Surgeons (AAOS) recommendations:
   i. Total Hip Replacement
      1. CHEST: Recommend against aspirin monotherapy (Grade 1A)
      2. AAOS: Aspirin, 325 mg 2x/day (reduce to 81 mg 1x/day if gastrointestinal symptoms develop), starting the day of surgery, for 6 weeks. (Level III, Grade B (choice of prophylactic agent), Grade C (dosage and timing))
   ii. Total Knee Replacement
      1. CHEST: Recommend against aspirin monotherapy (Grade 1A)
      2. AAOS: Aspirin, 325 mg 2x/day (reduce to 81 mg 1x/day if gastrointestinal symptoms develop), starting the day of surgery, for 6 weeks. (Level III, Grade B (choice of prophylactic agent), Grade C (dosage and timing))
   iii. Hip Fracture Surgery
      1. CHEST: Recommend against aspirin monotherapy (Grade 1A)
      2. AAOS: No specific recommendation

II. The Scottish Intercollegiate Guidelines Network (SIGN)\textsuperscript{15}

a. Prophylaxis of venous thromboembolism guidelines, published October 2002
   i. States, “All patients with hip fracture should receive aspirin 150mg orally, started on admission and continued for 35 days unless contraindicated” (Grade A)
   ii. AAOS, along with many review articles proposing aspirin in thromboprophylaxis, cite these guidelines to support their viewpoints.

b. Review Report of guidelines, published 2005\textsuperscript{16}
   i. In response to the question, “Based on the information given above [in the Review Report], and your own clinical judgment, does the guideline require revision in the light of new evidence?”
      1. The panel responded with, “Yes – more emphasis on LMWH and discussion regarding the role of Fondaparinux, aspirin should not be recommended”

III. The UK National Institute for Health and Clinical Excellence (NICE) Guidelines\textsuperscript{17}

a. Surgical thromboprophylaxis guidelines, published 2007
   i. Recommendation 1.2.3; for all patients, “do not regard aspirin or other antiplatelet agents as adequate prophylaxis for VTE”
IV. Surgical Care Improvement Project (SCIP) Guidelines (accepted by Joint Comm. and CMS)\(^{18}\)

a. For VTE prophylaxis in total joint surgery, use of the following drugs is allowed:
   i. LMWH
   ii. Fondaparinux
   iii. Warfarin

b. In the treatment of hip fractures, use of the following drugs is allowed:
   i. LMWH
   ii. Fondaparinux
   iii. Warfarin
   iv. LDUH

c. For hip fracture surgery or elective THA patients with a high risk for bleeding:
   i. The use of mechanical prophylaxis only is allowed
   ii. Patient’s high risk for bleeding must be documented

V. AAOS critique of their own recommendations\(^{14}\):

a. Limitations to the body of evidence included large clinical heterogeneity of:
   i. Interventions, procedures and cointerventions, doses, study populations,
      follow-up times, and definition of major bleeding

b. None of the studies were designed to investigate incidence of PE as the primary outcome

c. Study reporting of PE-related events was often incomplete and variable, with limited data available as to how many patients were evaluated for these events

d. The available evidence shows no differences among the interventions in rates of PE, PE-related death, total death, major bleeding, bleeding-related death, or rehospitalization when comparing systemic interventions (fondaparinux, LMWH, and warfarin) and mechanical devices or aspirin alone.

e. The only exception was the incidence of major bleeding, which was rare among patients receiving aspirin or mechanical devices alone (1 case in 697, or 0.14%, exact 95% CI 0.03-0.8%) compared to those who received systemic interventions (random effects model summary est. 1.8%, 95% CI 1.4-2.5%).

VI. Other Critiques of AAOS Guidelines

a. In 2009, a clinical commentary was published, arguing the ACCP guidelines were based upon randomized data, while the AAOS guidelines relied more on expert opinion\(^{19}\)
   i. This same commentary argued the AAOS guidelines were too focused on the prevention of PE, rather than DVT prevention, while the relationship between DVT as a precursor to PE was not adequately explored

b. In response, the AAOS issued a guidelines summary article reviewing the literature and stated four of the fourteen guideline recommendations were evidence-based\(^{20}\)

a. Limited to AAHKS membership, this survey explored the preferred anticoagulants for VTE prophylaxis, as well as the preferred set of guidelines  
b. Data collected was based on self-reported opinions and practices, and not on retrospective patient data  
c. Anticoagulants ranked for bleeding risk, wound drainage, ease of use and efficacy:  
   i. Aspirin was ranked to be easiest to use, with the least risk of bleeding or wound drainage  
      1. Aspirin was also ranked at the least effective of the six products  
      2. Enoxaparin was ranked as the most effective treatment, and the second easiest to use  
      3. Warfarin was ranked as 5th easiest to use, but second behind aspirin as having the least risk of bleeding and wound drainage  
d. When comparing ACCP and AAOS guidelines for VTE prophylaxis:  
   i. 74% of surgeons' hospitals recognized ACCP guidelines, rather than AAOS guidelines (31%)  
   ii. However, 82% of surgeons agreed with AAOS guidelines compared with ACCP (19%)  
   iii. 74% of surgeons did not believe ACCP guidelines were relevant to orthopedics  
e. Surgeons believed the guidelines most relevant to their practice were:  
   i. 3.1% believed ACCP guidelines were the most relevant  
   ii. 68% believed AAOS guidelines were the most relevant  
   iii. 27% believed elements of the ACCP and AAOS were both relevant  
   iv. 2.7% believed neither ACCP nor AAOS were relevant  

<table>
<thead>
<tr>
<th>Grading of Drug</th>
<th>Ease of Use</th>
<th>Efficacy</th>
<th>Bleeding</th>
<th>Drainage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (best)</td>
<td>Aspirin (1.16 ± 0.69)</td>
<td>Lovenox (2.29 ± 1.29)</td>
<td>Aspirin (1.56 ± 1.38)</td>
<td>Aspirin (1.50 ± 1.32)</td>
</tr>
<tr>
<td>2</td>
<td>Lovenox (2.92 ± 1.23)</td>
<td>Coumadin (2.68 ± 1.56)</td>
<td>Coumadin (2.58 ± 1.27)</td>
<td>Coumadin (2.57 ± 1.20)</td>
</tr>
<tr>
<td>3</td>
<td>Arixtra (3.10 ± 1.23)</td>
<td>Arixtra (2.87 ± 1.46)</td>
<td>Arixtra (3.98 ± 1.38)</td>
<td>Arixtra (3.99 ± 1.36)</td>
</tr>
<tr>
<td>4</td>
<td>Fragmin (3.34 ± 0.99)</td>
<td>Fragmin (3.16 ± 1.18)</td>
<td>Fragmin (4.06 ± 1.18)</td>
<td>Fragmin (4.01 ± 1.18)</td>
</tr>
<tr>
<td>5</td>
<td>Coumadin (4.59 ± 1.59)</td>
<td>Heparin (4.16 ± 1.70)</td>
<td>Lovenox (4.21 ± 1.42)</td>
<td>Lovenox (4.19 ± 1.47)</td>
</tr>
<tr>
<td>6 (worst)</td>
<td>Heparin (4.99 ± 1.19)</td>
<td>Aspirin (4.42 ± 1.84)</td>
<td>Heparin (4.36 ± 1.63)</td>
<td>Heparin (4.32 ± 1.61)</td>
</tr>
</tbody>
</table>
## Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin:  
**Pulmonary Embolism Prevention (PEP) Trial**\(^2\)

