Clinical and Economic Value of Anti-Xa Monitoring in Patients Receiving Unfractionated Heparin

Kathy Shingler, MT (ASCP)
Clinical Hemostasis
Disclosure

• Financial relationship of presenter: Employed by Instrumentation Laboratory

• The study presented in this presentation has been funded by Instrumentation Laboratory and has been accepted for publication. The retrospective cohort study assay methods were not restricted to a specific vendor.
Affordable Care Act: Triple Aim

- Improve quality of care
- Enhance patient experience
- Reduce costs through enhanced efficiencies
Objectives

• Describe the role of heparin as an anticoagulant
• Explain why monitoring unfractionated heparin (UFH) with Anti-Xa is superior to aPTT
• Review results of a study comparing Anti-Xa monitoring with aPTT in patients on UFH therapy
• Outline a plan to ensure a smooth transition from aPTT to Anti-Xa monitoring
What is Heparin?

- Widely used anticoagulant discovered in 1916
- Used for treatment and prevention of thrombotic diseases
- Maintains blood fluidity in extracorporeal devices
- Chains of sulfated glycosaminoglycans
- Molecular weight: 5,000 – 30,000 daltons

Heparin Molecule

http://circ.ahajournals.org
Clinical Use of Unfractionated Heparin

- Antithrombotic agent – high dose
  - Acute thrombosis
- Prophylaxis – low dose to prevent thrombosis
  - Pre/post-surgery: orthopedic, general, vascular
  - Prevention of VTE and preeclampsia recurrence during pregnancy
  - Acutely ill patients: congestive heart failure, severe respiratory disease
- Maintenance of arterial and venous lines
  - Possible heparin contamination
- Potentially high-risk
  - “Drug widely used…that has a high risk of patient injury when administered incorrectly.”

Clotting Enzyme Inactivation by Heparin

AT is a slow Inhibitor without heparin
AT is a slow inhibitor without heparin

- Heparin binds to AT through a high-affinity pentasaccharide
- Conformational change to AT converts AT from slow to rapid inhibitor (2-3X)
Clotting Enzyme Inactivation by Heparin

AT is a slow Inhibitor without heparin

- Heparin binds to AT through a high affinity pentasaccharide
- Conformational change to AT converts AT from slow to very rapid inhibitor (2-3X)

- AT binds covalently to clotting enzyme
- Heparin dissociates itself from the complex and can be reutilized

Chest 2008;133: 141-159
Coagulation Cascade: *in vitro* Model

HEPARIN  
A non-specific inhibitor
UFH-Binding Candidates

= Heparin
= AT
= Other Plasma Proteins

EC = Endothelial Cell
M = Macrophage

Monitoring UF Heparin

• For venous thrombosis
  - Heparin Anti-Xa: 0.3 – 0.7 Anti-Xa units
  - aPTT
    • Correlated to 0.3 – 0.7 Anti-Xa units
    • 0.2 – 0.4 units by protamine sulfate titration

• For coronary indications
  - The therapeutic range is unknown but is likely to correspond to heparin levels approximately 10% lower than used to treat patients with VTE

• Monitoring required
  - Variable dose-response rate, due to binding to proteins
  - Varying rates of heparin clearance
  - Ensures patient is not sub-therapeutic or over anti-coagulated

Heparin Monitoring with aPTT

• aPTT - traditional method (1.5 - 2.5x “control”)
  - Based on a retrospective study (1970s)
  - Not confirmed with randomized clinical trials

• In vitro heparin dose-response curve
  - Spiked normal plasma with UFH
  - Not recommended by CAP, over-estimates when compared with patient samples

• Ex vivo heparin therapeutic range using aPTT and Anti-Xa assay
  - Recommended method by CAP

