Optimization of Use of Anti-Thrombotic Medications and Treatment of Thrombotic Disorders

Patrick Klem, PharmD, BCPS
Katrina Babilonia, PharmD
The Who:
Anticoagulation Subcommittee

- Provide oversight for the safe use of anti-thrombotic medications at UCH
- Specifically charged with addressing regulatory requirements for safe and effective use of anticoagulation
- Interdisciplinary effort to work with physicians, nurses, departments, units, etc.

Co-chairs: Patrick Klem Toby Trujillo
MD Director: Kathy Hassell
Members:
Katrina Babilonia
Carolee Whitehill
Kristen Nordenholz
Greg Misky
Deborah Sherman
Dora Cheung
Chris Steckline
Larry Golightly
Sondra May
Ty Kiser
Carol Ruscin
The Who:
Anticoagulation Management Services

- **ACP Anticoagulation Clinic**
  - Established, Pharmacist manned
    - Patrick Klem
    - Gina Woodhouse
    - John Baer
  - Following approximately 450 patients
  - Establish Standards for use of anti-thrombotic medications in ambulatory clinics

- **Inpatient Anticoagulation – Thrombosis Management Service**
  - Available M-F 7 am to 5 pm
  - Pharmacy personnel
    - Toby Trujillo
    - Katrina Babilonia
    - Amy Go
  - 10% FTE for Medical Director
    - Kathy Hassell
  - Prospective surveillance of patients on warfarin, DTI’s, UFH and LMWH
The What:

Current Formulary Antithrombotic Agents UCH

- **IV/SQ anticoagulants**
  - Unfractionated Heparin (UFH)
  - Low Molecular Weight Heparin (LMWH)
    - Dalteparin
    - Enoxaparin
  - Fondaparinux
  - Argatroban
  - Bivalirudin

- **Oral anticoagulants**
  - Warfarin

- **Oral Antiplatelets**
  - ASA
  - Clopidogrel
  - Prasugrel

- **IV Antiplatelet Agents**
  - Abciximab (Reopro)
  - Eptifibatide (Integrelin)

- **Other**
  - Fibrinolytics
National Mandates on Safe Practices with Anticoagulation

- Joint Commission
  - NPSG
  - VTE Core Measures
- CMS
  - Never events
  - SCIP
- NQF
- Leapfrog

Institutions Need to have a coordinated and standardized approach to the safe and effective use of anti-thrombotic medications
2008 National Patient Safety Goals and Requirements

• Requirement 3E
  – Reduce the likelihood of patient harm associated with the use of anticoagulant therapy involving UFH, LMWH, warfarin, and other anticoagulants

• Rationale for Requirement 3E
  – “Medication management is one of the more complex processes used in caring for patients. Using anticoagulants is a high risk treatment and commonly leads to adverse drug events due to the complexity of dosing and monitoring of these medications and patient compliance with outpatient therapy”

National Patient Safety Goals

Requirement 3E: Selected Implementation Expectations

• Anticoagulation management program individualizes care to each patient
• When available, use only oral unit dose products and pre-mixed infusions
• Dispense warfarin in accordance with established monitoring procedures and monitor INR in all warfarin patients
• Use approved protocols for each anticoagulant for each condition treated
• Notify dietary services of all warfarin patients (use food/drug interaction protocol)
• Use programmable infusion pumps for heparin infusions
• Policies for baseline & ongoing lab testing for heparin and LMWH
• Anticoagulation therapy education to prescribers, staff, patients & families
• Patient/ caregiver education includes:
  – Importance of follow-up monitoring
  – Compliance issues
  – Dietary restrictions
  – Potential adverse effects and drug interactions
### The Joint Commission/NQF VTE Performance Measures

#### Risk Assessment and Prophylaxis

1. Documentation of VTE risk/prophylaxis within 24 hours of hospital admission
2. Documentation of VTE risk/prophylaxis within 24 hours of transfer to ICU

#### Treatment

3. VTE patients with overlap of parenteral and warfarin anticoagulation therapy
4. VTE patients receiving UFH with platelet monitoring
5. VTE discharge instructions

#### Outcomes

6. Incidence of potentially preventable hospital-acquired VTE

Anticoagulation Resources

- **Policies/Guidelines**
  - *UCH Policy and Procedure*
  - *Ambulatory Guideline*
  - *Acute Care Guideline*

- **Available order sets**
  - Anticoagulation Management Orders
  - Unfractionated Heparin
  - HIT/DTI
  - LMWH interchange

- **Other Resources**
  - Anticoagulation Calculators
  - Decentralized pharmacist
  - Inpatient anticoagulation service
Access to Policies/Guidelines

Policy and Procedure
Access to Polices/Guidelines

Policy and Procedure

Addresses issues considered all or none. Many NPSG’s are addressed here, as well as policies governing ambulatory AC management
Access to Policies/Guidelines
Acute and Ambulatory Guidelines
Access to Policies/Guidelines

Acute and Ambulatory Guidelines

Anticoagulation Management Orders – needed to refer patient to outpatient anticoagulation clinic

Acute Care Guideline - Provides guidance on the appropriate use (dosing-monitoring-therapeutic selection) of warfarin, UFH and LMWH in the acute care setting. In addition, the appropriate use of fondaparinux, as well as direct thrombin inhibitors is also addressed.

