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Heparin

Monitor with Confidence

Sandy Gardner, BS MT(ASCP)
Hemostasis Reagent Marketing Manager

Heparin: Monitor with Confidence

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Simplify Heparin Monitoring

- Easy to use, reliable assay
- Available 24/7

Control Monitoring

- True measurement of heparin
- Improve workflow from floor to lab

Improve Patient Outcomes

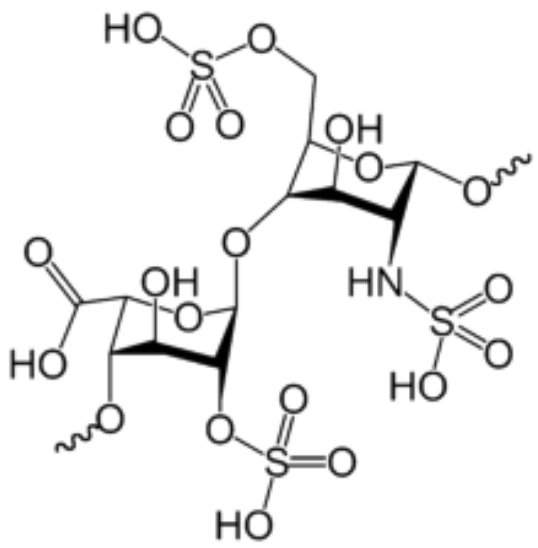
- Patients reach therapeutic range sooner
- Less bleeding and improved mortality

Guervil D. et al, The Annals of Pharmacotherapy. 2011 Jul/Aug;45.
Vandiver J, et al. Hospital Practice. 2013 Apr;41(2).

What is Heparin?

Heparin: Background Information

Disaccharide unit



Heparin Molecule

- Anticoagulant discovered over 90 years ago by McLean, et al
- Highly sulfated mucopolysaccharide
  - Typically prepared from porcine or bovine gut mucosa
  - Smallest active form requires 5 saccharide units
- Heterogeneous with respect to:
  - Molecular size/weight
  - Anticoagulant activity
  - Pharmacokinetic properties
- Endogenous heparin-like substances are present in the subendothelial extracellular matrix

CHEST, Antithrombotic Therapy and Prevention of Thrombosis, 9th ED:ACCP Guidelines

Lee MS, et al. Rev Cardiovasc Med. 2015;16:189-99.

What is Heparin?

Anticoagulant Drug

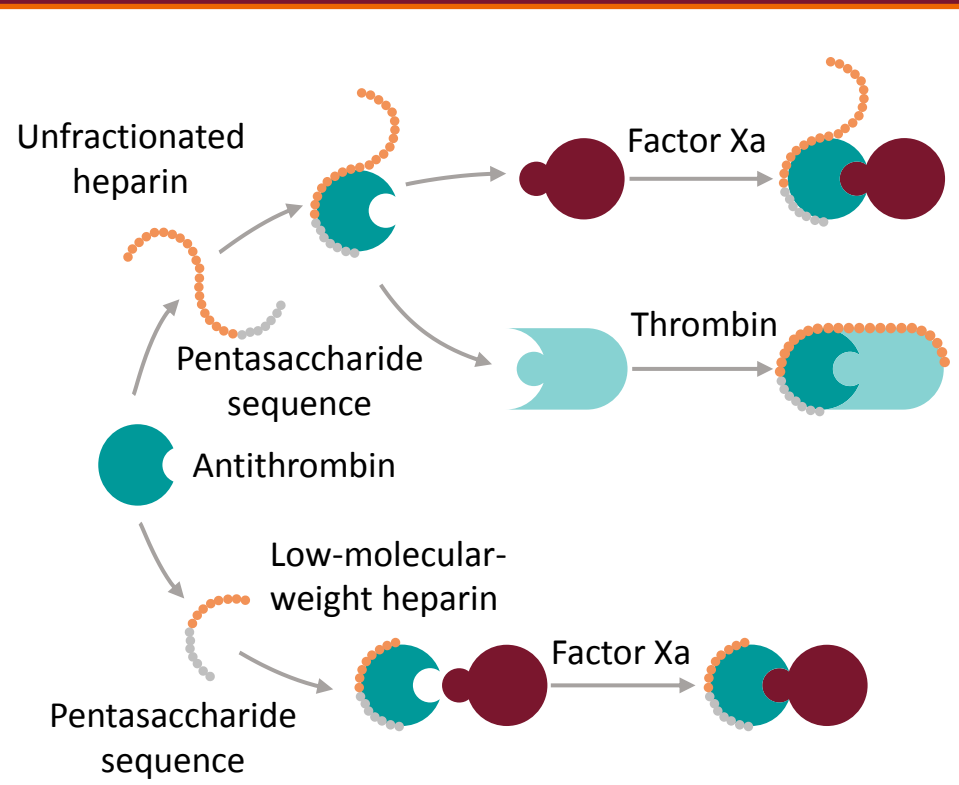
- Prevents blood from clotting

2 Forms

- Unfractionated (UFH)
- Low Molecular Weight (LMWH)

