Learning Objectives

• Explain the differences in heparins

• Discuss assays and approaches for heparin monitoring

• Assess differences and clinical implications for anti-Xa formulations

• List reasons for discordant aPTT and anti-Xa values

• Explain institutional considerations for changing heparin monitoring assays
Agenda

• Heparin introduction
• Methods for heparin monitoring
• aPTT and Anti-Xa discordance
• Discordance case study
• aPTT to Anti-Xa for Heparin Monitoring
• Conclusion
Heparin Introduction
Heparin

• Widely used antithrombotic

• Naturally occurring glycosaminoglycan produced by mast cells
  - Potentiates activity of Antithrombin

• Indications for use
  - Prevention & treatment of thrombosis
  - Drug of choice when rapid anticoagulant effect required
Adapted from: Van de Werf F *Circulation*. 2011;123:1833-1835
Heparin Comparison

**Unfractionated**
- Primarily obtained from porcine intestine
- Varied molecular weight
- Binds to plasma proteins, PF4, macrophages & endothelial cells
  - Limits bioavailability & accounts for varied response
- **MONITORING NECESSARY**

**Low Molecular Weight**
- Derived from UFH by depolymerization
  - Smaller molecules
- Lower affinity for binding proteins other than AT
  - More predictable response
UFH

LMWH

Heparin Use

$4 billion estimated global annual sales\textsuperscript{2}

North America led the global market share of heparin in recent years\textsuperscript{3}

12% expected compound annual growth to 2018\textsuperscript{3}
Venous Thromboembolism (VTE)

VTE

DVT
Deep Vein Thrombosis

PE
Pulmonary Embolism
VTE by the Numbers

An estimated 300,000-600,000 people are affected by VTE annually.

60,000-100,000 Americans are estimated to die each year from VTE.
Deep Vein Thrombosis (DVT)

A blood clot (thrombus) that forms in a deep vein of the leg or pelvis either partially or totally blocking the flow of blood.

Pulmonary Embolism (PE)

1. A Deep Vein Thrombosis (blood clot), or part of it, breaks off from the vein.
2. The break away clot travels through the bloodstream, to the heart and migrates towards the lung.
3. The clot blocks a vessel in the lung, interrupting blood supply.

VTE Risk Factors

- Prolonged immobility
- Major surgery/trauma
- Increasing age
- Cardiac failure
- Pregnancy

Potential Heparin Therapy Complications

Bleeding complications
• Difficult to define risk because dependent on numerous parameters: indication, dosage, method, duration of therapy, patient characteristics, co-medication

Non-bleeding complications
• Caused by heparin binding to proteins other than AT and cells
• HIT is the most severe complication
Heparin Induced Thrombocytopenia

- “Type II”
- Antibody-mediated
- Usually in patients receiving UFH, but reported in patients receiving LMWH and fondaparinux
- Serious form of disease associated with hemorrhage and thrombosis
High Alert Medications

- Drugs that bear risk of causing significant patient harm when used incorrectly

- Antithrombotic agents categorized as “High-Alert Medications” by the Institute for Safe Medication Practices (ISMP)⁶
  - Anticoagulants (e.g. warfarin, low-molecular-weight heparin, IV unfractionated heparin)
  - Factor Xa inhibitors (e.g. Fondaparinux)
  - Direct thrombin inhibitors (e.g. argatroban, bivalirudin, dabigatran etexilate, lepirudin)
  - Thrombolytics (e.g. alteplase, reteplase, tenecteplase)
  - Glycoprotein IIb/IIIa inhibitors (e.g. eptifibatide)
Joint Commission National Patient Safety Goal 03.05.01:

- Aims to reduce the likelihood of patient harm associated with the use of anticoagulant therapy.
  - Applies only to hospitals that provide anticoagulant therapy and/or long-term anticoagulation prophylaxis.

