“THE ASPIRIN STUDY”
FROM ADAPT TO PREVENT CLOT

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DISCLOSURE

Funded by PCORI for the Randomized Pragmatic Trial Comparing the Complications and Safety of Blood Clot Prevention Medicines Used in Orthopaedic Trauma Patients
IT STARTED WITH A "DISCUSSION"
LMWH CAUSES INCREASED COMPLICATION RATES?

- Observational study

- The rate of wound-related complications, SWI, DWI and wound drainage was
  - 0.45, 0.27, 0 and 0.18%, respectively, for patients who received aspirin
  - 3.5, 2.6, 0.2 and 0.7 %, respectively, for patients who received Coumadin

A total of 290 consecutive patients who underwent total hip and total knee arthroplasty were prospectively entered into a clinical anticoagulation trial using a 10-day course of Lovenox with the ACCP -1A guidelines.

Major complications occurred in 9% of patients:
- Symptomatic deep vein thrombosis occurred in 9 (3.8%) patients
- Nonfatal pulmonary embolism in 3 (1.3%) patients

Complications included:
- 4.7% readmissions
- 3.4% return to the operating room for wound incision and drainage
- 5.1% prolonged hospitalization (wound drainage)
- 3.4% injection site complications

Return to the operating room for wound complications occurred 3× more frequently with the use of Lovenox than previous study using warfarin.
ANTIPLATELET AGENTS FOR VTE PREVENTION?

- Antiplatelet therapy had previously not generally been accepted to DVT or PE
- All trials had been small

*Antiplatelet agents such as aspirin or hydroxychloroquine show limited efficacy in preventing deep vein thrombosis (table III); their effects on pulmonary embolism and mortality are not yet published.*

**TABLE III — Meta-analysis of incidence of deep vein thrombosis after major general surgery (defined by 125I fibrinogen scanning)**

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Mean incidence (%) (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prophylaxis</td>
<td>25.1 (23.9 to 26.5)</td>
</tr>
<tr>
<td>Low dose heparin</td>
<td>8.7 (7.8 to 9.7)</td>
</tr>
<tr>
<td>Graduated elastic compression stockings</td>
<td>9.3 (6.4 to 13.3)</td>
</tr>
<tr>
<td>Intermittent pneumatic compression</td>
<td>9.9 (6.9 to 13.9)</td>
</tr>
<tr>
<td>Dextran</td>
<td>16.6 (13.1 to 18.4)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>20.4 (16.5 to 25.0)</td>
</tr>
</tbody>
</table>

• 25% of patients allocated antiplatelet therapy versus 34% of appropriately adjusted controls had DVT

• Representing prevention in about 90 patients per 1000 allocated to antiplatelet therapy.

Collaborative overview of randomised trials of antiplatelet therapy—III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients

Antiplatelet Trialists’ Collaboration
Aspirin reduced the risk of PE and DVT by at least a third throughout a period of increased risk.

“Hence, there is now good evidence for considering aspirin routinely in a wide range of surgical and medical groups at high risk of venous thromboembolism.”

Since those original studies, many changes have occurred in the perioperative management, including:
- multi-disciplinary clinical care pathways
- multi-modal pain management protocols
- increased use of regional anesthesia
- modifications in surgical technique
- aggressive early ambulation and physical therapy
- early discharge to home

References:
ANTIPATELET AGENTS FOR VTE PREVENTION?

- Analyzed clinical and administrative data from 93,840 patients who underwent primary TKA at 307 U.S. hospitals over a 24 month period.

- 51,923 (55%) patients received warfarin, 37,198 (40%) received injectable agents, and 4,719 (5%) received aspirin.

- After adjustment for patient and hospital factors, patients who received aspirin had lower odds for thromboembolism compared to warfarin patients, but similar odds compared to injectable VTEP.

- There were no differences in risk of bleeding, infection or mortality after adjustment.

“Our results suggest that aspirin, when used in conjunction with other clinical care protocols, may be effective VTEP for certain TKA patients.”

A total of 1,568 consecutive patients undergoing hip and knee replacement surgery received multimodal thromboprophylaxis
- 1,115 received aspirin
- 426 received Coumadin
- 27 patients received LMWH and Coumadin with or without an IVC filter

The rate of VTE, PE, proximal DVT, and distal DVT was
- 1.2, 0.36, 0.45 and 0.36%, respectively, in patients who received aspirin.
- 1.4, 0.9, 0.47 and 0.47%, respectively, in patients who received coumadin
Multicenter randomized, controlled trial

Noninferiority design

12 tertiary care orthopedic referral centers in Canada

778 patients who had elective unilateral THA between 2007 and 2010

28 days of dalteparin (n 400) or aspirin (n 386)

The study was halted prematurely because of difficulty with patient recruitment.

Extended prophylaxis for 28 days with aspirin was noninferior to and as safe as dalteparin for the prevention of VTE after THA (in patients who initially received dalteparin for 10 days).