Heparin: Mechanism of Action

Clotting Enzyme Inactivation

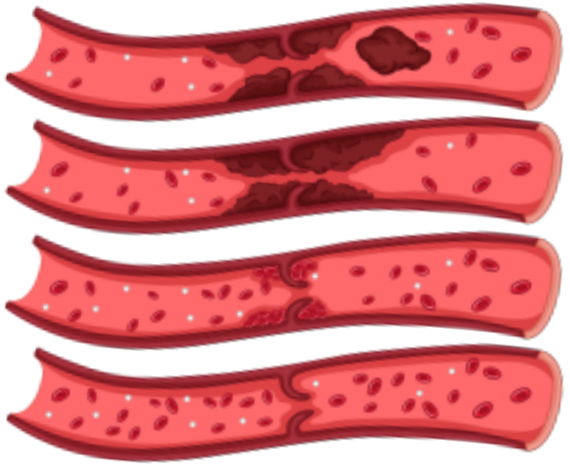


- Antithrombin (AT) inhibits FIIa, IXa, Xa, XIa, XIIa to regulate clotting, *primarily FIIa and FXa*
- Heparin binds to AT causing a change in shape that increases the effectiveness of AT inhibition
- 1000 – 2000 x increase in AT ability to inhibit
- AT binding to clotting enzymes irreversibly inactivates them
- Heparin dissociates itself from AT and is reused.

Garcia DA, et al. Chest. 2012;141(2 Suppl): e25S.
CHEST, Antithrombotic Therapy and Prevention of Theombosis, 9th ed: ACCP
Medscape, Aug 23, 2017; Heparins: Clinical Use & Laboratory Monitoring; Maureane Hoffman, MD, PhD

Clinical Uses of Heparin
Hospitalized Therapy

- Therapy deep vein thrombosis (DVT), lung embolism (PE) **UFH, LMWH**
  - ✓ UFH treatment $3,476.22 / patient
  - ✓ LMW treatment $3,056.42 / patient
- Prevention of thromboembolic events, e.g., post surgery, cancer patients, critically ill **UFH, LMWH**
- Anticoagulation during hemodialysis or extracorporeal circulation (blood outside body) **UFH**



UFH = Unfractionated Heparin
LMWH = low-molecular-weight heparin

Lee MS, et al. Rev Cardiovasc Med. 2015;16:189-99.
G. Merli, C. Ferrufino, J. Lin, M. Hussein, D.Batleman J Thromb Haemost 2008; 6: 1077-86

Heparin Anti-Xa Testing Target Population: LWMH Therapy Patients Who Should Be Monitored

- Pregnant women
- Infants and children
- Patients with kidney disease
- Patients at high risk for bleeding or recurrences
- Very obese or very underweight patients

Laboratories need assay available for these patients

CHEST /141 / 2 / February, 2012

How is Heparin Monitored?

Why is the Heparin Anti-Xa Assay an improvement over the APTT?

Current Status
Unfractionated Heparin Monitoring

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APTT primary assay for monitoring

- ~15M - 26M test per year (~30 – 50% of total APTT orders)
- limitations for predicting adequacy of anticoagulation
- cannot assay LMWH levels
- difficult for laboratory to validate therapeutic range with each reagent lot / new analyzer

Low Molecular Weight replacing Unfractionated Heparin

- no routine monitoring
- select patients may require monitoring
- cannot be monitored with APTT
- use of UFH will not go away entirely

Heparin Anti-Xa assay alternative

- ~3.4M test per year
- better measurement of UFH concentration
- better workflow and outcomes
- required for LMW Heparin
- can be used for new oral Direct Anti-Xa anticoagulants
- interest in adding Heparin Anti-Xa growing

% hospitals considering adding Heparin Anti-Xa

2011	2012	2013	2014	2015	2016
34.9	**45.4**	**46.0**	**46.7**	**54.4**	**55.4**

Market Monitor High Volume 2016

Evolution of Methods for Establishing APTT UFH Therapeutic Range

APTT: traditional method (1.5 – 2.5 x control)

- 1970's retrospective study
- Clinical relevance uncertain as range was not confirmed with randomized clinical trials
- Does not consider differences in reagents and instruments

In vitro heparin dose-response curve

- Normal plasma spiked with UFH
- Not recommended by CAP; over-estimates when compared with anti-Xa levels in patients
- Molecular distribution in vivo ≠ in vitro

Ex vivo heparin therapeutic range using APTT correlation vs. anti-Xa assay

- CAP recommended method

CAP: College of American Pathologists

Garcia DA, et al. Chest. 2012;141(2 Suppl):e28S-29S.