Ambulatory Care Guideline - It provides guidance on a number of anticoagulation management issues such as dosing/monitoring/patient education with warfarin, bridge therapy, as well as quality assurance measure for managing warfarin therapy.
Anticoagulation management program individualizes care to each patient

- Anticoagulant Subcommittee
  - ACP Anticoagulation Clinic
    - Standards/Policies
  - Inpatient Service
    - Standards of Practice for anti-thrombotic medications in development.
    - Goal implementation by end of year 2008
      » Order sets
      » Guidelines
National Patient Safety Goals

Yes/No expectations

• The hospital uses approved protocols for the initiation and maintenance of anticoagulant therapy
  – Existing Protocols
    • IV heparin, LMWH interchange program, DTI protocol
    • Warfarin guidelines need to be developed
    • Implementation by end of year 2008 in conjunction with standards of practice
National Patient Safety Goals

Yes/No expectations

• Notify dietary services of all warfarin patients and dietary responds accordingly according to food-drug interaction policy
  – Process in development between dietary and pharmacy
  – Goal implementation by end of year 2008

• Use programmable infusion pumps for heparin infusions
  – Done
National Patient Safety Goals

Yes/No expectations

• Hospital has a written policy for baseline & ongoing lab testing for UFH and LMWH
  – Will be addressed with development of Standards of Practice
  – Goal implementation by end of year 2008

• When available, use only oral unit dose products and pre-mixed infusions or pre-filled syringes are used
  – Done
National Patient Safety Goals

Ongoing Measurement Expectations

- Patients started on warfarin will have a baseline INR available, and for all patients receiving warfarin therapy a current INR is available
  - *Will be addressed with development of Standards of Practice*
  - *Goal is 100% compliance*
  - *Assessment every 6 months*
    - Reasonable sampling of patients retrospectively
    - Attempt to automate the process
The hospital provides education regarding anticoagulation therapy to prescribers, staff, patients and families

- Will be addressed with development of Standards of Practice
- Major goal is that all patients discharged from UCH on anticoagulant therapy receive appropriate education as defined in policy
  - Goal is 100%
  - Every 6 month evaluation
  - Development of a standard discharge note that will standardize process as well as facilitate assessment
The hospital evaluates its anticoagulation safety practices, takes appropriate action to improve, and measures the effectiveness.

- Anticoagulant subcommittee regularly reviews PSN’s dealing with anti-thrombotic medications or thrombotic disorders.
- Implementation of system changes to address issues as appropriate.
- Metric – PSN rate dealing with anti-thrombotic medications.
  - Need to establish baseline then track for improvement.
“I need to refer a patient for warfarin follow-up”

• ACP Anticoagulation Clinic is default
  – Anticoagulation Management Order
  – Serves as transition of care for indigent patients
  – Phone: 720-848-0577, pager -1069

• Other anticoagulation clinics for patients with established care:
  – UMGP- Lowry, Boulder, Cardiology
Programs in Development

- VTE Care Pathway – Drs. Misky and Nordenholz
- Standardized VTE prophylaxis risk assessment
Clinical Pearls with Anti-thrombotic Medications

Current Formulary Antithrombotic Agents UCH

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- **Other**
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Unfractionated Heparin (UFH)

• Despite limitations, still widely used  
  – Generally need IV therapy, variable response, need for monitoring

• Key Issues  
  – Weight based nomograms are standard of practice  
  – Dosing differs by indication (therapeutic and prophylaxis)  
  – aPTT goal range is institution specific  
    • 0.2 – 0.4 units/ml  
    • 0.3 – 0.7 anti-Xa units/ml  
  – Reversal  
    • Protamine  
      – 1 mg per 100 units of UFH given in last 3 hours

• Heparin Continuous Infusion Order Set
Low Molecular Weight Heparins (LMWH)

- Enoxaparin (Lovenox)
- Dalterapin (Fragmin)
- Tinzaparin (Innohep)
- UCH Therapeutic Interchange Policy
  - Fragmin preferred agent
  - Exclusions
    - ACS
    - Renal
LMWH’s focus issues

• Dose by indication
  – Enoxaparin (example)
    • Prophylaxis: 30 mg BID or 40 mg QD
    • Treatment: 1 mg/kg BID or 1.5 mg/kg QD