Drawbacks to aPTT

- Does not directly measure heparin
- Variable responsiveness of aPTT reagents
- aPTT cannot be used to monitor LMWH, fondaparinux, rivaroxaban, apixaban, edoxaban
- High base-line aPTT (Lupus Anticoagulant, Factor deficiency)
- Increased Factor VIII, Fibrinogen
Monitoring Anticoagulant Therapy Using the aPTT

- aPTT response to anticoagulant therapy is exaggerated
- Numerous factors may elevate aPTT
  - Concomitant warfarin therapy
  - Lupus anticoagulant
  - Factor deficiency
  - Liver disease
Monitoring with aPTT
Increases in Acute Phase Reactants

- Under-estimates anticoagulation level
- Factor VIII and Fibrinogen increases
  - Can shorten the aPTT in a clinically significant manner
  - Factor VIII increases from 100 - 600% can shorten aPTT by 33-50%
- One cause of *in vitro* drug “resistance”

aPTT vs Anti-Xa in Pregnant Population

Heparin Anti-Xa to aPTT Correlation (Treatment Dosing)

Unpublished study courtesy of Dr. D Adcock
Establishing the Therapeutic Range for aPTT with Anti-Xa

- Preferred method (e.g., ISTH, CAP)

- Collect samples from patients receiving heparin only
  - Normal PT
  - Minimum 50
  - No more than two samples from the same patient

- Perform aPTT and Anti-Xa testing
  - Can freeze samples for Anti-Xa testing later - follow CLSI guidelines
  - If samples are frozen, repeat aPTT after thawing for quality check

- Plot heparin vs aPTT using regression analysis

- Determine the aPTT therapeutic range corresponding to 0.3 - 0.7 U/mL
Therapeutic Heparin Range

Data obtained from a typical hospital laboratory
Evaluation of Outcomes in Anti-Xa Vs aPTT Monitored Patients Receiving Unfractionated Heparin
# Anti-Xa vs APTT Publications

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of Stay</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faster Time to Therapeutic</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Discordant Results</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fewer Dosage Changes/Tests</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Cost per Test</td>
<td></td>
<td></td>
<td></td>
<td>Xa $13.30 vs PTT $13.97</td>
<td>Xa $31.46 vs PTT $27.10</td>
</tr>
<tr>
<td>Adverse Outcomes</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Economic Outcomes</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Number of Sites</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Key Points of the IL Study

- **Scope**
  - Compare performance of Anti-Xa vs aPTT assays for patients on UFH treatment

- **Outcomes with Anti-Xa**
  - Significant hospital cost savings in patient care
  - Significant reduction in patient complications (e.g., major hemorrhage, VTE, mortality)

- **Disease state**
  - Focus on VTE, Acute Coronary Syndrome, Stroke and complications (e.g., hemorrhage, thrombosis)

- **Method**
  - Data Analytics Group retrospective review of key markers in large multi-hospital database

Database Contents

• Hospital characteristics
  - region, bed size, teaching status

• Patient demographics
  - Age, gender

• Diagnosis
  - ICD-9 diagnosis codes, clinical groupings (MS-DRG)

• Procedure
  - ICD-9 procedure codes, CPT codes, procedure date

• Metrics
  - Length of stay, mortality, readmissions
Anti-Xa Study Design

• Create a patient-matching algorithm to identify “like” patients in aPTT and Anti-Xa cohorts

• Matching variables for all populations included:
  - Hospital bed size and teaching status
  - Hospital region
  - Patient age
  - Gender
  - Patient comorbidities
  - Transfers to another facility and left against medical advice
Study Population

Patients on IV UFH discharged over 5 years (2009-2013)

Monitored with aPTT
- Venous Thromboembolism as primary diagnosis (VTE)
- Stroke
- Acute Coronary Syndrome (ACS)

Monitored with Anti-Xa
- Venous Thromboembolism as primary diagnosis (VTE)
- Stroke
- Acute Coronary Syndrome (ACS)