Ex vivo UFH Therapeutic Range
APTT correlation vs. anti-Xa assay

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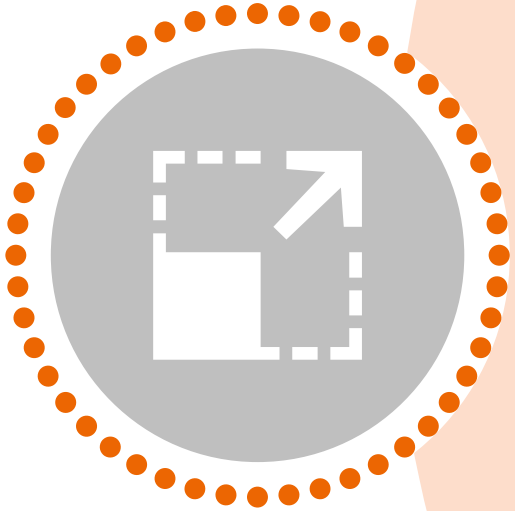


Preferred method (e.g. CAP)

Collect samples from patients receiving heparin only

- Minimum 50 samples
- Normal PT
- No more than two samples from the same patient

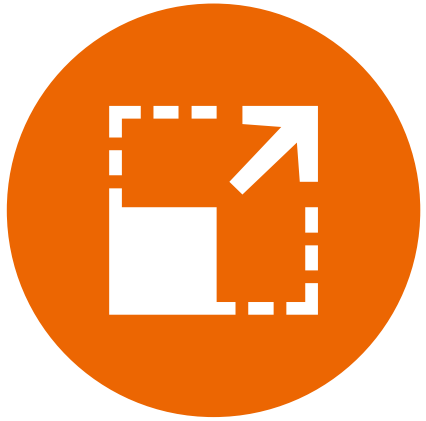
Perform APTT and anti-Xa testing

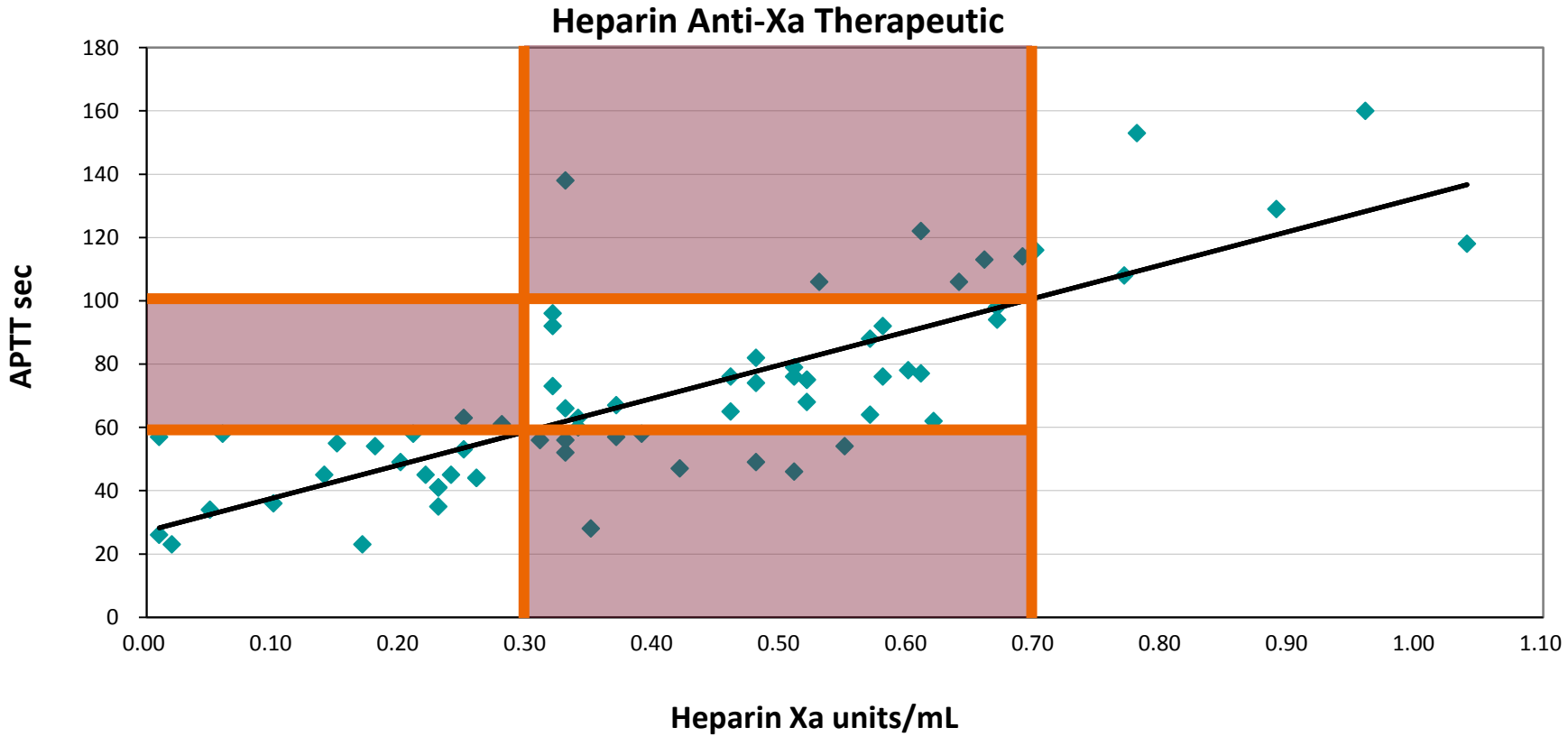
- Samples can be frozen for anti-Xa testing—follow CLSI guidelines
- For frozen samples, repeat APTT after thawing to verify result

