Anticoagulation in the Geriatric Patient: Detailed Issues in the Perioperative Period

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THE AMERICAN GERIATRICS SOCIETY
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CONTENT

• Review more detailed issues related to:
  - Warfarin
  - Heparins
  - Other agents

• Preoperative issues
  - Reversal
  - Timing of surgery

• Postoperative issues
  - What to use
  - Duration
WHY ARE PATIENTS ANTICOAGULATED?

• Cardiac — arrhythmia, valvular heart disease, thrombus, MI, stent

• Cerebrovascular — CVA, TIA

• Thromboembolic disease — DVT, PE
## REDUCTION IN RISK OF EMBOLISM WITH WARFARIN

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk without warfarin</th>
<th>Risk with warfarin</th>
<th>RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT, first 3 months(^1)</td>
<td>50%</td>
<td>4%–10%</td>
<td>80%–90%</td>
</tr>
<tr>
<td>Recurrent VTE, hypercoagulable states, cancer(^2)</td>
<td>15%/yr</td>
<td>3%/yr</td>
<td>80%</td>
</tr>
<tr>
<td>Non-valvular a-fib(^3)</td>
<td>4%–5%/yr</td>
<td>1%–2%/yr</td>
<td>65%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.5%/yr</td>
<td>N/A</td>
<td>81%</td>
</tr>
<tr>
<td>EF ≤28%(^4)</td>
<td>2.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical valve</td>
<td>4%/yr</td>
<td>0.7%–1%</td>
<td>75%–82%</td>
</tr>
</tbody>
</table>

FOR PTS ADMITTED ON WARFARIN

• Check INR level
  ➢ Goal for most conditions is 2–3
  ➢ Patients in typical outpatient practice are outside target range 50% of time

• Surgery goal: INR < 1.5

• Treatment options
  ➢ Vitamin K¹
  ➢ Fresh frozen plasma
  ➢ Waiting

VITAMIN K FOR COUMADIN REVERSAL: ORAL VS. IV

- Randomized trial
- Pts with INR 6–10 got 0.5 mg IV or 2.5 mg PO
- Pts with INR > 10 got 1 mg IV or 5 mg PO
- At 6 hours, IV was better
- At 24 hours, equivalent
- IV more likely to overcorrect

FRESH FROZEN PLASMA ALGORITHM

• Give 10–15 mg/Kg
• 1 unit = 190–240 mL
• **Example:** A person who weighs 70 kg needs 700–1050 mg, which is about 4 units of FFP

• Remember that FFP only lasts 6 hours
PTS ADMITTED ON CLOPIDOGREL

- Clopidogrel inhibits platelet aggregation
- PDR recommends discontinuing clopidogrel 5 days before elective surgery
- Survey: 73% of ortho residency programs felt waiting ≤3 days ok; 23% felt no delay needed\(^1\)
- Delay is associated with ↑ LOS and 30-day mortality\(^2\)
- ? Platelet transfusion
- No neuroaxial anesthesia

<table>
<thead>
<tr>
<th>Agent</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin</td>
<td>0.5 – 2 hours</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>2.1 – 5 hours</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>4.5 – 7 hours</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>18 hours</td>
</tr>
</tbody>
</table>
POSTOPERATIVE ANTICOAGULATION

- DVT incidence without prophylaxis is up to 75%; PE is 15%–20%
- Fatal PE occurs in 4%–7%
- Process starts early\(^1\)
- ACCP: Hip fracture surgery is highest risk for VTE\(^2\)
- DVT prophylaxis — not just meds!
- Little evidence about best regimen

\(^1\)Injury. 1999;30:605. \(^2\)Chest. 2004;126:338S.
RISK FACTORS FOR THROMBOEMBOLISM

- Advanced age
- Malignancy
- Previous VTE
- Obesity
- Heart failure
- Paralysis
- Presence of an inhibitor deficiency state
UNFRACTIONATED HEPARIN