The two cohorts were defined using CPT codes and the name of the assay. Matched cohorts included:
- N= 2207 for Venous Thromboembolism (VTE)
- N= 784 for Stroke
- N= 7411 for Acute Coronary Syndrome (ACS)
<table>
<thead>
<tr>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cost of care</td>
</tr>
<tr>
<td>Length of stay</td>
</tr>
<tr>
<td>Number of monitoring tests</td>
</tr>
<tr>
<td>Number of heparin dose changes</td>
</tr>
<tr>
<td>Readmissions</td>
</tr>
<tr>
<td>In-hospital mortality</td>
</tr>
</tbody>
</table>

**Complications:**
- RBC transfusions
- Protamine Sulfate
- Thromboses
Statistical Methods Used

- **Univariate**: Observing only one variable at a time
  - Numeric data
    - Variance (how widely point varies from the mean)
  - Qualitative data
    - Chi-square (compares the significant difference of two variables)

- **Multi-variate analysis**: Observing multiple variables to isolate the impact of Anti-Xa on outcomes
  - Regression (compares points to show cause and effect)

- $p$ value < 0.05 is considered significant
Venous Thromboembolism (VTE) Results
Median cost of care for patients monitored with Anti-Xa was $808 less than those monitored with aPTT. (N = 2207, p = 0.0022)
**VTE: Number of Heparin Dose Changes**

Average number of heparin dose changes was lower in patients monitored with Anti-Xa.

![Mean Number of Heparin Dose Changes](chart)

<table>
<thead>
<tr>
<th>Method</th>
<th>Mean Number of Dose Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Xa</td>
<td>1.48</td>
</tr>
<tr>
<td>aPTT</td>
<td>1.61</td>
</tr>
</tbody>
</table>

(N = 2207, p = 0.0365)
On average, patients monitored with Anti-Xa had two fewer tests than patients monitored with aPTT.

- For a larger hospital with 75-150 VTE patients on unfractionated heparin annually, this results in a difference of 150-300 tests.

(N = 2207, p < 0.0001)
Patients monitored with Anti-Xa had nearly 5% fewer RBC blood transfusions

- **Average cost of care for patients with a transfusion is twice as much** as those without transfusions ($29,943 vs. $11,248)

(N = 2207, p < 0.0001)
There were no significant differences for in-hospital mortality for patients monitored with Anti-Xa compared to those monitored with aPTT.

(N = 2207, p = 0.9213)
VTE: Multivariate Results

• Evaluation of the cost, length of stay, readmission and mortality measures using multi-variate regression showed estimated savings of $402 for patients with Anti-Xa

  ▪ For a large hospital with 75-150 VTE patients on UFH, this saves $30,000-$60,000 annually
VTE: Multi-variate Blood Complication Results

• Patients tested with aPTT were 2.8 times more likely to get a RBC transfusion than those patients tested with Anti-Xa.

• Controlled for
  - Patient age and gender
  - Diagnostic risks
  - Invasive procedures

The average cost of treating patients with a transfusion was 2x as those without transfusions ($29,943 vs. 11,248).
Stroke Results
The median cost of care for patients tested with Anti-Xa was $3,454 less than those who were using the aPTT; however, this result is not statistically significant.

(N = 784, p = 0.1526)
Stroke: Number of Heparin Dose Changes

The average number of heparin dose changes was lower in patients tested with Anti-Xa.

<table>
<thead>
<tr>
<th></th>
<th>Anti-Xa</th>
<th>aPTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1.67</td>
<td>1.96</td>
</tr>
</tbody>
</table>

(N = 784, p = 0.0276)
On average, patients monitored with Anti-Xa had approximately one more test than those monitored with aPTT.

(N = 784, $p = 0.0104$)
Patients monitored with Anti-Xa had approximately an 8% reduction in RBC transfusions.