### Reference

### Design
Randomized, placebo-controlled, double-blinded

### Objective
To confirm or refute the benefits of aspirin for use in prevention of DVT or PE.

### Population

**Inclusion criteria:**
- Patients with a femoral-neck fracture or other fracture of the femur, in Australia, New Zealand, South Africa, Sweden and the UK, or patients undergoing elective hip or knee arthroplasty in New Zealand
- Doctor uncertainty as to the balance of benefits and risks of low-dose aspirin

**Exclusion criteria:**
- Patients with a clear indication to aspirin (such as recent myocardial infarction)
- Patients with a clear contraindication to aspirin (such as active peptic ulcer)

**Interesting to note:**
- Use of SC UFH, or previous use of aspirin or NSAIDs, did not preclude patients from entry into the trial

### Outcome
Incidence of mortality and in-hospital morbidity up to 35 days post-op
- Follow-up for non-fatal events (DVT, PE, MI, stroke, bleeding) continued during hospital stay
- Follow-up for mortality continued during and after hospital stay

### Methods
- 13,356 patients hip-fracture and 4088 elective arthroplasty patients
- Hip-fracture and elective-arthroplasty groups were randomized to aspirin or placebo at a ratio of 1:1
- A 5-week calendar-packed supply of aspirin 160mg enteric-coated daily or matching placebo was given, with the first dose to be chewed or broken to obtain systemic antiplatelet activity rapidly
- Evaluations occurred at baseline and 35 days post-op
- Statistical analysis was done using intention to treat Cox’s proportional hazards models. Proportional differences and corresponding hazard ratios had 95% CI, and p-values were two-sided
- With VTE reported in 2.5% of patients assigned placebo, a study population of 13,000 – 14,000 had 90% power at \( p = 0.05 \) to detect a 1/3 reduction in risk with aspirin

### Results
- No statistical difference found between groups for any rating scale
- Hip-fracture patients had an absolute reduction of 9 VTE events per 1000 patients assigned aspirin
- No difference for non-PE vascular deaths (95% CI [0.86-1.26]) or non-vascular deaths (CI 95% [0.84-1.23])
- Among all 17,444 randomized patients, risk of PE or VTE was reduced by 34% (95 CI [17-47]; \( p = 0.0003 \))

#### Hip-fracture population: effects on VTE

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Symptomatic DVT</th>
<th>Definite or Probable PE</th>
<th>Fatal PE</th>
<th>PE, DVT or Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>69 (1.0%)</td>
<td>46 (0.7%)</td>
<td>18 (0.3%)</td>
<td>105 (1.6%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>97 (1.5%)</td>
<td>81 (1.2%)</td>
<td>43 (0.6%)</td>
<td>165 (2.5%)</td>
</tr>
<tr>
<td>Proportional Reduction with Aspirin</td>
<td>29% (95% CI 3-48; ( p = 0.03 ))</td>
<td>43% (95% CI 18-60; ( p = 0.002 ))</td>
<td>58% (95% CI 27-76; ( p = 0.002 ))</td>
<td>36% (95% CI 19-50; ( p = 0.0003 ))</td>
</tr>
</tbody>
</table>

#### Hip-fracture: effects on vascular events and mortality

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Non-fatal MI/ Fatal Ischemic Heart Disease</th>
<th>Non-fatal/Fatal Stroke</th>
<th>Fatal PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>105 (1.6%)</td>
<td>54 (0.8%)</td>
<td>18 (0.3%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>79 (1.2%)</td>
<td>49 (0.7%)</td>
<td>43 (0.6%)</td>
</tr>
<tr>
<td>Hazard Ratio with Aspirin</td>
<td>1.33 (CI 95% 1.00-1.78; ( p = 0.05 ))</td>
<td>1.10 (95% CI 0.75-1.62; ( p = 0.6 ))</td>
<td>58% (95% CI 27-76; ( p = 0.002 ))</td>
</tr>
</tbody>
</table>
**Hip-fracture: effects bleeding and related complications**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Fatal Bleeds</th>
<th>Hematemesis/Melena with Transfusion</th>
<th>Hematemesis/Melena without Transfusion</th>
<th>Post-operative Bleeding Requiring Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>13 (0.2%)</td>
<td>23 (0.3%)</td>
<td>182 (2.7%)</td>
<td>197 (2.9%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>15 (0.2%)</td>
<td>17 (0.3%)</td>
<td>122 (1.8%)</td>
<td>157 (2.4%)</td>
</tr>
</tbody>
</table>

**Significance**

<table>
<thead>
<tr>
<th></th>
<th>Aspirin</th>
<th>Placebo</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p = 0.3</td>
<td>p = 0.0005</td>
<td>Absolute increase of 6 per 1000, Proportional increase of 24% (CI 95% 1.53; p = 0.04)</td>
</tr>
</tbody>
</table>

**Elective hip or knee arthroplasty**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>PE or DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>23 (1.1%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>28 (1.4%)</td>
</tr>
</tbody>
</table>

**Hazard Ratio with Aspirin**

| Hazard Ratio with Aspirin | 0.81 (CI 95% 0.47-1.42) |

**Conclusion**

Aspirin reduces the risk of PE and DVT by 34%, regardless of other thromboprophylaxis, and should be used routinely in surgical and medical groups at high risk of VTE.