- Rationale:
  Anticoagulation medications are more likely to cause harm due to complex dosing, insufficient monitoring, and inconsistent patient compliance.
Methods for Heparin Monitoring
Heparin Monitoring Assays

APTT

ACT

Anti-Xa
Activated Clotting Time (ACT)

- Point-of-care, **whole blood** clotting test to monitor high-dose heparin therapy\(^8\)

- Often dose of heparin is beyond the range that can be measured with the aPTT\(^9\)
  - Cardiopulmonary bypass graft surgery (CPBG) may exceed 400 to 500 seconds\(^10\)
Activated Partial Thromboplastin Time (aPTT)

- A global test of the intrinsic coagulation pathway
  - Indirect sensitivity to heparin through its anti-IIa activity

- Subject to many interferences
  - Patient variables: factor levels (FVIII, fibrinogen, etc), presence of lupus anticoagulant or liver disease
  - Pre-analytical variables: citrate concentration, sample storage, phlebotomy errors (short fill, wrong tube) etc.
  - Analytical variables: reagent sensitivity, reagent/instrument system
Intrinsic Pathway

Extrinsic Pathway

Common Pathway

I = Fibrinogen
II = Prothrombin, IIa = Thrombin
TF = Tissue Factor

Protein C + Thrombomodulin
Protein S
Activated Protein C

XII \rightarrow XIIa
XIIa \rightarrow XIa
XIa \rightarrow Xa
X \rightarrow Xa

VIIIa \rightarrow Vlla

Vlla \rightarrow VII
VII \rightarrow TF

II \rightarrow IIa
IIa \rightarrow Ia

Ia \rightarrow Fibrin Clot

XIII \rightarrow XIIIa
aPTT monitoring of Heparin (UFH Only)

Historical method: 1.5 – 2.5x the baseline\textsuperscript{11}
(Not Recommended)
• Based on a retrospective study in the 1970’s
• Not confirmed by randomized trials in humans

\textit{In Vitro} Heparin Curve\textsuperscript{12}
(Not Recommended)
• Uses normal pool spiked with heparin to determine the aPTT values correlating to 0.3 – 0.7 IU/mL anti-Xa range
• Increases upper & lower aPTT range compared to \textit{Ex Vivo} method

\textit{Ex Vivo} Heparin Curve\textsuperscript{13}
• Uses samples from patients receiving UFH to determine the aPTT values correlating to 0.3 – 0.7 IU/mL anti-Xa range
### Need for Heparin Response Curve

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Therapeutic aPTT</th>
<th>Therapeutic aPTT ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reagent 1</td>
<td>59–84</td>
<td>2.3–3.2†</td>
</tr>
<tr>
<td></td>
<td>49–92 to 49–109†</td>
<td>1.9–3.7 to 2.1–4.6†</td>
</tr>
<tr>
<td></td>
<td>60–85</td>
<td>1.8–2.5</td>
</tr>
<tr>
<td></td>
<td>66–109</td>
<td>2.2–3.6</td>
</tr>
<tr>
<td></td>
<td>79–105</td>
<td>2.3–3.0</td>
</tr>
<tr>
<td></td>
<td>64–112</td>
<td>2.2–3.9†</td>
</tr>
<tr>
<td></td>
<td>55–78</td>
<td>1.9–2.7†</td>
</tr>
<tr>
<td></td>
<td>81–185</td>
<td>2.6–6.0</td>
</tr>
<tr>
<td></td>
<td>72–119 to 98–165†</td>
<td>2.6–4.3 to 3.7–6.2†</td>
</tr>
<tr>
<td></td>
<td>57–98 to 84–124†</td>
<td>2.1–3.5 to 2.6–3.8†</td>
</tr>
<tr>
<td></td>
<td>71–96</td>
<td>2.3–3.1</td>
</tr>
<tr>
<td></td>
<td>49–109 to 63–101†</td>
<td>1.7–3.8 to 1.9–3.3†</td>
</tr>
<tr>
<td></td>
<td>75–105</td>
<td>2.8–3.9</td>
</tr>
<tr>
<td></td>
<td>64–106</td>
<td>2.3–3.9</td>
</tr>
<tr>
<td></td>
<td>55–97</td>
<td>2.1–3.7†</td>
</tr>
<tr>
<td></td>
<td>70–158</td>
<td>2.0–4.5</td>
</tr>
<tr>
<td></td>
<td>44–75 to 58–112†</td>
<td>1.6–2.7 to 2.4–4.5†</td>
</tr>
</tbody>
</table>

aPTT monitoring of Heparin (UFH Only)

**Historical method:** 1.5 – 2.5x the baseline\(^\text{11}\)
*(Not Recommended)*
- Based on a retrospective study in the 1970’s
- Not confirmed by randomized trials in humans

**In Vitro Heparin Curve\(^\text{12}\)**
*(Not Recommended)*
- Uses normal pool spiked with heparin to determine the aPTT values correlating to 0.3 – 0.7 IU/mL anti-Xa range
- Increases upper & lower aPTT range compared to *Ex Vivo* method

