Total Joint Replacement: Trends in VTE Prophylaxis and The Path to Surgery/When to Refer

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Total Joint Replacement
Disclosures

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- Research Funding – South Carolina Translational Research Institute (TKA Arthrofibrosis)

- None relevant to this presentation
Trends in VTE Prophylaxis for Total Joint Replacement
Case 1

- 68M w/ Afib (Eliquis 5mg BID), HTN, h/o EtOH use, former smoker
- Posttraumatic DJD R Knee, failed PT, Injections, brace; unable to take NSAIDs
- Primary TKA – no complications, 2 day hospital stay, discharged home, restarts Eliquis 5mg BID on POD#1
- Calls 7 days postop with increased knee swelling and drainage after being seen in ER and receiving Rx for Keflex for redness.
- Massive effusion
- ESR/CRP elevated
- Aspiration: hemarthrosis, 11,500 WBC, 84% PMNs, culture negative
What went wrong?

• Appropriate DVT Prophylaxis?
  • Factor Xa inhibitor? Dose?
  • EtOH?
  • h/o smoking?
• Now what?...
  • Wound drainage after 7 days -> I&D
    • If unsuccessful, then 2-stage Exchange for Infection
  • How do you reverse Eliquis? How long do you wait to operate?
  • What about DVT Prophylaxis after reoperation?
    • Eliquis again? -> Risk of hematoma -> Risk of Infection/reoperation
Case #2

- 71 active M, Mild obesity, BPH, o/w healthy, non-smoker
- Primary THA for DJD
- Discharged to Rehab POD#3 on ASA 81 BID for VTE Prophylaxis
- At 3 week postop appointment, found to have significant painful edema in operative leg
- Duplex U/S positive for DVT at the popliteal vein.
- No SOB, CP
Now What?

- Should we have done something different?
  - Was ASA 81 BID appropriate?
  - History of thrombotic disorder – personal or family?
  - Rehab disposition?
- What now – symptomatic, provoked popliteal DVT while on ASA?
Conflicting Goals

• Pick your Poison
  • Bleeding risk
  • Threat of Clots/Fatal PE

• Outcomes of historical studies
  • +DVT on Postoperative scan
  • Bleeding events typically secondary Outcome Measure

• Benchmarking
  • VTE Incidence as QI Measure
Symptomatic VTE - Current Perspective

Inpatient vs. Post-Discharge Events 1996-2011 44,844 TJA

**Sx VTE**

- **THA**
  - In-Hospital: 15-20%
  - After Discharge: 80-85%
- **TKA**
  - In-Hospital: 50%
  - After Discharge: 50%

**Sx PE**

- **THA**
  - In-Hospital: 0.53%
  - After Discharge: 0.14%
- **TKA**
  - In-Hospital: 1.09%
  - After Discharge: 0.27%

“...the appropriateness of in-hospital VTE after THA or TKA as a patient safety indicator for QI or PFP ... is uncertain.”

JA Heit, MD

Convergence of ACP & AAOS Guidelines, 2016

• AAOS
  • Avoid PE and Clinically Significant Bleeding events
    • Have advocated for approval of Aspirin as VTE Prophylactic agent

• ACP:
  • Avoid PE
  • High intensity agents
    • Warfarin
    • LMWH & other Heparinoids

• 2016 ACP/AAOS Convergence
  • Addition of BOTH:
    • Aspirin, and
    • Direct Oral Anticoagulants (Factor Xa Inhibitors)
The PCORI PEPPER Trial: 2016-2020
PE Prevention after hiP & kneE Replacement

Large Pragmatic Clinical Trial - $14.4M over 4.5 yrs
25,000 pts at 25 centers - Non-inferiority design
PI Vincent Pellegrini, MD

Aspirin vs. Warfarin (INR 2) vs. Rivaroxaban - for 30 days

Clinical endpoints - ACM, PE, Sx DVT, clinical bleed, re-op
Decision support analysis tool - risk aversion PE vs bleed
The PCORI PEPPER Trial: Patient Preferences - Methods - 6 Item Survey

IRB-approved survey administered to 498 patients (316 preop, 182 post) containing important information about the different blood thinners:

<table>
<thead>
<tr>
<th>Blood Thinner</th>
<th>Bleed</th>
<th>Reoperation for Bleeding</th>
<th>Reoperation for Infection</th>
<th>Pulmonary Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>1:10</td>
<td>1:500 (0.2%)</td>
<td>1:500 (0.2%)</td>
<td>1:50 (2%)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1:1</td>
<td>1:100 (1.0%)</td>
<td>1:300 (0.33%)</td>
<td>1:100 (1%)</td>
</tr>
<tr>
<td>Xarelto</td>
<td>10:1</td>
<td>1:20 (5.0%)</td>
<td>1:50 (2.0%)</td>
<td>1:200 (.5%)</td>
</tr>
</tbody>
</table>

Rarely, pulmonary embolism, infection, or bleeding can all cause death.
The PCORI PEPPER Trial: Patient Preferences 6-Item Survey (498 Responses)

Most feared complication

PE > Deep infection > Hematoma
possible death reoperation/removal reoperation
84% 8.5% 7.5%

Patients view pulmonary embolism with a risk of death as the worst outcome.
The PCORI PEPPER Trial: Patient Preferences – 498 Responses

Considering all the different benefits and risks, which blood thinner would you choose to take after your TJA?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>41%</td>
</tr>
<tr>
<td>Warfarin</td>
<td>15%</td>
</tr>
<tr>
<td>Xarelto</td>
<td>14%</td>
</tr>
<tr>
<td>Unsure</td>
<td>30%</td>
</tr>
</tbody>
</table>

*Patients are confused (as much as their surgeons?) They choose a familiar drug*
Current VTE Prophylaxis

• Mechanical intermittent compression devices
  • In-hospital
  • Portable
• Compression stockings
  • *ACP recommends AGAINST for most hospitalized patients
• Early Mobilization
VTE Prophylaxis: Pharmacologic Options - 2016

1. Warfarin (VKA) - F II, VII, IX, X

2. AT-III Binding (heparinoid)
   Unfractionated heparin
   LMW heparin (Enoxap, Daltep)
   Pentasaccharide (Fondap)

3. Selective / Specific Inhibitors
   Xa inhibitors (Rivaroxaban)
   IIa inhibitors (Dabigatran)

4. Aspirin – pltlet, inflammation
Chemoprophylaxis - 2016

• **Warfarin**
  - + Gold standard, reversible
  - – requires monitoring, difficult to maintain within target range, early paradoxical hypercoagulability

• **Heparins**
  - + reversible, well-established track record
  - - injection, drainage/bleeding risk, HIT

• **Selective Inhibitors/Direct Oral Anticoagulants (DOAC)**
  - + PO without monitoring
  - - thought to have highest risk of bleeding complications; Reversal agents not readily available

• **Aspirin**
  - + PO without monitoring, lowest risk of bleeding complications
  - - no reversal agent, highest risk of VTED
The Holy Grail

• The VTE prophylaxis regimen that is:
  • Least potent
  • Most effective
  • Most convenient

• Must reduce risk of:
  • #1 Fatal PE
  • #2 Non-fatal PE
  • #3 Wound Healing Complications
  • #4 Symptomatic DVT
DOAC’s – High Risk of Bleeding?

- Metaanalysis
- Standard dosing for A-fib is 5mg BID
- Apixaban 2.5mg BID is comparable to enoxaparin BID in both safety and efficacy when used as VTE prophylaxis post-arthroplasty
- *Results underpowered*
DOAC’s – No Reversal Agent?

Specific antidotes against direct oral anticoagulants: A comprehensive review of clinical trials data

Ramyashree Tummala a, Ana Kavtaradze a, Anjan Gupta b, Raktim Kumar Ghosh a,*

- Activated charcoal, hemodialysis, activated prothrombin complex non specific and non-effective agents
- Adexanet – reversal agent for Xa inhibitors (rivaroxaban, apixaban)
  - Complete reversal within minutes
  - Currently in Phase IV trial
- Aripazine – reversal agent for Xa inhibitors, dabigatran, and heparinoids
  - Currently in Phase II trial
ASA – Effective Enough to Prevent Clots?

Fatal pulmonary embolism following elective total hip arthroplasty

a 12-year study

E. Bayley, S. Brown, N. S. Bhamber, P. W. Howard

• 7983 THA subjects in national database
• 3 fatal PE’s within 42 days of surgery
• 2 on LMWH, 1 on ASA
• Conclusions:
  • ASA is non-inferior to LMWH
  • LMWH had higher all-cause mortality than ASA
ASA – Effective Enough to Prevent Clots?