**Strengths**

- Showed that aspirin is 34% more effective than placebo at reducing VTE events
- Large trial, which met its power for prevention of VTE
- One of the few trials which has studied TKA, THA and hip fracture surgery together

**Weaknesses**

- Little venographic data was included, which was a reason this trial was excluded from ACCP guidelines
- VTE events not recorded if they did not present clinically, were not fatal, or occurred after discharge
- There was little discussion in the trial regarding the primary endpoint of mortality, and much more focus placed on the secondary endpoints of DVT, PE and any VTE
- Treatment with aspirin was not compared with any other pharmacologic regimen
- The severity of GI bleeding was not clarified
- Because the trial had 400 deaths from vascular causes unrelated to PE, there was less than 50% power to detect a reduction in vascular death
- Less than 100 non-fatal MIs or strokes, so power was insufficient to detect reduction in mortality
- PE was the cause of death for less than 10% of participants in this trial
- 10% of patients never started their assigned study treatment
- 20% of patients did not complete the 5-week course of therapy
- The use of other VTE prophylactic measures (such as heparin) did not preclude patient entry into the hip-fracture or elective arms of the trial, nor did previous use of aspirin or NSAIDs
Figure 2: Proportional effects of aspirin on pulmonary embolism and symptomatic deep-vein thrombosis after hip fracture

Figure 3: Absolute effects of aspirin on pulmonary embolism and deep-vein thrombosis after hip fracture

Table 2: Effects of aspirin on bleeding episodes and related complications in hip-fracture patients up to day 35
### Methods
- 3473 patients (3813 knees); 3402 patients received aspirin 325mg twice daily for 6 weeks
  - Of the 71 patients not given aspirin, 67 were continued on warfarin due to preexisting medical conditions, and the remaining 4 had a history of PE or thrombophilia and were treated with a vena cava filter and warfarin or LMWH
  - Patients with a past history of DVT without PE were given aspirin alone
- Observed a minimum of 6 weeks, the period during which > 95% of PEs occur after total joint surgery
- > 95% of patients had spinal and epidural anesthesia, which was continued for 36 hours after surgery
- All patients were started on physical therapy with a walker the morning after surgery
- All patients had mechanical compression with pneumatic foot pumps while in bed after hospitalization
- Adverse events were recorded during initial hospitalization
- PE or symptomatic DVT after discharge was recorded when suspected or confirmed by medical specialist
- Bleeding was considered major if patients were readmitted to the hospital or re-operated

### Results
- No patients were lost to follow-up during the 6-week observation period
- Best-case estimate of death from PE was determined by considering only documented fatal PE
  - 2 patients (0.06%)
- Worst-case estimate of death from PE was determined if cause of death not clearly defined
  - 5 patients (0.14%)

### Prevalence of Post-Surgical Events

<table>
<thead>
<tr>
<th>Documented Fatal PE</th>
<th>Documented PE + Undefined COD</th>
<th>Nonfatal PE</th>
<th>Proximal DVT</th>
<th>Nonfatal Ischemic Stroke</th>
<th>GI Bleeding</th>
<th>Adverse Bleeding Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (0.06%)</td>
<td>5 (0.14%)</td>
<td>9 (0.26%)</td>
<td>7 (0.2%)</td>
<td>2 (0.06%)</td>
<td>1 (0.03%)</td>
<td>13 (0.4%)</td>
</tr>
</tbody>
</table>

- Of the 13 patients with adverse bleeding events:
  - 2 patients were receiving LMWH
  - 2 patients were receiving warfarin
  - 9 patients were receiving aspirin
- 8 patients (8 knees, 0.24%) had needle aspiration for effusion and/or hematoma
- The risk of adverse bleeding events was 0.3% with aspirin, which is lower than the risk of other thromboprophylactic agents, which allows it to be used along with regional anesthesia

### Conclusion
Aspirin, along with early mobilization, regional anesthesia, and pneumatic foot pumps is associated with a risk of fatal PE of approximately 0.1% in postoperative TKA patients

### Strengths
- Evaluated the benefit of a multimodal protocol
- No patients were lost to follow-up
- Provided “best case” and “worst case” results
- The study showed that aspirin may be used in patients with regional anesthesia, in contrast to LMWH, where use with spinal or epidural anesthesia is contraindicated due to risk of hematoma

### Weaknesses
- No control group was used in this study
- Exclusion criteria was vague and ill-defined
- The study was carried out over a 10-year period, during which orthopedic practice had changed
- Hematomas were only recorded if they occurred in the operating room, and any hematomas which may have occurred in the outpatient setting as a result of surgery were not included
The Incidence of Fatal Pulmonary Embolism after Primary Hip and Knee Replacement in a Consecutive Series of 4253 Patients


Methods
- 2050 patients with TKR and 2203 patients with THR
- Data were recorded prospectively by outcomes assessment nurses
- Patients given aspirin 150mg daily, starting on the first post-operative day and for 6 weeks
  - 46 patients were mistakenly given LMWH, which was stopped and changed to aspirin
  - 136 patients with contraindication to aspirin received no chemical prophylaxis
  - 11 patients with history of treated PE were given warfarin
- Spinal anesthesia was used for all patients when possible
- Whenever possible, patients were mobilized either on day of surgery, or the first post-operative day
- Perioperative and 90-day morbidity and mortality data were recorded for all patients
- Patients were reviewed at 6 weeks after THR and 3 months for TKR, and then at one year
  - No patients were lost to follow-up
- Clinical diagnosis of DVT was confirmed by duplex ultrasonography or venography, and PE by V/Q scan
  - Proximal DVT was treated with warfarin for three months
  - Confirmed PE was treated with warfarin for six months
- Fatal PE was confirmed from the post mortem record or death certificate, and deaths of unknown cause within three months of operation were considered to be the result of PE

Results
- Death was reported in 13 patients (0.31% of all procedures)
  - 5 deaths occurred after THR (0.23% of all THRs)
  - 8 deaths occurred after TKR (0.39% of all TKRs)
  - All patients for which mortality data was recorded received aspirin only
- Overall, only three deaths (0.07% of all procedures) were attributed to PE
  - One death after THR (0.05% of all THRs)
  - Two deaths after TKR (0.1% of all TKRs)

Overall 90-day Morbidity and Mortality Rates

<table>
<thead>
<tr>
<th>Event</th>
<th>All Procedures</th>
<th>No Prophylaxis</th>
<th>Aspirin Only</th>
<th>LMWH and Aspirin</th>
<th>Warfarin Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal DVT</td>
<td>14 (0.33%)</td>
<td>2</td>
<td>11</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Non-fatal PE</td>
<td>28 (0.66%)</td>
<td>2</td>
<td>27</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>3 (0.07%)</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hematoma (TKR)</td>
<td>15</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematoma (THR)</td>
<td>8</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged bleeding (TKR)</td>
<td>49</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged bleeding (THR)</td>
<td>29</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serosanguinous ooze (TKR)</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Serosanguinous ooze (THR)</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Fatal GI hemorrhage (TKR)</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Fatal GI hemorrhage (THR)</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion
Aspirin is safe with a low complication rate, despite risk of GI ulceration or bleeding in a small number of patients.