Table 2. Primary Outcome Results*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LMWH Recipients (n = 398)</th>
<th>Aspirin Recipients (n = 386)</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>0.227</td>
<td>1.0 (−0.5 to 2.5)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>3 (0.8)</td>
<td>0 (0.0)</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; LMWH = low-molecular-weight heparin.
* Values reported are numbers (percentages).
† Aspirin was noninferior (P < 0.001) but not superior to dalteparin.

Table 3. Bleeding Results*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LMWH Recipients (n = 398)</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 (0.0)</td>
<td>1.00</td>
<td>0.25 (−4.9 to 1.0)</td>
</tr>
<tr>
<td>Clinically significant normajor 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 (0.0)</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>Hematoma</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Leechismosis</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 (0.0)</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Conjunctival</td>
<td>2 (0.5)</td>
<td>0 (0.0)</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

LMWH = low-molecular-weight heparin.
* Values reported are numbers (percentages).
† All events were wound hematomas.

Table 4. Secondary Outcomes*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LMWH Recipients (n = 398)</th>
<th>Aspirin Recipients (n = 385)</th>
<th>P Value</th>
<th>LMWH = low-molecular-weight heparin.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound infection</td>
<td>10 (2.5)</td>
<td>12 (2.1)</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Deep incision</td>
<td>3 (0.8)</td>
<td>3 (0.8)</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Superficial</td>
<td>6 (1.5)</td>
<td>7 (1.8)</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Deep incision &gt; 30 d from procedure</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Superficial &gt; 30 d from procedure</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2 (0.5)</td>
<td>0 (0.0)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.3)</td>
<td>0 (0.0)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (0.3)</td>
<td>0 (0.0)</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

* Values reported are numbers (percentages).

ANTIPLATELET AGENTS FOR VTE PREVENTION?

- Single institution
- 28,923 patients underwent TJA
- Multivariate analysis and 3:1 and 5:1 propensity score matching for comorbid and demographic variables.

“Aspirin offers suitable prophylaxis against symptomatic PE in selected patients”

ANTIPLATELET AGENTS FOR VTE PREVENTION?

- The American Academy of Orthopaedic Surgeons (AAOS) has endorsed aspirin for VTE prevention after TJA.

- In 2012, the American College of Chest Physician (ACCP) evidence-based clinical practice guidelines (9th edition), for the first time, acknowledged the use of aspirin as a means of PE chemoprophylaxis after TJA (Grade IB recommendation).


WHICH TURNED INTO A COLLABORATION
SO...WE DECIDED TO DO AN RCT

- First order of business…cute acronym

- A Different Approach to Preventing Thrombosis = ADAPT

- Second order of business…establishing our primary outcome metric and methodology

- Discrete choice experiment
PATIENT PREFERENCES

- Discrete choice experiments (DCE) are a quantitative technique used to measure individual preferences in a variety of healthcare settings by administering surveys that ask individuals to choose the best option between two or more hypothetical scenarios or choice sets.

- Options are described with a fixed set of attributes levels that vary in each scenario.

- The data collected can be used to assess the relative importance of each

PATIENT PREFERENCES

- A DCE was prospectively administered to orthopaedic trauma patients at a level 1 trauma center.

- 232 adult trauma patients with pelvic or acetabular fractures or operative extremity fractures.

- Primary and secondary outcome measures
  - Relative preferences and trade-off estimates for a 1% reduction in complications were estimated using multinomial logit modelling.
  - Interaction terms were added to the model to assess heterogeneity in preferences.

PATIENT PREFERENCES

- Patients preferred oral tablets over subcutaneous injections (marginal utility, 0.16; 95% CI: 0.11 - 0.21, P<0.0001)

- Preferences changed in favor of subcutaneous injections with an absolute risk reduction of
  - 6.98% in bleeding
  - 4.53% in wound complications
  - 1.27% in VTE
  - 0.07% in death from PE

We conducted an open-label randomized clinical trial of adult patients admitted to an academic trauma center with an operative extremity fracture, or a pelvis or acetabular fracture.

Patients were randomized to receive LMWH (enoxaparin 30-mg) twice daily (n = 164) or aspirin 81-mg twice daily (n = 165).

The primary outcome was a composite endpoint of:
- bleeding complications
- dSSI
- DVT
- PE
- death within 90 days of injury

ADAPT STUDY

- Weighting of study outcomes
  - Outcome weights were derived for the study outcomes based on the results of the DCE
  - The relative importance of the component outcomes was used to calculate the outcome weights and determined a hierarchy of severity for the observed combination of events experienced during the first 90 days from injury

<table>
<thead>
<tr>
<th>Component Outcome</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1.000</td>
</tr>
<tr>
<td>VTE Event (Pulmonary Embolism or Deep Vein Thrombosis)</td>
<td>0.055</td>
</tr>
<tr>
<td>Deep Surgical Site Infection</td>
<td>0.015</td>
</tr>
<tr>
<td>Bleeding Complication</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Overall, 18 different combinations of outcomes were experienced by patients in the study.