- Average cost of care for patients with transfusion is >3X those without ($88,630 vs. $25,575)
No significant difference in hospital mortality for patients monitored with Anti-Xa vs. aPTT

N = 784, p = 0.6705
Stroke Multivariate Results

• Evaluation of the cost, length of stay, readmission and mortality measures using multi-variate regression demonstrated:
  - Estimated savings of $1,932 for patients with Anti-Xa

• For a large hospital with 200-350 stroke patients treated with UFH, this would result in estimated $350,000 - $700,000 savings annually*

• No significant differences in length of stay, readmissions or mortality

Stroke: Multivariate Blood Complication Results

- Patients monitored with aPTT were **2.5 times** more likely to receive an RBC transfusion than those on Anti-Xa
- Study was controlled for:
  - Patient age and gender
  - Diagnostic risks
    - (e.g., anemia, renal insufficiency, trauma)
  - Invasive procedures
    - (e.g., cardiac catheterization, hemodialysis, coronary artery bypass graft)
Acute Coronary Syndrome (ACS) Results
Median cost of care for patients monitored with Anti-Xa was $3,982 less than those monitored with aPTT.

(N = 7411, p < 0.0001)
Average length of stay for patients monitored with Anti-Xa was more than **half a day less** than those monitored with aPTT.
Average number of heparin dose changes was higher in patients monitored with Anti-Xa (N = 7411, p < 0.0001).
ACS: Number of Monitoring Tests Administered

On average, patients monitored with Anti-Xa had **0.44 fewer tests** than those monitored with aPTT.

- For a larger hospital with 500-900 ACS patients on unfractionated heparin annually, this would translate to a difference of 200-400 tests annually.

![](image)

*Mean Number of Tests Administered*

<table>
<thead>
<tr>
<th>Tests</th>
<th>Anti-Xa</th>
<th>aPTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>3.80</td>
<td>4.24</td>
</tr>
</tbody>
</table>

N = 7411, p < 0.0001
Patients monitored with Anti-Xa had nearly **18% fewer** RBC blood transfusions.

- **Average cost of patients with a transfusion was 2x that of those without transfusions ($51,650 vs. $22,373)**

(N = 7411, p < 0.0001)
Mortality rate in patients monitored with Anti-Xa was nearly 1% less than that in patients monitored with aPTT.

\[(\text{N} = 7411, \ p = 0.0275)\]
ACS Multi-variate Results

Evaluation of the cost, length of stay, readmission and mortality measures using multi-variate regression demonstrated:

- **Estimated savings of $741 for patients monitored with Anti-Xa**
  - For a large hospital with 500-900 ACS patients on UFH, annual mean savings estimated to be $350,000 - 700,000

- **Estimated savings of 9.9 hospital hours for patients monitored with Anti-Xa**
  - For a large hospital with 500-900 ACS patients treated with UFH, estimated 200-375 days annually
ACS: Multivariate Blood Complication Results

- Patients monitored with aPTT were 6.3 times more likely to receive a RBC transfusion and 1.7 times more likely to receive protamine sulfate than patients monitored with Anti-Xa.

- Controlled for:
  - Patient age and gender
  - Diagnostic risks
    - (e.g., anemia, renal insufficiency, trauma)
  - Invasive procedures
    - (e.g., cardiac catheterization, hemodialysis, coronary artery bypass graft)
VTE: Summary of the Advantages of Anti-Xa

Anti-Xa

- 2 less tests per VTE patient
- $808 reduction in cost of care per patient
- Fewer RBC transfusions
- Fewer dose changes

aPTT

Note: Length of stay, mortality, readmission, thrombotic complication rate, and protamine titration incidence were not significantly different.
Stroke: Summary of the Advantages of Anti-Xa

Anti-Xa

$3,454 lower cost of care pp
Fewer dose changes
fewer RBC transfusions

aPTT

Fewer monitoring tests

Note: Length of stay, mortality, thrombotic complications, readmission rate and protamine titration incidence were not significantly different.
ACS: Summary of the Advantages of Anti-Xa