Strengths
- No patients lost to follow-up
- Diagnosis of DVT/PE was clinically confirmed through V/Q scan, venography or duplex ultrasonography
- A multimodal approach to treatment was used

Weaknesses
- No exclusion criteria noted
- Comparison of patient population between groups was not elaborated upon
- For 80% power, 67,500 patients were needed in each arm of the trial to detect a difference in mortality
Methods

- Aspirin was compared to VTE prophylaxis recommended by ACCP Guidelines
- ICD-9 charges to were monitored, and patients were grouped into three categories
  - Patients who received aspirin vs other agents
  - Patients who received warfarin vs other agents
  - Patients who received injectable agents vs other agents
- An analysis of aspirin vs guideline-approved therapies was also performed
- Post-operative complications were monitored using diagnosis codes for:
  - Any VTE event, proximal DVT, PE only, surgical site bleeding, surgical site infection, and any readmissions within 30 days of discharge
- Mortality and readmission were determined using flags in administration data

Results

- Of the 93,840 patients in the study:
  - 4,719 (5.0%) patients received aspirin alone
  - 37,190 (39.6%) patients received injectable agents (LMWH or fondaparinux)
  - 51,923 (55.3%) patients received warfarin

### Unadjusted Patient Outcomes

<table>
<thead>
<tr>
<th>Intervention</th>
<th>DVT or PE</th>
<th>Bleeding related to surgical site</th>
<th>Wound infection</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>110 (2.3%)</td>
<td>30 (0.6%)</td>
<td>559 (12.0%)</td>
<td>9 (0.2%)</td>
</tr>
<tr>
<td>LMWH/fondaparinux</td>
<td>1152 (3.1%)</td>
<td>459 (1%)</td>
<td>4366 (12.0%)</td>
<td>46 (0.1%)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>2009 (4.0%)</td>
<td>548 (1%)</td>
<td>6349 (12.0%)</td>
<td>54 (0.1%)</td>
</tr>
<tr>
<td>Aspirin vs injectables</td>
<td>P = 0.0037</td>
<td>P &lt; 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin vs warfarin</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Adjusted Patient Outcomes

<table>
<thead>
<tr>
<th>Intervention</th>
<th>DVT or PE</th>
<th>Bleeding related to surgical site</th>
<th>Wound infection</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectables vs Aspirin</td>
<td>OR 1.34</td>
<td>OR 1.95</td>
<td>OR 0.99</td>
<td>OR 0.65</td>
</tr>
<tr>
<td>(Unadjusted)</td>
<td>(95% CI 1.10-1.63)</td>
<td>(95% CI 1.35-2.83)</td>
<td>(95% CI 0.90-1.09)</td>
<td>(95% CI 0.32-1.34)</td>
</tr>
<tr>
<td>Warfarin vs Aspirin</td>
<td>OR 1.69</td>
<td>OR 1.67</td>
<td>OR 1.04</td>
<td>OR 0.54</td>
</tr>
<tr>
<td>(Unadjusted)</td>
<td>(95% CI 1.39-2.05)</td>
<td>(95% CI 1.15-2.41)</td>
<td>(95% CI 0.95-1.24)</td>
<td>(95% CI 0.27-1.10)</td>
</tr>
<tr>
<td>Injectables vs Aspirin</td>
<td>OR 1.03</td>
<td>OR 1.11</td>
<td>OR 1.10</td>
<td>OR 0.63</td>
</tr>
<tr>
<td>(Adjusted)</td>
<td>(95% CI 0.76-1.39)</td>
<td>(95% CI 0.77-1.60)</td>
<td>(95% CI 0.95-1.24)</td>
<td>(95% CI 0.30-1.34)</td>
</tr>
<tr>
<td>Warfarin vs Aspirin</td>
<td>OR 1.36</td>
<td>OR 0.97</td>
<td>OR 1.10</td>
<td>OR 0.54</td>
</tr>
<tr>
<td>(Adjusted)</td>
<td>(95% CI 1.02-1.82)</td>
<td>(95% CI 0.65-1.47)</td>
<td>(95% CI 0.96-1.26)</td>
<td>(95% CI 0.25-1.15)</td>
</tr>
</tbody>
</table>
Patients who received aspirin for VTE prophylaxis had lower odds for thromboembolism compared to warfarin, but had similar odds compared with injectable VTE prophylaxis. No difference in risk of bleeding, infection or mortality was seen. Aspirin, if used with other protocols, may be effective VTE prophylaxis for some TKA patients.

Strengths
- Well-defined inclusion and exclusion criteria
- Large patient population involved in study, which included a broad range or primary and secondary diagnosis and procedure codes from 307 different hospitals
- Provided both adjusted and unadjusted outcome data
- A multimodal treatment protocol was used
- These findings support the idea that patient selection, surgical technique, and multimodal perioperative care methodology may be as important as aspirin in reducing risk for VTE and bleeding.
- Determining a patient’s risk level for VTE or bleeding will be extremely important to determine the appropriateness of aspirin for VTE prophylaxis in the future
- The authors state the conclusions of this trial should be considered hypothesis generating rather than conclusive evidence for the safety and efficacy of aspirin for VTE prophylaxis after TKA

Weaknesses
- Aspirin patients were different from patients in other categories in the following ways:
  - Lower baseline VTE risk score than warfarin or injectable groups (p < 0.001)
  - Lower All Payer Refined Diagnosis Related Groups (APR DRG) severity of illness scores, indicating fewer medical comorbidities than the injectable group (p = 0.001), but similar to the warfarin group (p = 0.69)
  - Less likely to have hypertension, chronic iron deficiency anemia, and diabetes without chronic complications
  - More likely to be obese
  - Less likely to receive compression devices postoperatively (p < 0.001)
  - Shorter length of stay and more likely to be discharged home, rather than to an extended care facility (p < 0.0001)
- The study was limited to admissions and readmissions within a 30-day period. Therefore, any VTE events which may have occurred after the 30-day discharge would not have been recorded
- Data collection was limited by its dependence on proper documentation by study hospitals
- Compared to aspirin patients, unadjusted odds ratios for DVT or PE were significantly higher in the warfarin and LMWH/fondaparinux groups. However, after adjusting for patient factors and propensity score, the magnitude between the aspirin and warfarin decreased, and the difference between aspirin and the LMWH/fondaparinux group was no longer statistically significant
- The adjusted outcome data do not support the widely held belief that aspirin use is associated with lower risk for bleeding or surgical site infections