**Ex Vivo Heparin Curve\(^\text{13}\)**
- Uses samples from patients receiving UFH to determine the aPTT values correlating to 0.3 – 0.7 IU/mL anti-Xa range
Comparison of \textit{In Vitro} & \textit{Ex Vivo} Curves$^{12}$

\textit{In Vitro} Range: 86 – 139 seconds

\textit{Ex Vivo} Range: 72 – 113 seconds

Graph from: Gausman JN, Marlar RA. Inaccuracy of a “Spiked Curve” for Monitoring Unfractioned Heparin Therapy” \textit{Am J Clin Pathol}. 2011; 135:870-876
aPTT monitoring of Heparin (UFH Only)

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*Ex Vivo* Heparin Curve
- Uses samples from patients receiving UFH to determine the aPTT values correlating to 0.3 – 0.7 IU/mL anti-Xa range
Defining an aPTT Ex Vivo Heparin Curve

- Samples obtained from patients receiving UFH
- Both aPTT and anti-Xa activity are measured
- Perform the correlation between anti-Xa activity (X axis) and aPTT (Y axis)
- Regression analysis
- Determine aPTT range corresponding to 0.3 - 0.7 anti-Xa IU/mL
HEPARIN THERAPEUTIC RANGE

- Y-axis: PTT Result [sec]
- X-axis: Anti-Xa Assay (IU/ml)

The graph illustrates the relationship between the PTT result and the Anti-Xa Assay. The shaded areas represent the therapeutic range.

We ❤ Coag
The optimum number of samples is 30 or more for an accurate HTR determination and the absolute minimum number of samples is 20.
Influence of Warfarin on HTR\textsuperscript{17}

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Reagent A</th>
<th>Reagent B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INR &gt; 1.3 and &lt;1.5</td>
<td>INR &gt; 1.5 and &lt;2.0</td>
</tr>
<tr>
<td>0</td>
<td>64–105</td>
<td>64–105</td>
</tr>
<tr>
<td>10</td>
<td>64–104</td>
<td>64–104</td>
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<tr>
<td>25</td>
<td>65–107</td>
<td>65–107</td>
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<tr>
<td>50</td>
<td>68–106</td>
<td>68–106</td>
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<tr>
<td>75</td>
<td>67–108</td>
<td>67–108</td>
</tr>
<tr>
<td>100</td>
<td>70–112</td>
<td>70–112</td>
</tr>
</tbody>
</table>

Table from: Marlar RA, Gausman J. The Optimum Number and Types of Plasma Samples Necessary for an Accurate Activated Partial Thromboplastin Time-Based Heparin Therapeutic Range. Arch Pathol Lab Med. 2013; 137: 77–82
Influence of Same Patient Samples on HTR$^{17}$

10% begins to influence HTR and may be clinically significant.

<table>
<thead>
<tr>
<th>Percentage of Samples From the Same Patient*</th>
<th>Lot 1</th>
<th>Lot 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (all different)</td>
<td>65–104</td>
<td>58–101</td>
</tr>
<tr>
<td>8</td>
<td>65–104</td>
<td>57–101</td>
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<tr>
<td>25</td>
<td>63–104</td>
<td>57–103</td>
</tr>
<tr>
<td>50</td>
<td>63–106</td>
<td>62–105</td>
</tr>
<tr>
<td>75</td>
<td>58–106</td>
<td>62–109</td>
</tr>
<tr>
<td>100 (all the same)</td>
<td>60–105</td>
<td>64–109</td>
</tr>
</tbody>
</table>

*The percentage of 24 patients

Table from: Marlar RA, Gausman J. The Optimum Number and Types of Plasma Samples Necessary for an Accurate Activated Partial Thromboplastin Time-Based Heparin Therapeutic Range. Arch Pathol Lab Med. 2013; 137: 77-82
Influence of Lot Variation on HTR$^{17}$

Table from: Marlar RA, Gausman J. The Optimum Number and Types of Plasma Samples Necessary for an Accurate Activated Partial Thromboplastin Time-Based Heparin Therapeutic Range. *Arch Pathol Lab Med*. 2013; 137: 77-82