Aspirin Versus Anticoagulation for Prevention of Venous Thromboembolism Major Lower Extremity Orthopedic Surgery: A Systematic Review and Meta-Analysis

• Metaanalysis: 1408 participants
• ASA vs anticoagulants
• Hip Fracture: comparable bleeding rates, VTE rate higher with ASA
• Arthroplasty: comparable bleeding and VTE rates between ASA and anticoagulant groups
ASA – Effective Enough to Prevent Clots?

A Comparison of Two Dosing Regimens of ASA Following Total Hip and Knee Arthroplasties

Michael J. Feldstein, MD, SM a, *, Sara L. Low, MD b, Antonia F. Chen, MD, MBA c, Laura A. Woodward, DNP, ANP-C c, William J. Hozack, MD c

- RCT: ASA 325 BID versus ASA 81 BID for TJA

- 1 DVT in 81 group, none in 325 group
- Rate of GI Bleed Comparable between 2 groups (0.9% vs 0.7%)
- Less GI upset/Nausea in 81 group (0.8% vs 3.2%)
Chemoprophylaxis - 2016

• Warfarin
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  • – requires monitoring, difficult to maintain within target range, early paradoxical hypercoagulability

• Heparins
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Risk Stratification

Individualized Risk Model for Venous Thromboembolism After Total Joint Arthroplasty

Javad Parvizi, MD, FRCS, Ronald Huang, MD, Maryam Rezaee, MS, Behrad Bagheri, MS, Mitchell G. Malenfort, PhD

- Metastatic Cancer
- Chronic pulmonary heart Dz
- Hypercoagulability State
- Sepsis
- Stroke
The Effectiveness of a Risk Stratification Protocol for
Thromboembolism Prophylaxis After Hip and Knee Arthroplasty

Denis Nam, MD, MSc, Ryan M. Nunley, MD, Staci R. Johnson, Med, James A. Keeney, MD, John C. Clohisy, MD, Robert L. Barrack, MD

Age ≥70 y

History of deep vein thrombosis with negative preoperative ultrasound examination

Active cancer

Hypercoagulable states (protein C, protein S, factor V Leiden, and so forth)

Multiple medical comorbidities (2 of the following 3 conditions: heart disease, lung disease, diabetes)

Morbid obesity (BMI ≥40 kg/m²)

Family history of deep vein thrombosis or pulmonary embolism

Immobility (ie, limited weight bearing)—surgeon’s discretion
Individualized Risk Model for Venous Thromboembolism After Total Joint Arthroplasty

Javad Parvizi, MD, FRCS \textsuperscript{a}, Ronald Huang, MD \textsuperscript{a}, Maryam Rezapoor, MS \textsuperscript{a}, Behrad Bagheri, MS \textsuperscript{b}, Mitchell G. Maltenfort, PhD \textsuperscript{a, *}

\textsuperscript{a} Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA
\textsuperscript{b} University of Maryland School of Medicine, Baltimore, Maryland, USA

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**Risk Factors**
- History of Hypercoagulable State
- History of Venous Thromboembolism (VTE)
- Active Cancer
- History of Non-Cutaneous Malignancy
- Pulmonary Hypertension

**Patient History**
- Surgery Type:
  - Unilateral
  - Bilateral

**Medical History**
- Chronic Inflammatory Bowel Disease
- Recent Severe Weight Loss
- Varicose Veins
- Obstructive Sleep Apnea
- History of MI
- Myeloproliferative Disorders
- Congestive Heart Failure

**Results**
- Age: 65
- Unilateral
- Recent Severe Weight Loss
- Varicose veins

You need to consider the use of strong anticoagulation drugs such as LMWH, Pentasaccharide, Warfarin, factor X inhibitors.
Risk Stratification

- **High Risk (20%)**
  - Warfarin
    - Goal INR 1.8-2.2
  - Factor Xa inhibitors (apixaban, rivaroxaban)
    - *1/2 Dose
  - Heparinoids (LMWH)

- **Standard Risk (80%)**
  - ASA 81mg PO BID x 4 weeks
Case 1

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- Now what?...
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    - If unsuccessful, then **2-stage Exchange for Infection**
  - How do you reverse Eliquis? How long do you wait to operate?
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Hip/Knee Pain: When to Refer/Red Flags
Case 3: BD