Plot heparin concentration vs. APTT using regression analysis

Establish APTT sec therapeutic range, equivalent to 0.3–0.7 IU/mL anti-Xa

Typical Laboratory Study
APTT correlation vs. Heparin Anti-Xa assay





27% of study samples do not correlate clinically APTT vs Heparin Anti-Xa

Laboratory & Physician Comfort Zone
Advantages of APTT Monitoring of UFH

- Widely used global marker for clotting
- Physician familiarity with results
- Inexpensive
- Readily available in all size laboratories
- Highly automated

Did You Know?
Disadvantages of APTT Monitoring of UFH

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More frequent monitoring required

Often only 50% APTT change due to heparin dose

Does not measure heparin concentration

No standardization of APTT reagents between vendors or reagents

Pre-analytical Variables effect results

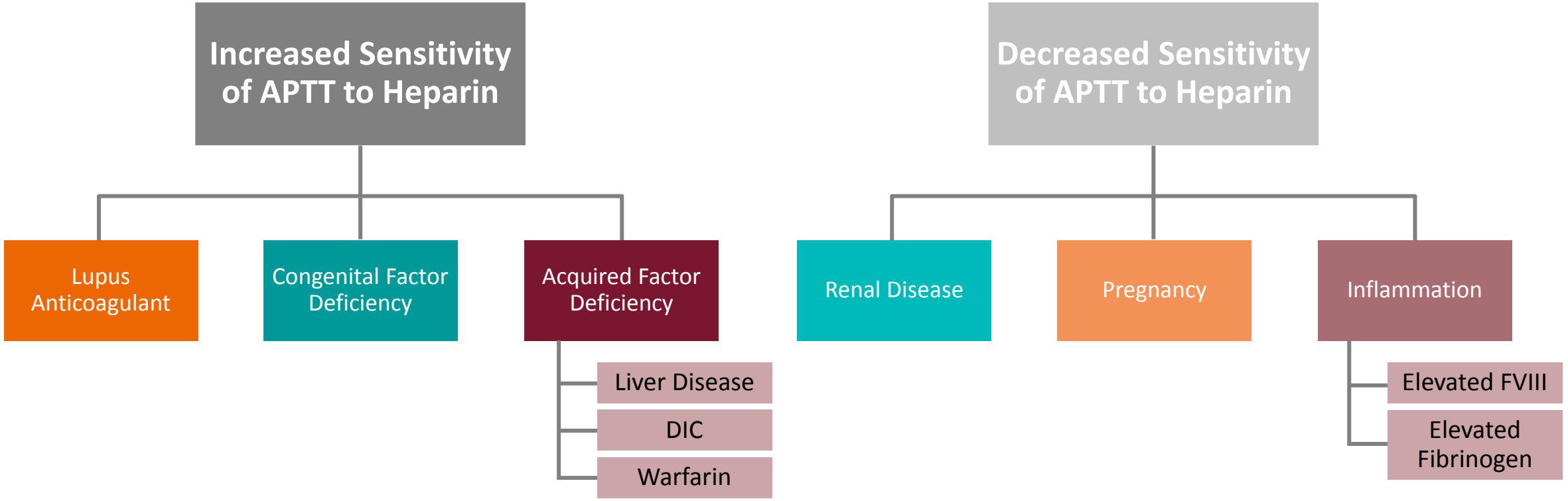
Yearly APTT reagent lot establishment of UFH therapeutic range:

- Lot to lot changes can result in therapeuticrange change
- Time, labor for laboratory staff
- Samples difficult to obtain over full range

Cannot be used to measure LMW Heparin, Fondaparinux, Direct Anti-Xa inhibitor drugs

Guervil D. et al, The Annals of Pharmacotherapy. 2011 Jul/Aug;45.
Vandiver J, et al. Hospital Practice. 2013 Apr;41(2).