<table>
<thead>
<tr>
<th>Reagent Lot</th>
<th>HTR No. 1, s</th>
<th>HTR No. 2, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reagent A-lot 1</td>
<td>62–93</td>
<td>63–93</td>
</tr>
<tr>
<td>Reagent A-lot 2</td>
<td>63–95</td>
<td>63–95</td>
</tr>
<tr>
<td>Reagent A-lot 3</td>
<td>63–94</td>
<td>63–95</td>
</tr>
<tr>
<td>Reagent C-lot 1</td>
<td>55–87</td>
<td>55–87</td>
</tr>
<tr>
<td>Reagent C-lot 2</td>
<td>58–90</td>
<td>58–90</td>
</tr>
<tr>
<td>Reagent C-lot 3</td>
<td>54–83</td>
<td>55–85</td>
</tr>
</tbody>
</table>

Uses the same 20 patients done in duplicate (HTR No.1 & No. 2)
CAP Lot Change Recommendations$^{13,18}$

- Establish a new therapeutic range

- Compare the original PTT reagent lot to the new PTT lot to determine clinically equivalent response on samples of patients receiving UFH
  - The mean difference must not exceed 7 seconds
  - Each subsequent reagent lot is compared against the preceding lot, so laboratories must monitor the sum of differences from the reagent lot used in the original validation to ensure that the **cumulative mean** PTT difference does not exceed 7 seconds
### Cumulative Summation of Reagent Mean Differences - UF Heparin Samples

**Instrument:** STAR-Evolution  
**Reagents:** STA-PTT Automate  
**HTR:** 62-94  
**Rev cd 24/11**

<table>
<thead>
<tr>
<th>Lot Conversion Sequence</th>
<th>Patient Data Set* Date</th>
<th>Current Lot #</th>
<th>Current Lot Mean, Seconds</th>
<th>New Lot #</th>
<th>New Lot Mean, Seconds</th>
<th>Difference in Seconds (New lot - Current Lot)</th>
<th>% Diff from Current Reagent</th>
<th>Cumulative Summation Difference in Seconds</th>
<th>Significant?</th>
<th>Therapeutic Range Change</th>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>Mar-05</td>
<td>033221</td>
<td>59.4</td>
<td>041681</td>
<td>56.8</td>
<td>-2.63</td>
<td>-4.43</td>
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<td>041681</td>
<td>66.7</td>
<td>050343</td>
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<td>-1.84</td>
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<td>050343</td>
<td>70.1</td>
<td>61982</td>
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<td>-0.21</td>
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<td>4th</td>
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<td>061982</td>
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<td>101122</td>
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<td>0.32</td>
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<tr>
<td>5th</td>
<td>Mar-09</td>
<td>101122</td>
<td>70.7</td>
<td>102997</td>
<td>73.3</td>
<td>2.59</td>
<td>3.67</td>
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<td>6th</td>
<td>Feb-10</td>
<td>102997</td>
<td>66.6</td>
<td>105261</td>
<td>67.2</td>
<td>0.63</td>
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<td></td>
<td></td>
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<tr>
<td>8th</td>
<td>Feb-11</td>
<td>105261</td>
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<td>106272</td>
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<td>9th</td>
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<td>66.6</td>
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<td>-4.64</td>
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<td>10th</td>
<td>Jan-13</td>
<td>107812</td>
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<td>67.6</td>
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<td>Feb-14</td>
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<td>78.7</td>
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</tr>
</tbody>
</table>

*Reagents Change  
Significance: (Archives ref for HTR change: < 5 seconds is insignificant; >5<7 is cause for concern; >7 necessitates action [probable change of range])

*Cumulative Sum*
Anti-Xa Assay

• Quantitative determination of the plasma levels of both UFH and LWMH
  - Direct sensitivity to heparin through measurement of anti-Xa activity on antithrombin

• Few interferences
  - Patient variables: not susceptible to interference from elevated factor VIII or fibrinogen and not influenced by factor deficiencies
  - Pre-analytical variables: not affected by under-filled collection tubes
  - Analytical variables: reagents are calibrated to international standards for UFH and LMWH
Anti-Xa Methodology

| CBS | =Reagent 1 |
| Excess Xa | =Reagent 2 |

LMWH or UFH + Free AT + CBS → [LMWH or UFH + AT] + CBS

Signal: pNA measured at 405 nm

Inhibition of Xa by [LMWH or UFH + AT] + Residual Xa + CBS

2 "Excess Xa"

3
Anti-Xa Methodology

There is an inverse relationship between chromogenic readout and drug levels

- Heparin concentration
- Inhibition of F.Xa
- Hydrolysis of the chromogenic substrate
- Color development
CALIBRATION

LIQUID ANTI XA HYBRID

reading (OD/mn)