- 74 M, rheumatoid arthritis, CAD, COPD, h/o gastric ulcer
- Progressive Left knee deformity has made it difficult to walk over the past 18 months
- Reliant on Wheelchair in Home now, self transfers
- Reports “mild” pain; Denies significant injury/event
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AAOS Clinical Practice Guidelines “Treatment of Osteoarthritis of the Knee” – 2013

Strong Recommendations

- **Recommended**
  - Self-Management, Strengthening, Low-Impact Aerobic Exercise, Neuromuscular Education
  - **NSAIDs**
  - Tramadol
  - Weight loss for BMI >25 (*Moderate)

- **Not** recommended (lack of efficacy, no evidence of harm)
  - Hyaluronic acid
  - Acupuncture
  - Glucosamine/Chondroitin
    - Individual studies: benefit vs placebo
    - Metaanalyses: NO statistically significant benefit over placebo
Inconclusive Recommendations

- Manual therapy (i.e. massage, chiropractic, joint mobilization)
- Electrotherapeutic modalities (i.e. TENS)
- Unloader brace
- Heel wedges
- Unable to recommend for or against Tylenol, opioids, or pain patches
- Unable to recommend for or against intraarticular corticosteroids
- Unable to recommend for or against growth factor injections or PRP
Platelet-Rich Plasma

- Since AAOS CPG in 2013, additional studies with mounting evidence in support of PRP
- Current data now suggests:
  - Intraarticular PRP > Placebo
  - Intraarticular PRP > Hyaluronic acid
  - Intraarticular PRP is less effective with more advanced DJD
- It remains unclear how PRP compares to intraarticular corticosteroids
- Technical details remain to be sorted out:
  - Leukocyte rich vs leukocyte poor
  - Single vs. double spinning technique
  - Single vs. multiple injections
  - $$$

Systematic Review


Efficacy of Intra-articular Platelet-Rich Plasma Injections in Knee Osteoarthritis: A Systematic Review

Carlos J. Meheux, M.D., Patrick C. McCulloch, M.D., David M. Lintner, M.D., Kevin E. Varner, M.D., and Joshua D. Harris, M.D.
Bottom Line

• Platelet Rich Plasma
  • AAOS: Cannot recommend for nor against
JAMA Clinical Evidence Synopsis

December 27, 2016

Intra-articular Corticosteroids for Osteoarthritis of the Knee

Bruno R. da Costa, PhD; Roman Hari, MD; Peter Jüni, MD, FESC

• Metaanalysis
  • *more liberal than prior metaanalyses via inclusion of steroid plus lavage/exercise studies versus Placebo
• Intraarticular corticosteroids versus Placebo
  • Moderate improvement in Pain thru 2, minimal thru 6 weeks
  • Minimal improvement in Function thru 6 weeks
Original Investigation
May 16, 2017

Effect of Intra-articular Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients With Knee Osteoarthritis
A Randomized Clinical Trial

Timothy E. McAlindon, DM, MPH¹; Michael P. LaValley, PhD²; William F. Harvey, MD¹; et al

- Intraarticular corticosteroid versus Placebo
  - At 2 years, no difference in pain
  - At 2 years, greater decrease in cartilage volume in steroid group
  - Conclusion: Intraarticular steroids do not alleviate pain, but do accelerate cartilage degeneration
  - Recommendation: Intraarticular steroids should not be routinely used
Bottom Line

- Intraarticular Steroids
  - AAOS: Cannot recommend for nor against
**TABLE I:**

Rates of Accuracy of Intra-Articular Injections

<table>
<thead>
<tr>
<th>Portal</th>
<th>Total No. of Injections</th>
<th>Placement of Needle (no. of injections)</th>
<th>Accuracy Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Extra-Articular</td>
<td></td>
</tr>
<tr>
<td>Anterolateral</td>
<td>80</td>
<td>23</td>
<td>71%</td>
</tr>
<tr>
<td>Anteromedial</td>
<td>80</td>
<td>20</td>
<td>75%</td>
</tr>
<tr>
<td>Lateral midpatellar</td>
<td>80</td>
<td>6</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intra-Articular</td>
<td></td>
</tr>
</tbody>
</table>
Schematic representation of the anterolateral (AL) and anteromedial (AM) portals.
Diagram showing the lateral midpatellar portal.
Part 2: The Path to TJR/When to Refer