**Potent Anticoagulants are Associated with a Higher All-Cause Mortality Rate After Hip and Knee Arthroplasty**

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Meta-analysis and systematic review of peer-reviewed publications</td>
</tr>
<tr>
<td>Objective</td>
<td>To determine whether the incidence of all-cause mortality and pulmonary embolism in patients undergoing total</td>
</tr>
<tr>
<td></td>
<td>joint arthroplasty differs with currently used thromboprophylaxis protocols</td>
</tr>
<tr>
<td>Population</td>
<td>Twenty studies were reviewed</td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria:</td>
</tr>
<tr>
<td></td>
<td>- Published from 1998 to 2007</td>
</tr>
<tr>
<td></td>
<td>- English language publications</td>
</tr>
<tr>
<td></td>
<td>- 6-week or 3-month incidence of all-cause mortality and symptomatic, non-fatal PE</td>
</tr>
<tr>
<td></td>
<td>- Series with elective unilateral or bilateral THA and TKA, as well as revision arthroplasty</td>
</tr>
<tr>
<td></td>
<td>- Limited to consecutive case series with documented patient follow-up and randomized trials</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria:</td>
</tr>
<tr>
<td></td>
<td>- Series that studied specific cohorts, such as patients with cirrhosis, renal failure, obesity, or</td>
</tr>
<tr>
<td></td>
<td>exclusively bilateral joint arthroplasty</td>
</tr>
<tr>
<td></td>
<td>- Personal communications, expert opinions, and studies focusing only on DVT as the endpoint</td>
</tr>
<tr>
<td></td>
<td>- Patients with surgeries &gt; 15 years ago</td>
</tr>
</tbody>
</table>
## Methods
- The reviewed studies were separated into three groups:
  - Group A: 15,839 patients receiving LMWH, ximelagatran, fondaparinux or rivaroxaban
  - Group B: 7,193 patients receiving regional anesthesia, pneumatic compression and aspirin
  - Group C: 5,006 patients receiving warfarin alone
- Studies belonging in the three categories were further divided into 6-week and 3-month follow-ups
- Variations in study populations included:
  - Group A
    - 36% (3785 of 10,437) of patients received spinal or epidural anesthesia
  - Group B
    - 8% (570 of 7193) of patients received warfarin, either due to high risk of VTE or it being prescribed prior to surgery for other medical complications
    - 6% (438 of 7193) of patients received general, rather than regional, anesthesia
    - Intra-operative heparin was used in one study for TKA
  - Group C
    - 29% (397 of 1342) of patients received spinal or epidural anesthesia
- Fixed and random effects were the modeling techniques used to calculate estimated mortality and PE rates, as well as relative risk estimates for these rates, using 95% CI and p values

## Results
- All-cause mortality was lower in Group B patients (14 of 7193 [0.19%]) than Group A (65 of 15,839 [0.41%]) or Group C (20 of 5006 [0.40%])
- The rates of all-cause mortality in the studies were:
  - Group A: 0% to 0.62%
  - Group B: 0% to 0.29%
  - Group C: 0.1% to 0.67
- Relative risks of all-cause mortality between groups was:
  - Fixed effects:
    - Group A vs Group B (p = 0.01)
    - Group B vs Group C (p = 0.04)
    - Group A vs Group C (no difference)
  - Random effects:
    - Group A vs Group B (p = 0.01)
    - Group B vs Group C (p = 0.03)
    - Group A vs Group C (no difference)
- The rates of symptomatic non-fatal PE were higher in Group A vs Group B
  - 94 of 15,839 patients [0.60%] vs 25 of 7193 [0.35%]; p = 0.019
- The rates of non-fatal PE between groups was:
  - Group A: 0% to 1.2%
  - Group B: 0% to 0.62%
  - Group C: 0.1% to 0.8%
- Relative risks of non-fatal PE between groups was:
  - Fixed effects:
    - Group A vs Group B (p = 0.02)
    - Group B vs Group C (no difference)
    - Group A vs Group C (no difference)
  - Random effects:
    - Group A vs Group B (p = 0.04)
    - Group B vs Group C (no difference)
    - Group A vs Group C (no difference)

## Conclusion
- Group A was associated with the highest all-cause mortality of the three modalities studied
- All-cause mortality was higher in Group A than in Group B (0.41% vs 0.19%)
- Group B was associated with the lowest all-cause mortality after total joint arthroplasty
- Incidence of clinical non-fatal PE was higher in Group A than in Group B (0.60% vs 0.35%)
- All-cause mortality and non-fatal PE in Group C was similar to those in Group A (0.4% vs 0.52%)
- Study Level of Evidence: Level III per publishing journal

## Strengths
- Trial reviewed by ACCP guidelines
- Patients were limited to surgeries which occurred in the last 15 years. This helps to account for updated practice methods, such as modern anesthesia, surgical and rehabilitation techniques, and use of LMWH
### Weaknesses
- No significant benefit or inferiority when compared with LMWH
- Authors had to compare outcomes between trials
  - Most Group A trials were randomized, controlled studies
  - Most Group B trials were cohort studies
  - Most Group C trials were randomized and non-randomized studies
- Incidence of major bleeding events was not measured
- The differences seen between Group A and Group B may be due to:
  - Regional anesthesia was used in 36% of Group A and 94% of Group B patients
    - In a meta-analysis of anesthetic types, regional anesthesia has a 30-50% reduction in mortality compared with general anesthesia in orthopedic surgery patients
  - All Group B studies were performed in high-volume centers, and some Group A and Group C studies may have been performed in low-volume centers
  - Bleeding may be more common in Group A therapies, which may cause increased mortality

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### Venous Thromboembolism Prophylaxis After Major Orthopaedic Surgery:
A Pooled Analysis of Randomized Controlled Trials

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Pooled analysis of randomized controlled trials cited by ACCP guidelines for VTE prophylaxis after major orthopedic surgery. Fourteen trials were included in the analysis, including two which were excluded from ACCP guidelines due to lack of venographic testing. THA was reviewed in 9 trials, TKA in 8 trials and hip fracture surgery in 2 trials. Three trials included both THA and TKA. One trial included THA, TKA and hip fracture surgery.</td>
</tr>
</tbody>
</table>

### Objective
To determine if aspirin decreases the rate of operative bleeding without increasing thromboembolic events when used for VTE prophylaxis after major orthopedic surgery.

### Outcomes
- Data was reviewed based upon different elements of the trials, including patients screened, procedure type, cancelled procedures, VTE prophylactic agent, subgroup patient population, duration of VTE prophylaxis, use of compression stockings, use of pneumatic compression devices, use of NSAIDs, use of venography, time to venogram, positive venograms, positive non-invasive studies, symptomatic DVTs, PEs, fatal PE, major operative site bleeding complications, major non-operative bleeding, and total major bleeding events.