99 patients in the aspirin group (59.9%) and 98 patients in the LMWH group (59.4%) were event-free within 90 days of injury.

Using a Global Rank test, the LMWH had a 50.4% (95% CI, 47.7–53.2%, p = 0.73) probability of treatment superiority over aspirin.

ADAPT STUDY

• A secondary analysis of patients enrolled in the ADAPT RCT.

• To compare inpatient compliance with venous thromboembolism prophylaxis regimens.

• The primary outcome measure was the number of doses missed compared with prescribed number of doses.

• Results
  • A total of 329 patients were randomized to receive either LMWH 30mg BID (164 patients) or aspirin 81mg BID (165 patients).
  • No differences observed in % of patients who missed a dose (aspirin: 41.2% vs LMWH: 43.3%, P=0.7) or mean number of missed doses (0.6 vs 0.7 doses, P=0.4).
  • The majority of patients (57.8%, n=190) did not miss any doses.

• Concluded
  • “These data should reassure clinicians that inpatient compliance is similar for low molecular weight heparin and aspirin regimens.”

Haac BE, et al. Inpatient compliance with venous thromboembolism prophylaxis after orthopaedic trauma: results from a randomized controlled trial of aspirin versus low molecular weight heparin. OTAI (2021) e150
Patients prescribed outpatient prophylaxis were contacted between 10-21 days after discharge to assess adherence measured by the Morisky Medication Adherence Scale (MMAS-8).

Adherence scores were compared between the two treatment arms with similar results for intention-to-treat and as-treated analyses.

As-treated multivariable logistic regression was performed to determine factors associated with low-medium adherence scores.

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**Morisky Medication Adherence Scale (MMAS-8 Item)**

You indicated that you are taking medication(s) for your (name of health condition). Individuals have identified several issues regarding their medication-taking behavior, and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experience with this (name of health condition) medication(s).

<table>
<thead>
<tr>
<th>(Please mark your response below)</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you sometimes forget to take your (name of health condition)-related medication(s)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. People sometimes miss taking their medication(s) for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your (name of health condition)-related medication(s)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Have you ever cut back or stopped taking your medication(s) without telling your doctor, because you felt worse when you took it?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. When you travel or leave home, do you sometimes forget to bring along your (name of health condition)-related medication(s)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Did you take your (name of health condition)-related medication(s) yesterday?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. When you feel like your (name of health condition)-related condition is under control, do you sometimes stop taking your medication(s)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Taking medication(s) every day is a real inconvenience for some people. Do you ever feel ashamed about sticking to your (name of health condition)-related condition treatment plan?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. How often do you have difficulty remembering to take all your medication(s)?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Please circle your answer below)

*Never/Rarely*
*Once in a while*
*Sometimes*
*Usually*
*All the time*
150 patients (64 on LMWH, 86 on aspirin) on chemoprophylaxis at time of follow-up completed the questionnaire.

As-treated analysis showed that adherence was high overall (mean MMAS 7.2 out of 8, SD 1.5) and similar for the two regimens (LMWH: 7.4 vs. aspirin: 7.0, p = 0.13).

Patients on LMWH were more likely to feel hassled by their regimen (23% vs. 9%, p = 0.02).

In a multivariable model, low-medium adherence was associated with:
- taking LMWH as the prophylaxis medication (aOR 2.34, CI 1.06–5.18, p = 0.04)
- having to self-administer the prophylaxis (aOR 4.44, CI 1.45–13.61, p < 0.01)
- male sex (aOR 2.46, CI 1.10–5.49, p = 0.03)
- younger age (aOR 0.72 per additional 10 years of age, CI 0.57–0.91, p < 0.01).

SO...WE DECIDED TO DO A MULTICENTER RCT

- First order of business…cute acronym

- PREVENTion of CLot in Orthopaedic Trauma study = PREVENT CLOT

- Second order of business…secure funding
The trial was funded by the Patient-Centered Outcomes Research Institute.

PREVENT CLOT was co-led by:
- University of Maryland School of Medicine’s Department of Orthopaedics
- Major Extremity Trauma and Rehabilitation Consortium (METRC) Coordinating Center (MCC) at the Johns Hopkins Bloomberg School of Public Health.

PREVENT CLOT

- A multicenter, randomized, pragmatic trial
- Enrolled ~12,200 adult patients admitted to 1 of 21 participating centers

Inclusion criteria
1. Must be 18 years of age or older.
2. Have a planned operative or non-operative pelvis or acetabular fracture, or any operative extremity fracture proximal to the metatarsals or carpals.
3. Will receive a VTE prophylactic regimen per standard of care at the treating center.

The primary outcome is all-cause mortality.

Secondary efficacy outcomes include
- cause-specific mortality
- non-fatal PE
- DVT

Safety outcomes include
- bleeding complications
- wound complications
- deep surgical site infections

I'M SO EXCITED! AND I JUST CAN'T HIDE IT...
THANK YOU!

Questions?