Interference with APTT Assessment Effect of Heparin
APTT Never Designed to Monitor Hepain



None of these interfere with Heparin Anti-Xa monitoring of Heparin

Heparin Anti-Xa and APTT for UFH Monitoring, James Zehnder MD
Professor of Pathology and Medicine (Hematology)
Stanford University, Stanford CA, May 6 2017

Pre-analytical Variables effect APTT

Platelet Factor 4 neutralizes heparin

- traumatic venipuncture
- time plasma on cells > 1 hour
- time to assay > 4 hours
- improper centrifugation, plasma not platelet poor
- frozen sample not platelet poor plasma

Tube under fill prolongs clot assays

- falsely elevated APTT result

Line draw contaminated with heparin

- falsely elevated APTT result

Different Approach to Monitor UFH
Why the Heparin Anti-Xa assay?

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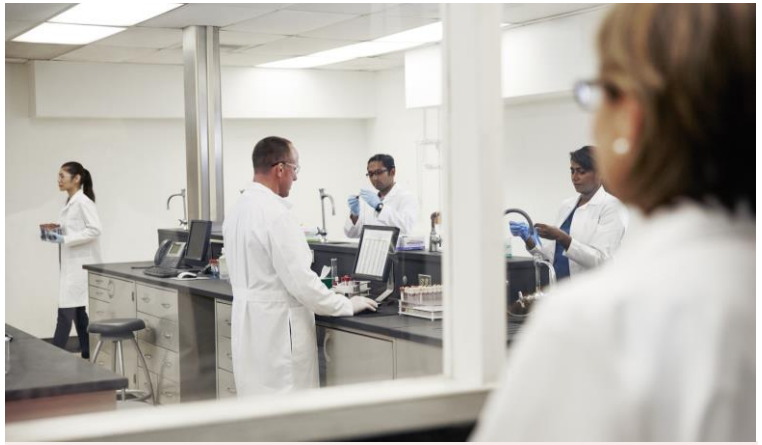
Better Patient Care

- Smoother Dose Response
- Patient Therapeutic Faster
- Stable Heparin Levels
- Improved Outcomes

Improve Workflow

- Fewer Lab Tests
- Fewer Dose Changes



Efficient

- Overall Cost Minimal Change
- Lab and Nursing Labor Savings

Guervil D. et al, The Annals of Pharmacotherapy. 2011 Jul/Aug;45.
Vandiver J, et al. Hospital Practice. 2013 Apr;41(2).

Advantage of Heparin Anti-Xa monitoring for Heparin

- Direct measure of heparin's functional activity
- Little or no effect based on variables of patient clinical status
- Limited effect due to pre-analytical variables
- Literature based therapeutic range, no need for laboratory to establish range

Guervil D. et al, The Annals of Pharmacotherapy. 2011 Jul/Aug;45.
Vandiver J, et al. Hospital Practice. 2013 Apr;41(2).

Two Studies: APTT versus Heparin Anti-Xa Monitoring for UFH

852-bed medical center; IV UFH infusion[1]
May 1, 2005–April 31,2007 (APTT); 50 patients
June 1, 2007–Sept 1, 2009 (Heparin Anti-Xa); 50 patients

Outcome	APTT	Heparin Anti-Xa
Mean time therapeutic (hours)	48	28
Tests in goal range (%)	42	66
# of monitoring tests per 24 hours	2.8	2.5
Infusion rate changes per 24 hours	1.6	0.8
Mean hospital stay (days)	25	17
Mortality rate (%)	6	2

371-bed medical center; IV UFH infusion for DVT/PE[2]
March 1, 2009–May 31, 2010 (APTT); 98 patients
Aug 1, 2010–Oct 31, 2010 (Heparin Anti-Xa); 88 patients

Outcome	APTT	Heparin Anti-Xa
Mean time therapeutic (hours)	39.8	22.2
Tests in goal range (%)	41	66
# of monitoring tests per 24 hours	2.73	2.08
Infusion rate changes per 24 hours	1.47	0.62
Mean hospital stay (days)	6.5	5.9
Mortality rate (%)	3	1.1

[1].Guervil D. et al, The Annals of Pharmacotherapy. 2011 Jul/Aug;45.
[2]. Vandiver J, et al. Hospital Practice. 2013 Apr;41(2).