### Methods
- 15 statistical comparisons conducted, reviewing ASA vs fondaparinux, LMWH, and VKA across 5 rates:
  - Symptomatic DVT
  - PE
  - Fatal PE
  - Major operative site bleeding
  - Major non-operative site bleeding
- Binomial pooled rates were compared using Chi-Square tests
  - When cell values were < 5, Fisher's test was used
  - Significance level was p = 0.05
  - Bonferroni correction for statistical significance was calculated to be 0.05/15=0.0033

### Results
- Symptomatic DVT rates
  - Aspirin vs warfarin (p=3.5x10^-6)
- Fatal PE
  - Aspirin vs warfarin (not statistically significant after Bonferroni correction, p = 0.0033)
- Operative site bleeding
  - Aspirin vs warfarin (p=5.4x10^-18)
  - Aspirin vs LMWH (p=1.0x10^-35)
  - Aspirin vs fondaparinux (p=4.7x10^-15)
Outcomes by VTE Prophylactic Treatment

<table>
<thead>
<tr>
<th></th>
<th>Pooled Subjects</th>
<th>Veno- graphic DVT</th>
<th>Sympto -matic DVT</th>
<th>PE</th>
<th>Fatal PE</th>
<th>Operative Site Bleeding Events</th>
<th>Non-Operative Site Bleeding</th>
<th>Total Bleeding Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fondaparinux</td>
<td>3616</td>
<td>6.50%</td>
<td>0.94%</td>
<td>0.80%</td>
<td>0.30%</td>
<td>1.91%</td>
<td>0.47%</td>
<td>2.38%</td>
</tr>
<tr>
<td>LMWH</td>
<td>9269</td>
<td>17.87%</td>
<td>1.28%</td>
<td>0.45%</td>
<td>0.13%</td>
<td>2.92%</td>
<td>1.33%</td>
<td>3.66%</td>
</tr>
<tr>
<td>Warfarin</td>
<td>4518</td>
<td>32.69%</td>
<td>2.01%</td>
<td>0.40%</td>
<td>0.04%</td>
<td>2.24%</td>
<td>1.49%</td>
<td>2.57%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>8726</td>
<td>-</td>
<td>0.96%</td>
<td>0.62%</td>
<td>0.22%</td>
<td>0.46%</td>
<td>2.57%</td>
<td>3.03%</td>
</tr>
<tr>
<td>Placebo</td>
<td>8718</td>
<td>-</td>
<td>1.33%</td>
<td>1.02%</td>
<td>0.52%</td>
<td>0.47%</td>
<td>1.79%</td>
<td>2.26%</td>
</tr>
</tbody>
</table>

Pooled Rates Comparing Aspirin vs Fondaparinux, LMWH, and Warfarin

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic DVT</th>
<th>PE</th>
<th>Fatal PE</th>
<th>Operative Site Bleeding</th>
<th>Non-Operative Site Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fondaparinux vs ASA</td>
<td>p = 0.91</td>
<td>p = 0.26</td>
<td>p = 0.37</td>
<td>p = 4.70E-15</td>
<td>p = 1.80E-14</td>
</tr>
<tr>
<td>LMWH vs ASA</td>
<td>p = 0.057</td>
<td>p = 0.13</td>
<td>p = 0.15</td>
<td>p = 1.00E-35</td>
<td>p = 2.40E-08</td>
</tr>
<tr>
<td>Warfarin vs ASA</td>
<td>p = 3.50E-06</td>
<td>p = 0.1</td>
<td>p = 0.019</td>
<td>p = 5.40E-18</td>
<td>p = 0.0012</td>
</tr>
</tbody>
</table>

Relative Risks and Comparing Aspirin to Fondaparinux, LMWH and Warfarin

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic DVT</th>
<th>PE</th>
<th>Fatal PE</th>
<th>Op Site Bleeding Events</th>
<th>Non-Op Site Bleeding Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fondaparinux vs ASA</td>
<td>RR 0.98 (CI 95% 0.66-1.45)</td>
<td>RR 1.3 (CI 95% 0.83-2.03)</td>
<td>RR 1.4 (CI 95% 0.67-2.93)</td>
<td>RR 4.16 (CI 95% 2.83-6.13)</td>
<td>RR 0.18 (CI 95% 0.11-0.30)</td>
</tr>
<tr>
<td>LMWH vs ASA</td>
<td>RR 1.33 (CI 95% 0.99-1.78)</td>
<td>RR 0.73 (CI 95% 0.49-1.09)</td>
<td>RR 0.59 (CI 95% 0.29-1.22)</td>
<td>RR 6.38 (CI 95% 4.56-8.92)</td>
<td>RR 0.52 (CI 95% 0.41-0.66)</td>
</tr>
<tr>
<td>Warfarin vs ASA</td>
<td>RR 2.09 (CI 95% 1.52-2.88)</td>
<td>RR 0.64 (CI 95% 0.38-1.10)</td>
<td>RR 0.2 (CI 95% 0.05-0.87)</td>
<td>RR 4.88 (CI 95% 3.28-7.27)</td>
<td>RR 0.58 (CI 95% 0.42-0.81)</td>
</tr>
</tbody>
</table>

Conclusion

- Warfarin has a higher rate of symptomatic DVT compared to aspirin
- No other significant difference in VTE outcomes
- The PEP trial was included in this analysis, and the authors state the results contradict the ACCP guidelines statement of there being no evidence available that aspirin is effective in reducing VTE
- The authors claim the ACCP guidelines are incomplete, stating:
  - The importance of symptomatic DVT, PE, fatal PE and adverse bleeding was minimized.
  - The PEP trial was excluded from ACCP guidelines, and it is the only trial to observe a 1% difference in symptomatic DVT after major orthopedic surgery.
  - ACCP placed a low value on prevention of venographic VTE and a high value on minimizing bleeding complications, but excluded the PEP trial because it lacked venographic studies.
  - ACCP cited no trials using warfarin after hip fracture surgery, but guidelines support its use.
  - They stated six of the seven ACCP drafting committee members had potential conflicts of interest with pharmaceutical companies.
- The authors believe CMS should reassess SCIP guidelines to include aspirin as a part of multimodal VET prophylaxis, to be used with regional anesthesia, compression devices and early mobility.