0.728
0.509
0.367
0.282
0.111

-0.10  0.21  0.52  0.83  1.13  1.44  1.75

concentration U1/ml
Reagent Formulation Differences: Antithrombin

Reagent may add in exogenous AT or rely on patient’s own AT

<table>
<thead>
<tr>
<th>CBS</th>
<th>=Reagent 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess Xa</td>
<td>=Reagent 2</td>
</tr>
</tbody>
</table>

LMWH or UFH + Free AT + CBS 1 [LMWH or UFH + AT] + CBS

Signal: pNA measured at 405 nm

Inhibition of Xa by [LMWH or UFH + AT] + Residual Xa + CBS

Excess Xa

We ♥ Coag
Reagent Formulation Differences: Antithrombin

**Containing Exogenous AT**
- Standard AT concentration in the reaction
  - Measuring a standardized heparin inhibitory activity in the sample
- Possibility for overestimation of heparin levels\(^\text{19}\)
  - Drug unbound to AT in vitro (inactive) to bind exogenous AT an have an anticoagulant effect in vitro

**Without Exogenous AT**
- AT-Heparin complex is already formed in the sample
  - Heparin activity depends on the sample concentration of AT
- Reaction of the AT-Heparin complex inhibiting FXa happens all in one step
  - Measures the true heparin inhibitory activity in the sample
- *In vitro* effect closely emulates *in vivo* effect\(^\text{19}\)
Reagent Formulation Differences: Dextran Sulfate (DS)

Dextran sulfate releases UFH bound non-specifically to ‘off-target’ proteins

- Reagents *containing* dextran sulfate measure all UFH present in plasma and may overestimate heparin levels\(^{19}\)

- Reagents *without* DS measure only that portion of UFH participating in the anticoagulant effect (ie not bound to ‘off-target’ proteins)
The (+) DS assay continued to demonstrate activity after samples were neutralized to baseline APTT and TT whereas the (-) DS assay gave baseline results.

aPTT and Anti-Xa Discordance
Assay Discordance

Discordance between the aPTT and anti-Xa assays is a well documented problem

- Preanalytic variables
- Biologic factors
- aPTT reagent/instrument combination variability
- Differences in testing targets
HEPARIN THERAPEUTIC RANGE

13/60 results are concordant & therapeutic

21.6%
HEPARIN THERAPEUTIC RANGE

18/60 results are concordant & sub-therapeutic
30.0%
29/60 results are discordant 48.3%
Frequency & Impact of Discordance

- Stanford began using anti-Xa for UFH monitoring in 2007

- Anecdotally noted a discrepancy in values and published a study formalizing this observation
  - Continued to collect concomitant aPTT values to screen for coagulation abnormalities
  - Data analyzed including demographics, coagulation status, indication for UFH and clinical outcomes
  - Determined the Impact of discordance on clinical outcomes
aPTT values were discordant with anti-Xa the majority of the time.
### Assay Discordance: Demographics & Outcomes

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>aPTT &amp; Anti-Xa Consistently Concordant (n=112)</th>
<th>aPTT Consistently High Relative to Anti-Xa (n=85)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant Warfarin &amp; UFH</td>
<td>23 (21%)</td>
<td>47 (55%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UFH only</td>
<td>89 (79%)</td>
<td>38 (45%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Treatment for acute VTE</td>
<td>16 (14%)</td>
<td>29 (34%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Treatment for ACS</td>
<td>38 (34%)</td>
<td>15 (18%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Elevated PT prior to UFH start</td>
<td>48/98 (49%)</td>
<td>67/80 (84%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated aPTT prior to UFH start</td>
<td>9/93 (10%)</td>
<td>53/77 (69%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death within 30 days after first data pair</td>
<td>6 (5%)</td>
<td>18 (21%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Baseline PT and aPTT of patients who died within 30 days in group with consistently high aPTT values relative to anti-Xa values.

Discordance Case Study
Presentation

• 41-yr old patient, 25 weeks gestation, twin pregnancy

• Left lower extremity pain & swelling

• Ultrasound showed occlusive clots
Treatment

- UFH with an Initial bolus of 6,300 units and infusion of 1,400 u/hour

- Dose was adjusted & monitored using aPTT
  - The aPTT range was correlated to anti-Xa

- Patient required 48,000 units UFH/day to achieve therapeutic APTT levels
Laboratory Results

Anti-Xa levels performed in addition to aPTT

APTT results significantly depressed compared to anti-Xa
Follow Up

• FVIII level 566% (normal range 50 – 150%)