- Wait 12–24 hours after surgery to start anticoagulation, to avoid bleeding

- Low-dose heparin (5000 units SC BID)
  - Meta-analysis (n=623) — 64% RRR of DVT vs. placebo¹
  - Only 2 studies specifically in hip fracture pts
    - Significant reduction in VTE
    - Wide confidence intervals
  - RCT of heparin 5000 U TID vs. dalteparin 5000 U daily²:
    - DVT 14% vs. 32% by venogram
    - High probability VQ 0% vs. 14%

LOW-MOLECULAR-WEIGHT HEPARIN: ENOXAPARIN, DALTEPARIN

- Well absorbed from SC administration
- Cleared primarily by kidney
- Less likely to induce thrombocytopenia
- Can be dosed daily
- Dalteparin 5000 units daily vs. placebo (n=68) led to 50% RRR (58% vs. 30%) of DVT incidence\(^1\)
- Cochrane review:
  - Insufficient evidence about whether LMWH is superior to unfractionated heparin
  - Insufficient evidence for either LMWH or unfractionated heparin regarding PE prevention or mortality

\(^1\)Clin Orthop Relat Res. 1992;278:95.
WARFARIN

- Inhibits Vitamin K–dependent factors
- Many drug interactions
- Frequent monitoring (but no injections)
- Long half-life
- Goal of INR of 2–3
- Some recommend bridge with LMWH or fondaparinux until therapeutic
WARFARIN — COMMON INTERACTIONS

<table>
<thead>
<tr>
<th>Increased effect</th>
<th>Decreased effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>Anti-seizure</td>
</tr>
<tr>
<td>• Cipro</td>
<td>• Carbamazepine</td>
</tr>
<tr>
<td>• Erythromycin/clarithromycin</td>
<td>• Phenytoin</td>
</tr>
<tr>
<td>• Metronidazole</td>
<td>• Phenobarbital</td>
</tr>
<tr>
<td>• Trimethoprim / sulfamethoxazole</td>
<td></td>
</tr>
<tr>
<td>Cardiac: Amiodarone</td>
<td>Herbal meds: Alfalfa, ginseng, St. John’s</td>
</tr>
<tr>
<td></td>
<td>wort</td>
</tr>
<tr>
<td>GI</td>
<td></td>
</tr>
<tr>
<td>• Omeprazole</td>
<td></td>
</tr>
<tr>
<td>• Cimetidine</td>
<td></td>
</tr>
<tr>
<td>Endocrine: L-thyroxine</td>
<td></td>
</tr>
<tr>
<td>CNS: Alcohol</td>
<td></td>
</tr>
</tbody>
</table>
WARFARIN EFFICACY

• Warfarin (INR goal 2–2.7) vs. ASA 650 mg/day vs. placebo¹
  ➢ VTE: 20% warfarin, 41% ASA, 46% placebo ($P = .005$)
  ➢ Prox DVT/PE: 9% vs. 11% vs. 30% ($P = .001$)

• 3 other trials of warfarin vs. placebo show 61% RRR for DVT

• No direct comparison with low-dose unfractionated heparin; RRR similar

• Warfarin vs. LMWH: incidence of VTE 21% vs. 7%—but:
  ➢ INR target of 1.5
  ➢ Endpoint of asymptomatic DVT

EFFECTS OF AGE ON WARFARIN

• Age-related decline in metabolism +/− clearance

• Warfarin is 99% protein-bound

• Age-related reduction in albumin
  ➢ Lower with poor nutrition

• Changes in pharmacodynamics
  ➢ Interactions (metabolism Cy P450, protein-protein binding)
  ➢ Comorbidities — Liver compromise and CHF

• ↓ doses in women (BMI)
## INITIATING WARFARIN IN ELDERLY MEDICAL INPATIENTS

**Table 1** Loading dose schedule for warfarin initiation according to the international normalized ratio in elderly patients*