What Does Heparin Monitoring Cost Hospital?

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Time

- Heparin Anti-Xa achieves goal range 4 hours sooner than APTT

Accuracy

- Heparin Anti-Xa assay provides more accurate monitoring of heparin therapy

Clinical Outcomes

- Heparin Anti-Xa higher % within therapeutic range
- Heparin Anti-Xa fewer monitoring tests and dose adjustments

Labor

- Decreased tech, phlebotomy, nurse time with Heparin Anti-Xa monitoring improves workflow

Patient Safety

- Mortality and bleeding rates decrease with Heparin Anti-Xa monitoring

Guervil D. et al, The Annals of Pharmacotherapy. 2011 Jul/Aug;45.
Vandiver J, et al. Hospital Practice. 2013 Apr;41(2).

Comparison of Red Blood Cell Transfusion Utilization between anti-Xa and APTT Monitoring in Patients Receiving Unfractionated Heparin

Belk KW, et al. J Thromb Haemost. 2016;14:2148-57.

Study Design

Retrospective Cohort Study: Patients on Intravenous UFH (2009–2013)

Monitored with APTT			Monitored with anti-Xa		
VTE*	**Stroke**	**ACS†**	**VTE**	**Stroke**	**ACS**
n = 2207	n = 784	n = 7411	n = 2207	n = 784	n = 7411

- Propensity score techniques were used to match anti-Xa cases to APTT controls.
- RBC transfusions were identified from hospital billing data.
- Multivariable logistic regression was used to identify significant drivers of transfusion.
- p value <0.05 is considered significant.

Study outcome: red blood cell (RBC) transfusion rate in matched cohort

*VTE: venous thromboembolism; †ACS: acute coronary syndrome

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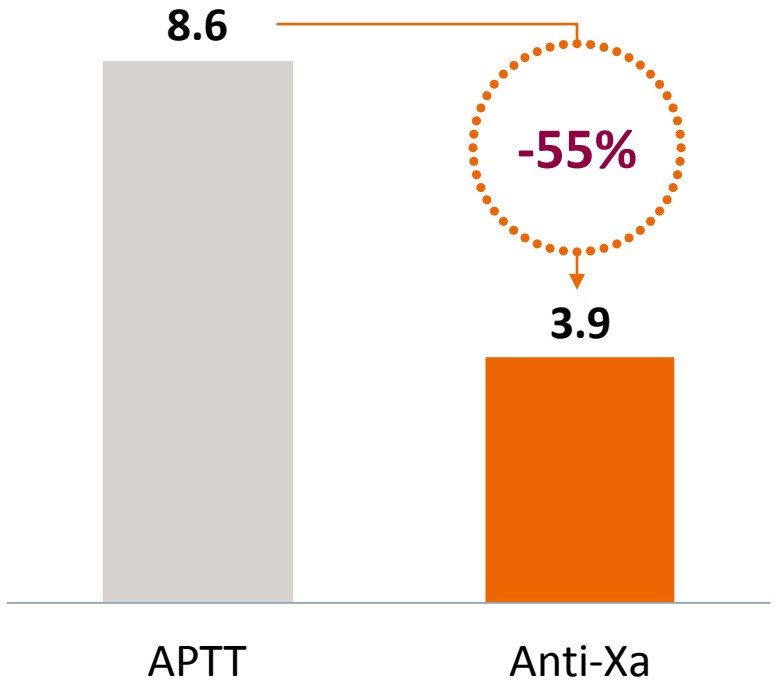
Reduction of RBC Transfusions in VTE