- Mortality decreased 1%
- Fewer tests ACS patients
- $3,982 lower cost of care
- 9.9 hour reduction in hospital stay
- 18% fewer RBC transfusions
- Fewer dose changes

Note: Re-admission and thrombotic complication rate were not significantly different
Multi-variate Results

- Examination of the cost, length of stay, readmission and mortality measures using multi-variate regression demonstrated:
  - **Estimated savings of**
    - $402 for VTE patients with Anti-Xa
      - For a large hospital with 75–150 VTE patients treated with UFH, this saves $30,000–$60,000 annually
    - $1,932 for Stroke patients with Anti-Xa
      - For a large hospital with 200–350 Stroke patients on UFH, this saves $350,000–$700,000 annually
    - $741 for ACS patients with Anti-Xa
      - For a large hospital with 500–900 ACS patients on UFH, this saves $350,000–$700,000 annually
    - **9.9 hours ACS for patients with Anti-Xa**
      - For a large hospital with 500–900 ACS patients on UFH, this saves estimated 200–375 hospital days annually
Estimate of Financial Benefit – Large U.S. Hospital

<table>
<thead>
<tr>
<th></th>
<th>VTE</th>
<th>Stroke</th>
<th>ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients/Year</td>
<td>75 – 250</td>
<td>200 – 350</td>
<td>500 - 900</td>
</tr>
<tr>
<td>Cost savings/Patient ($)</td>
<td>402</td>
<td>1932</td>
<td>741</td>
</tr>
<tr>
<td>Savings/year ($)</td>
<td>30,150 – 60,300</td>
<td>386,400 – 676,200</td>
<td>370,500 – 666,900</td>
</tr>
</tbody>
</table>

TOTAL Annual Savings = $790,000 – $1,400,000
Hypothesis to Explain Link Between Decline in RBC Transfusions and Anti-Xa Monitoring

- Anti-Xa assay use focuses more attention on the use of blood products, which causes a reduction in use.
- Monitoring Heparin therapy with Anti-Xa assay involves more specialists in coagulation and transfusion medicine, resulting in more careful, evidenced-based transfusion decisions.
- The use of the Anti-Xa assay provides a more accurate assessment of anticoagulant-associated bleeding risk and, thus, reduces the need for RBC transfusions.
Successful Implementation of the Anti-Xa Assay
Educate and Convince

• Present to pharmacy department to demonstrate value
  - Lab leadership: meet with pharmacy leadership and present data/references demonstrating the benefit of the Anti-Xa assay

• Present the change to caregivers
  - Lab and Pharmacy jointly present to Nursing and Physician leadership
  - Present the benefits of the change
    • Improved patient care
    • Cost benefit
    • More precise measurement of heparin concentration
Add to Electronic Medical Record

• Set up new orderable Anti-Xa assay(s)
  - Include therapeutic ranges for both UFH and LMWH
    • UFH = 0.3 – 0.7 IU/mL
    • LMWH = varies by type
    • List the range for the most commonly used drugs

• Set up new heparin protocol(s) based on Anti-Xa monitoring
  - For VTE (DVT and PE)
  - For ACS/Stroke – patients with an increased risk of bleeding
### Heparin Dosing for VTE

<table>
<thead>
<tr>
<th>Anti-Xa (IU/mL)</th>
<th>Bolus Dose (units/kg)</th>
<th>Stop Infusion (min)</th>
<th>Rate Change (Units/kg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial dose</td>
<td>80</td>
<td></td>
<td>18 (initial rate)</td>
</tr>
<tr>
<td>&lt;0.2</td>
<td>80</td>
<td></td>
<td>Increase by 4</td>
</tr>
<tr>
<td>0.2-0.29</td>
<td>40</td>
<td></td>
<td>Increase by 2</td>
</tr>
<tr>
<td>0.3-0.07</td>
<td>No</td>
<td></td>
<td>No change</td>
</tr>
<tr>
<td>0.71-0.8</td>
<td>No</td>
<td></td>
<td>Decrease by 1</td>
</tr>
<tr>
<td>0.81-0.9</td>
<td>No</td>
<td>30</td>
<td>Decrease by 2</td>
</tr>
<tr>
<td>&gt;0.9</td>
<td>No</td>
<td>60</td>
<td>Decrease by 3</td>
</tr>
</tbody>
</table>
## Low Intensity Heparin Dosing for ACS and Stroke