<table>
<thead>
<tr>
<th>Day</th>
<th>INR value 10 AM</th>
<th>Warfarin dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>Do not measure</td>
<td>4</td>
</tr>
<tr>
<td>Day 1</td>
<td>Do not measure</td>
<td>4</td>
</tr>
<tr>
<td>Day 2</td>
<td>Do not measure</td>
<td>4</td>
</tr>
<tr>
<td>Day 3</td>
<td></td>
<td>Predicted maintenance dose</td>
</tr>
<tr>
<td>&lt;1.3</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>1.3 ≤ INR &lt; 1.5</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>1.5 ≤ INR &lt; 1.7</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>1.7 ≤ INR &lt; 1.9</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>1.9 ≤ INR &lt; 2.5</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>INR ≥ 2.5</td>
<td></td>
<td>Measure INR daily and omit doses until INR &lt; 2.5, then give 1 mg</td>
</tr>
</tbody>
</table>

*INR = international normalized ratio. *This algorithm does not apply to patients who have received warfarin within the preceding week, or who have a pretreatment INR > 1.3. 

FONDAPARINUX

• Binds to antithrombin, inactivating factor Xa

• Fondaparinux 2.5 mg vs. enoxaparin 40 mg daily (n=1,711):¹ VTE incidence of 8% vs. 19%

• Caveats:
  ➢ Contraindicated for <50 kg or CrCl < 30 mL/min
  ➢ “New kid on the block”

# COST OF MEDICATIONS

<table>
<thead>
<tr>
<th>Medication</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fondaparinux 2.5 mg</td>
<td>$67.43</td>
</tr>
<tr>
<td>Enoxaparin 40 mg</td>
<td>$46.09</td>
</tr>
<tr>
<td>Unfractionated heparin 5000 units</td>
<td>$3.07</td>
</tr>
<tr>
<td>Warfarin 5 mg</td>
<td>$1.43</td>
</tr>
</tbody>
</table>
ANTIPLATELET THERAPY

• Patients treated with aspirin have an OR of 0.69 for DVT and 0.40 for PE\(^1\)

• Risk reduction is less than for other agents
  - **LMWH vs. ASA:** DVT/PE incidence 28% vs. 44%\(^2\)
  - **Warfarin vs. ASA vs placebo:** 20% vs. 41% vs. 46%\(^3\)

\(^1\) BMJ. 1994;308:235.
\(^3\) Arch Intern Med. 1989;149:771.
VENA CAVA FILTERS: POTENTIAL INDICATIONS

• Can’t anticoagulate
• GI bleeder
• Multiple clots in past
• Protein deficiency
DURATION OF PROPHYLAXIS

- Optimal duration unknown
- Most authorities recommend 2–4 weeks or until mobile
- PENTHIFRA-PLUS (n=656)¹
  - All received 6–8 days of daily fondaparinux, then randomized to 19–23 days of fondaparinux 2.5 mg/day SC or placebo
  - Incidence of VTE 1.4% vs. 35.0% (RRR = 95.9%)
  - Trend toward more major bleeding with fondaparinux
  - No difference in incidence of bleeding leading to death, reoperation, or critical organ bleeding

¹Arch Intern Med. 2003;163:1337.
RECOMMENDATIONS

• American College of Chest Physicians
  ➢ Recommends against the use of aspirin alone as thromboprophylaxis (Grade of evidence: 1A)
  ➢ Routine prophylaxis with
    • Fondaparinux (Grade 1A)
    • LMWH (Grade 1B)
    • Warfarin (INR target 2.5, range 2–3; Grade 1B) or
    • LDUH (Grade 1B)
  ➢ Continue thromboprophylaxis >10 days up to 35 days

• American Society of Regional Anesthesia
  ➢ For those with spinal anesthesia, do not remove catheter until 12 hours after LMWH dose given
  ➢ Once catheter pulled, wait 2 hours before next dose
  ➢ No guidance about fondaparinux
JCAHO, CMS, AND LIABILITY

- Risk assessment
- Pay for performance measures / SCIP
- PQRI 2009 (#23) “Peri-operative Care: VTE Prophylaxis”
- Scorecard performance
- Liability for no therapy

www.cms.gov  PQRI, 2009
TAKE-HOME POINTS

• For patients who are anticoagulated on admission, assess short-term risk of venous and arterial emboli

• Hip fracture patients are in the highest risk group for VTE

• Limiting time to surgery is part of a comprehensive VTE prophylaxis program

• There is no clear choice for postoperative prophylaxis — individualize treatment
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