• Dose adjustment for renal dysfunction (CrCl < 30 ml/min)
  – Enoxaparin
    • Prophylaxis: 30 mg QD
    • Treatment: 1 mg/kg QD
  – CI in dialysis or anuria

• Prophy dose adjustment for body size
  – < 50 kg
  – > 150 kg or BMI > 40
LMWH’s focus issues

• Monitoring
  – Generally not needed
  – Special populations
    – Body weight extremes
    – Renal dysfunction with prolonged administration
    – Changes in Vd
  – aPTT not useful
  – Anti-Xa levels can be used
    • Goal peak level 0.5-1.0 units/ml
Optimize the Diagnosis and Treatment of Heparin-Induced Thrombocytopenia (HIT)

- Diagnosis of HIT challenging
  - Current guidelines exist
- Direct thrombin inhibitors are costly medications
- Inpatient Service will proactively follow patients on DTI’s to help encourage appropriate use
  - Goal is to decrease direct costs of DTI’s for treatment of HIT by 20% during January-June of 2009
Direct Thrombin Inhibitors

- Bivalirudin
- Argatroban
- Mainly used in the treatment of heparin induced thrombocytopenia (HIT)
- Bival also an option for patients with acute coronary syndromes and PCI as an alternative to UFH/LMWH
DTI focus issues

- Presence of hepatic or renal dysfunction
  - Renal – avoid lepirudin
  - Hepatic – avoid argatroban
  - Both – bivalirudin best choice

- Dosing for special populations
  - Argatroban
    - Typical dose 2 ug/kg/min
    - Critically ill – 1.0 ug/kg/min
  - Lepirudin
    - Omit bolus in critically ill, renal insufficiency (reduce dose)

- Dosing Per indication
  - Bivalirudin
    - ACS – 0.1 mg/kg bolus, 0.25 mg/kg/hr infusion
    - PCI – 0.75 mg/kg bolus, 1.75 mg/kg/hr infusion

- Monitoring
  - Lepirudin
    - 1.5-2.5 times the patient’s control value
    - Example baseline aPTT 36, goal range 54-90
  - Argatroban/bivalirudin
    - 1.5-2.5 times the patient’s control value
• Immune mediated allergic reaction to heparin/platelet factor 4 complex
  - Leads to global platelet activation
  - Endothelial cell damage and expression of tissue factor
  - Activation of the coagulation cascade and generation of thrombin

• Occurs in up to 5% of patients receiving UFH

• Incidence with LMWH lower (1%)

• Unlike other thrombocytopenias, clinical presentation is thrombosis, not bleeding

• Thrombocytopenia
  - Look for a percentage drop in platelet count, not the absolute number
  - 30-50% drop from baseline
  - Need to exclude other causes of thrombocytopenia

• Timing
  - Immune mediated, so typical onset is 5-7 days after heparin has been initiated
  - Acute presentation can occur is heparin exposure in last 100 days

• Thrombocytopenia can present with or without thrombosis
  - Treatment no different
  - Thrombosis can be venous or arterial
HIT Pathophysiology

1. Formation of PF4–heparin complexes
2. Formation of immune complexes (PF4–heparin–IgG)
3. Platelet activation
4a. PF4 release
4b. Microparticle release
5. EC injury
HIT – Key Treatment Points

• Stopping UFH is not adequate

• If patient develops HIT on UFH, can switch over to LMWH

• Stopping heparin and initiating warfarin alone is not an appropriate management strategy

• If clinical suspicion is strong, alternative anticoagulation with an agent that won’t cross-react with HIT antibodies needs to be initiated immediately after heparin cessation

• Transition to warfarin should take place AFTER platelet count has returned to baseline and will also depend on whether long term anticoagulation is needed
## Evaluation of HIT - 4T’s

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<td><strong>Thrombocytopenia</strong></td>
<td>&gt; 50% fall or nadir of $\geq 20 \times 10^9$</td>
<td>30-50% fall or nadir of $10-19 \times 10^9$</td>
<td>&lt; 30% fall or nadir $&lt; 10 \times 10^9$</td>
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<td><strong>Timing of platelet</strong></td>
<td>Yes (day 5-10) or &lt; day 4 (recent heparin)</td>
<td>Possible (&gt; day 10)</td>
<td>No (&lt; day 4) with no recent exposure</td>
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<td><strong>count fall consistent</strong></td>
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Fondaparinux focus issues

• Dose by indication
  • Prophylaxis: 2.5 mg QD
  • Treatment ACS: 2.5 mg QD
  • Treatment VTE: 5 mg (< 50 kg), 7.5 mg (50-100 mg), 10 mg (> 100 kg)

• Dose adjustment for renal dysfunction
  – Not available, contraindicated in patients with Clcr < 30 ml/min, anuria, dialysis

• Monitoring
  – Generally not needed
  – Minimal info on whether anti-Xa can be used