<table>
<thead>
<tr>
<th>Xa Level</th>
<th>LOW INTENSITY HEPARIN PROTOCOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00 – 0.09</td>
<td>Response: Bolus 25 units/kg; increase infusion by 3 units/kg/hr Next heparin level: 6 hours</td>
</tr>
<tr>
<td>0.10 – 0.19</td>
<td>Response: Increase infusion by 2 units/kg/hr Next heparin level: 6 hours</td>
</tr>
<tr>
<td>0.20 – 0.29</td>
<td>Response: Increase infusion by 1 unit/kg/hr Next heparin level: 6 hours</td>
</tr>
<tr>
<td>0.30 – 0.60</td>
<td>Response: NO CHANGE Next heparin level: 6 hours Once therapeutic x 2, may change to QAM</td>
</tr>
<tr>
<td>0.61 – 0.69</td>
<td>Response: Decrease infusion by 1 unit/kg/hr Next heparin level: 6 hours</td>
</tr>
<tr>
<td>0.70 – 0.79</td>
<td>Response: STOP INFUSION for 1 hr, then decrease by 2 units/kg/hr Next heparin level: 6 hours after restart</td>
</tr>
<tr>
<td>0.80 – 0.89</td>
<td>Response: STOP INFUSION for 1 hr, then decrease by 3 units/kg/hr Next heparin level: 6 hours after restart</td>
</tr>
<tr>
<td>0.90 – 0.99</td>
<td>Response: STOP INFUSION for 2 hr, then decrease by 4 units/kg/hr Next heparin level: 6 hours after restart</td>
</tr>
<tr>
<td>&gt; 1.00</td>
<td>Response: STOP INFUSION for 2 hr, then decrease by 5 units/kg/hr and notify MD Next heparin level: 6 hours after restart</td>
</tr>
</tbody>
</table>

Used with permission from Univ of NM MC Pharmacy
Caregiver Training on New Heparin Protocols

• Nursing continuing education/competency program
  - Available as online presentation or live
  - Educates on **why** the change to Anti-Xa and the benefits

• Physician training
  - Grand Rounds
  - Department meetings
Who to Target: Pharmacy & Therapeutics Committees

• Pharmacy Newsletter Article
  - Briefly describe reason behind the change

Pharmacy Newsletter

A new method for heparin monitoring: Antifactor Xa Assay
Notification of the Change

- Laboratory bulletins
  - Include other hospitals using Anti-Xa (local if possible)
  - Describe assay and its benefits vs. the APTT
  - Include new therapeutic range
  - State what is changing (i.e. dosing nomogram) and what is not
  - Mention that pharmacy is in agreement/involved

Letter courtesy of Dr. Higgins, UHS San Antonio, TX
Challenges to Acceptance

• Need to move beyond a departmental budget and to a focus on **improving patient care**
  - Reagent costs will increase for the lab
  - **Overall cost to the medical center will be reduced**
  - Nursing department must have adequate time for complete training before “going live” with Anti-Xa
Conclusions

- Monitoring UFH therapy with the Anti-Xa assay can help achieve the “Triple Aim” for healthcare improvement
  - **Patient care will improve** by maintaining levels of anticoagulation and reducing RBC transfusions
  - **Patient experience** will improve with fewer tests and fewer dose changes
  - **Cost of hospital care** is reduced
Our Passion.
Your Results.