• UFH monitored with anti-Xa and dose reduced
  - Subsequent lab tests:
    o All anti-Xa values were therapeutic
    o 10/11 aPTT were sub-therapeutic

• Symptoms resolved and patient was discharged
Conclusions

• Apparent heparin resistance due to elevated FVIII
  - Decreased aPTT response despite adequate anti-Xa activity and antithrombotic effect
  - Likely due to pregnancy-related elevation of factor VIII

• Sub-therapeutic aPTT results led to increased UFH dosing

• Testing with anti-Xa allowed for reduction in heparin dose and a good clinical outcome
aPTT to Anti-Xa for Heparin Monitoring
Experience at Exempla St. Joseph’s

• Switching to anti-Xa requires lab and pharmacy to work together to improve patient care while accepting higher reagent costs

• Electronic Medical Record (EMR) conversion and healthcare provider education are critical

• Hospital-wide results
  - Widespread satisfaction among nursing and lab staff with the switch
  - Some resistance from clinicians, especially surgeons who worry about excessive bleeding post-surgery
  - Practitioners are discouraged from requesting both an APTT and anti-Xa

• Baseline aPTTs are collected to screen for coagulopathies
<table>
<thead>
<tr>
<th></th>
<th>Anti-Xa</th>
<th>APTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number tests /patient / day</td>
<td>2.08</td>
<td>2.73</td>
</tr>
<tr>
<td>Mean number UFH dosage adjustments /patient / day</td>
<td>0.62</td>
<td>1.47</td>
</tr>
<tr>
<td>Reagent cost</td>
<td>$2.55 / test</td>
<td>$0.65 / test</td>
</tr>
<tr>
<td></td>
<td>$5.30 / patient / day</td>
<td>$1.77 / patient / day</td>
</tr>
<tr>
<td>Lab tech and phlebotomy labor</td>
<td>$3.08 / test</td>
<td>$3.08 / test</td>
</tr>
<tr>
<td></td>
<td>$6.40 / patient / day</td>
<td>$8.41 / patient / day</td>
</tr>
<tr>
<td>Nurse labor</td>
<td>$2.58 / dosage adjustment</td>
<td>$2.58 / dosage adjustment</td>
</tr>
<tr>
<td></td>
<td>$1.60 / patient / day</td>
<td>$2.58 / patient / day</td>
</tr>
<tr>
<td>Total cost / patient / day</td>
<td>$13.30</td>
<td>$13.97</td>
</tr>
</tbody>
</table>

Data from: Vandiver JW, Vondracek TG. Antifactor Xa levels versus activated partial thromboplastin time for monitoring unfractionated heparin. *Pharmacotherapy* 2012; 32: 546-558
Study at Shands Hospital, University of Florida

- Compared PTT to Anti-Xa at an 852-bed academic medical center
- Concluded that monitoring intravenous UFH infusions with the anti-Xa:
  - Achieves therapeutic anticoagulation more rapidly
  - Maintains the values within the goal range for a longer time
  - Requires fewer adjustments in dosage and repeated tests

Study at Shands Hospital, University of Florida

Cumulative % of patients who achieved therapeutic anticoagulation (2 consecutive therapeutic test values)

Study at Shands Hospital, University of Florida\textsuperscript{26}

- Odds of reaching therapeutic anticoagulation at 24 hours are \textbf{3.5 times higher} for anti-Xa patients than for aPTT patients

- At 48 hours the likelihood of achieving therapeutic anticoagulation increased to \textbf{10 times greater} for anti-Xa patients
• Heparin is widely used and continues to be an anticoagulant of choice

• Both aPTT and anti-Xa are important to determining anticoagulation status
  - aPTT is a screening assay & indirect for heparin
  - Anti-Xa is used to establish aPTT-based HTR
  - Discordance between methods occurs
    o aPTT is influenced by many factors (Less specific)
    o Anti-Xa measures inhibition of Factor Xa (More specific)

• Laboratory testing for heparin has institutional benefits and inter-disciplinary collaboration is key
Learning Objectives

• Explain the differences in heparins

• Discuss assays and approaches for heparin monitoring

• Assess differences and clinical implications for anti-Xa formulations

• List reasons for discordant aPTT and anti-Xa values

• Explain institutional considerations for changing heparin monitoring assays
References


References


17. Marlar RA, Gausman J. The Optimum Number and Types of Plasma Samples Necessary for an Accurate Activated Partial Thromboplastin Time-Based Heparin Therapeutic Range. *Arch Pathol Lab Med*. 2013; 137: 77-82