Strengths

- All the studies cited in the ACCP guidelines, and two that were excluded, were analyzed in this review
- Extensive data reporting
Weaknesses

- Information was selectively chosen and generalized, with apparent author bias
- No meta-analysis of the data was performed
- This analysis relied upon published studies, and some of these studies have previously had their strengths and weaknesses described (specifically PEP and Lotke, et al)
- Cites the Scottish Intercollegiate guidelines, which have been reviewed since publication

### Table 2. Pooled Rates Stratified by VTE Prophylactic Treatment

<table>
<thead>
<tr>
<th>Total Subjects</th>
<th>Pooled Venographic Deep Vein Thrombosis</th>
<th>Symptomatic Deep Vein Thrombosis</th>
<th>Pulmonary Embolus</th>
<th>Fatal Pulmonary Embolus</th>
<th>Operative Site Bleeding Events</th>
<th>Non-Operative Site Bleeding Events</th>
<th>Total Bleeding Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentasaccharide</td>
<td>3616</td>
<td>6.50%</td>
<td>0.94%</td>
<td>0.80%</td>
<td>0.30%</td>
<td>1.91%</td>
<td>0.47%</td>
</tr>
<tr>
<td>LMWH</td>
<td>9269</td>
<td>17.87%</td>
<td>1.28%</td>
<td>0.45%</td>
<td>0.13%</td>
<td>2.92%</td>
<td>1.33%</td>
</tr>
<tr>
<td>Warfarin</td>
<td>4518</td>
<td>32.69%</td>
<td>2.01%</td>
<td>0.40%</td>
<td>0.04%</td>
<td>2.24%</td>
<td>1.49%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>5726</td>
<td>-</td>
<td>0.96%</td>
<td>0.62%</td>
<td>0.22%</td>
<td>0.46%</td>
<td>2.57%</td>
</tr>
<tr>
<td>Placebo</td>
<td>8718</td>
<td>-</td>
<td>1.33%</td>
<td>1.02%</td>
<td>0.52%</td>
<td>0.47%</td>
<td>1.79%</td>
</tr>
</tbody>
</table>

### Table 3. Chi-Square P-Values for Pooled Rates Comparing Aspirin to Pentasaccharides, LMWH, and Warfarin (Bonferroni correction 0.05/15 = 0.0033)

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic Deep Vein Thrombosis</th>
<th>Pulmonary Embolus</th>
<th>Fatal Pulmonary Embolus</th>
<th>Operative Site Bleeding Events</th>
<th>Non-Operative Site Bleeding Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentasaccharide vs ASA</td>
<td>0.91</td>
<td>0.26</td>
<td>0.37</td>
<td>4.7E-15</td>
<td>1.8E-14</td>
</tr>
<tr>
<td>LMWH vs ASA</td>
<td>0.057</td>
<td>0.13</td>
<td>0.15</td>
<td>1.0E-35</td>
<td>2.4E-08</td>
</tr>
<tr>
<td>Warfarin vs ASA</td>
<td>3.5E-06</td>
<td>0.10</td>
<td>0.019</td>
<td>5.4E-18</td>
<td>0.0012</td>
</tr>
</tbody>
</table>

### Table 4. Binomial Relative Risks and 95% Confidence Intervals of Pentasaccharides, LMWH, and Warfarin Compared to Aspirin

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic Deep Vein Thrombosis</th>
<th>Pulmonary Embolus</th>
<th>Fatal Pulmonary Embolus</th>
<th>Operative Site Bleeding Events</th>
<th>Non-Operative Site Bleeding Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Risk</td>
<td>95% Confidence Interval</td>
<td>Relative Risk</td>
<td>95% Confidence Interval</td>
<td>Relative Risk</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Pentasaccharide vs ASA</td>
<td>0.98</td>
<td>0.66-1.45</td>
<td>1.30</td>
<td>0.83-2.03</td>
<td>1.40</td>
</tr>
<tr>
<td>LMWH vs ASA</td>
<td>1.33</td>
<td>0.99-1.78</td>
<td>0.73</td>
<td>0.49-1.09</td>
<td>0.59</td>
</tr>
<tr>
<td>Warfarin vs ASA</td>
<td>2.09</td>
<td>1.52-2.88</td>
<td>0.64</td>
<td>0.38-1.10</td>
<td>0.20</td>
</tr>
</tbody>
</table>

### Summary and Conclusions

- Guidelines differ on whether aspirin should be used for VTE prophylaxis after orthopedic surgery
- ASA is an attractive therapeutic option because it is inexpensive, easy to administer and does not require monitoring
- ASA is clearly efficacious in preventing VTE compared to placebo or no treatment, but appears to be less efficacious than the low molecular weight heparins in small trials, and there is little data for ASA in comparison with UFH or warfarin
- A large randomized controlled trial is required to clarify the role of ASA compared to contemporary anticoagulant strategies for the prevention of VTE
From the CHEST 2008 Guidelines:

**Total Hip Replacement**
Although metaanalyses have shown that thromboprophylaxis with LDUH or aspirin is superior to no thromboprophylaxis, both agents are less effective than other thromboprophylaxis regimens in this high-risk group. Aspirin should not be used as the only prophylactic agent after THR. *For patients undergoing THR, we recommend against the use of any of the following: aspirin, dextran, LDUH, GCS, or VFP as the sole method of thromboprophylaxis (all Grade 1A).*

**Total Knee Replacement**
*For patients undergoing TKR, we recommend against the use of any of the following as the only method of thromboprophylaxis: aspirin (Grade 1A), LDUH (Grade 1A), or VFP (Grade 1B).*

**Hip Fracture Surgery**
Aspirin and other antiplatelet drugs provide much less protection against VTE compared with other thromboprophylaxis methods. *For patients undergoing HFS, we recommend against the use of aspirin alone (Grade 1A).*

**CHEST Grading of Recommendations**

<table>
<thead>
<tr>
<th>Grade of Recommendation*</th>
<th>Benefit vs Risk and Burden</th>
<th>Methodologic Quality of Supporting Evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong recommendation, high-quality evidence, Grade 1A</td>
<td>Desirable effects clearly outweigh undesirable effects, or <em>vice versa</em></td>
<td>Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies</td>
<td>Recommendation can apply to most patients in most circumstances; further research is very unlikely to change our confidence in the estimate of effect</td>
</tr>
<tr>
<td>Strong recommendation, moderate quality evidence, Grade 1B</td>
<td>Desirable effects clearly outweigh undesirable effects, or <em>vice versa</em></td>
<td>Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies</td>
<td>Recommendation can apply to most patients in most circumstances; higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate</td>
</tr>
<tr>
<td>Strong recommendation, low or very low-quality evidence, Grade 1C</td>
<td>Desirable effects clearly outweigh undesirable effects, or <em>vice versa</em></td>
<td>Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence</td>
<td>Recommendation can apply to most patients in many circumstances; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate</td>
</tr>
<tr>
<td>Weak recommendation, high-quality evidence, Grade 2A</td>
<td>Desirable effects closely balanced with undesirable effects</td>
<td>Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies</td>
<td>The best action may differ depending on circumstances or patient or society values; further research is very unlikely to change our confidence in the estimate of effect</td>
</tr>
<tr>
<td>Weak recommendation, moderate-quality evidence, Grade 2B</td>
<td>Desirable effects closely balanced with undesirable effects</td>
<td>Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies</td>
<td>Best action may differ depending on circumstances or patient or society values; higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate</td>
</tr>
<tr>
<td>Weak recommendation, low or very low-quality evidence, Grade 2C</td>
<td>Desirable effects closely balanced with undesirable effects</td>
<td>Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence</td>
<td>Other alternatives may be equally reasonable; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate</td>
</tr>
</tbody>
</table>