RBC transfusion % in VTE



Patients monitored with anti-Xa had a nearly

55% lower RBC transfusion rate

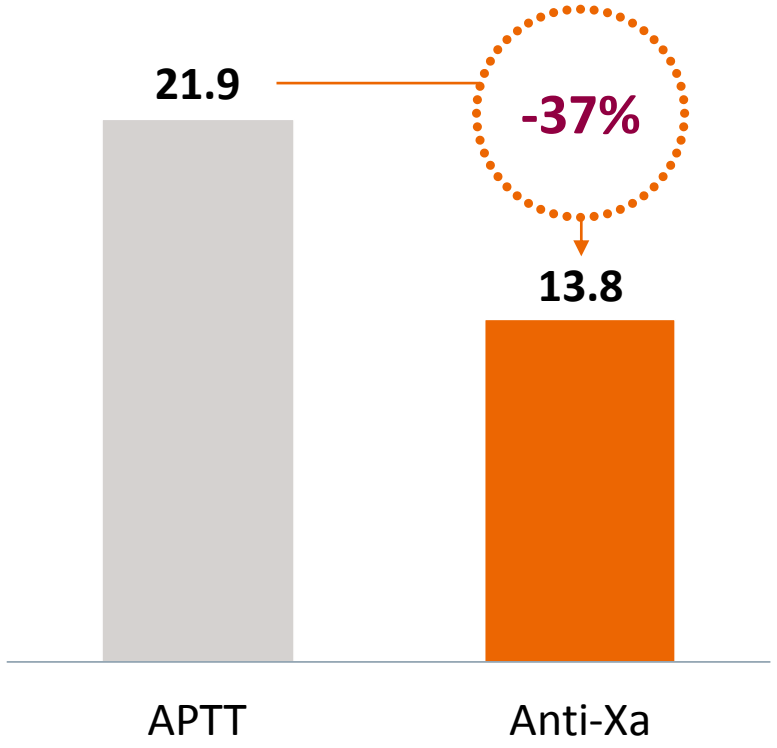
compared to APTT-monitored patients.

$p < 0.0001$

Belk KW, et al. J Thromb Haemost. 2016;14:2148-57

Reduction of RBC Transfusions in Stroke

RBC transfusion % in stroke



Patients monitored with anti-Xa had a nearly

37% lower RBC transfusion rate

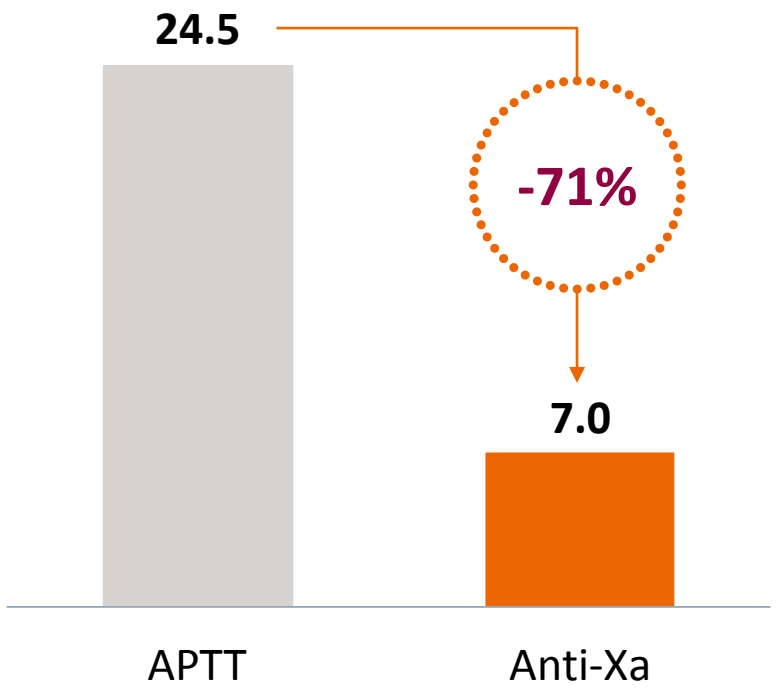
compared to APTT-monitored patients.

$p < 0.0001$

Belk KW, et al. J Thromb Haemost. 2016;14:2148-57

Reduction of RBC Transfusions in ACS

RBC transfusion % in ACS



Patients monitored with anti-Xa had a

71% lower RBC transfusion rate

compared to APTT-monitored patients.

$p < 0.0001$

Belk KW, et al. J Thromb Haemost. 2016;14:2148-57

Reduced Need for Blood Transfusions: Impact on Triple Aim

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Quality of care

- ↓ risk of complications among hospitalized UFH treated patients
- ↓ intensity and duration of UFH treatment

Patient experience

- ↓ length of stay in hospital
- ↓ dependence on mechanical ventilation

Cost reduction

- Estimated incremental hospitalization cost associated with RBC transfusions range from $4408 for intraoperative transfusion to over $10,000 for postoperative transfusions.

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How does a Hospital convert from APTT to Heparin Anti-Xa Monitoring for UFH?