Knee Pain & DJD on Imaging

- Weight Loss
- Activity Modification
- Strengthening *if weak
- OTC NSAIDs PRN (Topical if GI intolerance)
- Walking Aids
Knee Pain & DJD on Imaging

- Weight Loss
- Activity Modification
- Strengthening *if weak
- OTC NSAIDs PRN
- Walking Aids

Rx NSAIDs

Intraarticular Corticosteroid Injection (every 3 mos, indefinitely)

Tramadol

Arthroplasty
Modifiable Risk Factors Are Common in Early Revision Hip and Knee Arthroplasty

James R. Kee, MD *, Simon C. Mears, MD, Paul K. Edwards, MD, C. Lowry Barnes, MD

- >40% of Revision TJA Patients had 1+ Modifiable Risk Factor
- Infected THA Patients were More likely to have BMI >40
- Infected TKA Patients were more likely to smoke & have poor dentition
Optimization of Modifiable Risk Factors

- **Weight Loss**
  - Soft Cutoff of BMI 40
- **Smoking Cessation**
  - Trend towards absolute contraindication
- **Diabetes Management**
  - HbA1c <7.5, though perioperative BG most important
- **Dentition**
- **Malnutrition**
  - If Prealbumin, transferrin, ALL low -> Boost, etc.
- **Vitamin D**
- **MRSA Colonization**
Optimization of Modifiable Risk Factors

- Weight Loss
  - Soft Cutoff of BMI 40

Percentage of Patients with Combined Complications by BMI

<table>
<thead>
<tr>
<th>BMI Range</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5-24.99</td>
<td>15.36</td>
</tr>
<tr>
<td>25-29.99</td>
<td>14.55</td>
</tr>
<tr>
<td>30-34.99</td>
<td>15.56</td>
</tr>
<tr>
<td>35-39.99</td>
<td>15.84</td>
</tr>
<tr>
<td>40-44.99</td>
<td>16.78</td>
</tr>
<tr>
<td>45-49.99</td>
<td>17.96</td>
</tr>
<tr>
<td>&gt;50</td>
<td>23.81</td>
</tr>
</tbody>
</table>

Complications of Morbid Obesity in Total Joint Arthroplasty: Risk Stratification Based on BMI

Derek T. Ward, MD \(^a\), Lionel N. Metz, MD \(^a\), Patrick K. Horst, MD \(^a\), Hubert T. Kim, MD, PhD \(^a\), Alfred C. Kuo, MD, PhD \(^b\)
Hypoalbuminemia is a better predictor of postoperative TJA complications than obesity.

Hypoalbuminemia actually increases with increasing obesity.
• Retrospective review 126 Revision TJA
• Low Vitamin D was found to be independently associated with increased risk of 90 day complications as well as infection after Revision TJA
• Low Vitamin D was not found to be associated with malnutrition
Red Flags

• 4 Item Screen for Urgent Hip/Knee Pain
  • Are you able to **Bear Full Weight**?
  • Does your Hip/Knee Feel as though it **Gets Stuck/Locks**?
  • Have you noticed **Worsening/Progressive Deformity**?
  • Have you noticed **Diminishing Range of Motion**?
Inability to Bear Weight

- Stress Fracture
- Occult Fracture
Acute Knee Pain with Mechanical Symptoms

- Meniscal Tear/Flap can Create Mechanical Block to Motion
- Even with DJD, Mechanical symptoms that persist despite rest, NSAIDs, and Injections can be appropriate for surgery
Progressive Valgus Deformity

- Surgery Becomes Less Predictable with Advanced Valgus Deformity
Progressive ROM Loss

- ROM with DJD can be difficult to regain, even with Surgery
Case 3: BD

- 74 M, rheumatoid arthritis, CAD, COPD, h/o gastric ulcer
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- +/- PT
- No NSAIDs (PUD)
- +/- Intraarticular Steroids
- *Progressive Loss of ROM
- *Progressive Valgus Deformity

- Preoperative Optimization of Modifiable Risk Factors
  - *Malnutrition/Vitamin D
Dissatisfaction with Previous TJR
Dissatisfaction with Previous TJR
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