*We use the wording we recommend for strong (Grade 1) recommendations and we suggest for weak (Grade 2) recommendations.*
From the AAOS Clinical Guideline on Prevention of Symptomatic PE in Patients Undergoing THA or TKA

**Recommendation 3.3.1 Patients at standard risk of both PE and major bleeding** should be considered for one of the chemoprophylactic agents evaluated in this guideline, including-in alphabetical order: Aspirin, LMWH, synthetic pentasaccharides, and warfarin. (Level III, Grade B (choice of prophylactic agent), Grade C (dosage and timing))

a) Aspirin, 325 mg 2x/day (reduce to 81 mg 1x/day if gastrointestinal symptoms develop), starting the day of surgery, for 6 weeks.

b) LMWH, dose per package insert, starting 12-24 hours post-operatively (or after an indwelling epidural catheter has been removed), for 7-12 days (N.B., the LMWHs have not been sufficiently evaluated for longer periods to allow recommendation beyond this period).

c) Synthetic pentasaccharides, dose per package insert, starting 12-24 hours postoperatively (or after an indwelling epidural catheter has been removed), for 7-12 days (N.B., the synthetic pentasaccharides have not been sufficiently evaluated for longer periods to allow recommendation beyond this period).

d) Warfarin, with an INR goal of ≤2.0, starting either the night before or the night after surgery, for 2-6 weeks.

**Recommendation 3.3.3 Patients at standard risk of PE and at elevated (above standard) risk of major bleeding** should be considered for one of the chemoprophylactic agents evaluated in this guideline, including-in alphabetical order: Aspirin, Warfarin, or none. (Level III, Grade C)

Note: The grade of recommendation was reduced from B to C for dosage and timing because of the lack of consistent evidence in the literature on risk stratification of patient populations.

a) Aspirin, 325 mg 2x/day (reduce to 81 mg 1x/day if gastrointestinal symptoms develop), starting the day of surgery, for 6 weeks.

b) Warfarin, with an INR goal of ≤2.0, starting either the night before or the night after surgery, for 2-6 weeks.

c) None

**Recommendation 3.3.4 Patients at elevated (above standard) risk of both PE and major bleeding** should be considered for one of the chemoprophylactic agents evaluated in this guideline, including-in alphabetical order: Aspirin, Warfarin, or none. (Level III, Grade C)

Note: The grade of recommendation was reduced from B to C for dosage and timing because of the lack of consistent evidence in the literature on risk stratification of patient populations. No studies currently include patients at elevated risk of major bleeding and/or PE in study groups.

a) Aspirin, 325 mg 2x/day (reduce to 81 mg 1x/day if gastrointestinal symptoms develop), starting the day of surgery, for 6 weeks.

b) Warfarin, with an INR goal of ≤2.0, starting either the night before or the night after surgery, for 2-6 weeks.

c) None
Pulmonary embolism

Hip arthroplasty

There were 25 studies that met criteria and reported PE rates with various interventions after hip arthroplasty. The summary estimates of PE rates were higher in patients who received systemic prophylaxis than those who were treated with aspirin or mechanical devices alone, though this finding may be due to chance alone and may be related to the relatively small number of patients evaluated with aspirin or mechanical devices alone.

Knee arthroplasty

There were 21 studies that met criteria and reported PE rates with various interventions after knee arthroplasty, with the rates of PE found to be similar across different interventions. There was no evidence across studies of different rates of PE related to dose, intensity, or timing of intervention, duration of follow-up, study quality or applicability.

Pulmonary embolism-related death

Hip arthroplasty

There were 19 studies that provided sufficient data to estimate rates of death due to confirmed PE with various interventions after hip arthroplasty, none of which evaluated aspirin.

Knee arthroplasty

There were 19 studies that provided sufficient data to estimate rates of death due to confirmed PE with various interventions after knee arthroplasty. The summary estimates of PE deaths for specific interventions were mostly similar, generally 0.1% or less. Three PE deaths occurred in the small studies of mechanical devices used alone, however the very small number of events precludes an accurate estimate of the PE death rate.

AAOS Grading of Recommendations

AAOS Levels of Evidence:

- **Level I** evidence is from high quality randomized clinical trials (e.g., a randomized trial comparing revision rates in patients treated with cemented and uncemented total hip arthroplasty).
- **Level II** evidence is from cohort studies (e.g., revision rates in patients treated with uncemented THA compared with a control group of patients treated with cemented THA at the same time and institution).
- **Level III** evidence is from case-control studies (e.g., the rates of cemented and uncemented THA in patients with a particular outcome called "cases"; i.e. revised THA, are compared to those who did not have outcome, called "controls"; i.e. non-revised THA).
- **Level IV** evidence is from an uncontrolled case series (e.g., a case series of patients treated with uncemented THA).
- **Level V** evidence is from expert opinion. The table is relatively simple with four types of studies and five levels.

AAOS Grading of Recommendations

- **Grade A**: Good evidence (Level I Studies with consistent finding) for recommending intervention.
- **Grade B**: Fair evidence (Level II or III Studies with consistent findings) for recommending intervention.
- **Grade C**: Poor quality evidence (Level IV or V) for recommending intervention.
References:

13. CHEST 2008 Guidelines
   http://chestjournal.chestpubs.org/content/133/6_suppl
14. AAOS Guidelines
   http://www.aaos.org/research/guidelines/PE_guideline.pdf
   http://www.sign.ac.uk/guidelines/fulltext/62/index.html
17. The UK National Institute for Health and Clinical Excellence (NICE) Surgical Thromboprophylaxis Guidelines
   http://www.nice.org.uk/nicemedia/pdf/CG92NICEGuidelinePDF.pdf
18. AACP vs AAOS Guidelines concerning CMS and The Joint Commission (SCIP Guidelines)