Why Convert to Anti-Xa Monitoring of UFH

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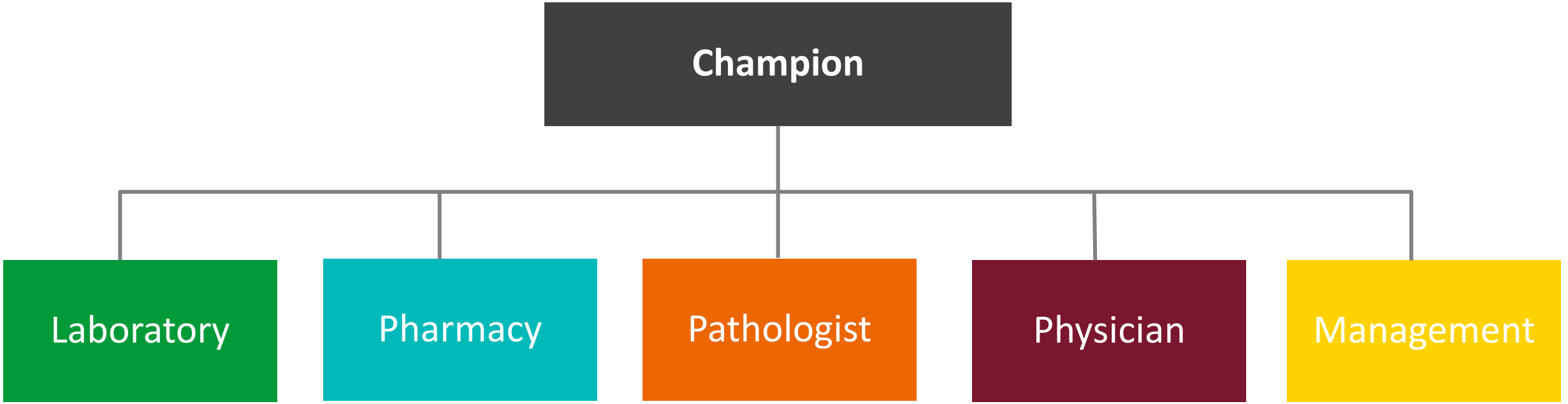
Improve Overall Hospital Efficiency

- Decrease Laboratory Test
- Decrease Dose Adjustments by Nurse
- Improve Patient Outcomes

- More accurate results
- Consistent Therapeutic Range

Develop a Champion
Drive Change



Heparin anti-Xa assay Monitoring
Advantages to Laboratory and Patients

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Heparin Assay	
ADVANTAGE	BENEFIT
Liquid Reagents, ready to use	Less tech time, no manual preparation
Hybrid Calibration Curve	Single curve for UFH & LMWH Single order from floor Time and financial savings
Stable Calibration Curve	Less tech time to perform frequent calibration Reagent savings Improved quality results
Standardized Therapeutic Range	Yearly savings in lab resources Consistent therapeutic range

Heparin Anti-Xa assay Monitoring	
ADVANTAGE	BENEFIT
Patient therapeutic within 24 hours	Improved outcome
Fewer laboratory tests	Improved workflow Savings material and time
Fewer dose changes	Improved patient care Savings time, workflow improved
Standardized Therapeutic Range	Yearly savings in lab resources Consistent therapeutic range
Patient Outcome	At 12 weeks, less VTE and minor/major bleeding Some studies exhibit improved mortality rates

INNOVANCE Heparin IFU
Guervil D. et al, The Annals of Pharmacotherapy. 2011 Jul/Aug;45.
Vandiver J, et al. Hospital Practice. 2013 Apr;41(2).

Financial Analysis Example

Variable	Heparin Anti-Xa	APTT
mean no tests/patient/day	2.08	2.73
mean no. UFH dose adjustments/patient/day	0.62	1.47
reagent cost / test	$ 2.55	$ 0.65
lab tech cost / hr (US avg)	$ 25.00	$ 25.00
phlebotomy cost / hr (US avg)	$ 14.34	$ 14.34
RN cost / hr (US avg)	$ 30.82	$ 30.82

Cost	Heparin Anti-Xa	APTT
reagent cost / patient/day	$ 6.07	$ 1.75
lab tech cost / patient / day @ 5 min	$ 4.33	$ 5.69
phlebotomy cost / patient / day @ 5 min	$ 2.49	$ 3.26
RN cost / patient / day @ 5 min	$ 1.59	$ 3.78
Total Overall Hospital Cost	**$ 13.72**	**$ 14.50**

Heparin Anti-Xa reimbursement $17.96 National Rate

APTT reimbursement $ 8.24 National Rate

*Vandiver, JW and Vodracek, TG; Pharmacotherapy, Vol 32, No 6, 2012
**Payscale.com Feb 2017 Avg/Hr
CodeMap®

Educate Key Departments

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Decision makers

Discuss with decision makers to demonstrate value

Lab management: Meet with e.g., pharmacy, procurement, and physician management to present advantages of the Heparin Anti-Xa assay.

Provide proof sources.

Develop Champion to drive process.

Hospital Staff

Discuss the change with staff

Lab and Pharmacy management together present to nursing and medical director

Present Heparin Anti-Xa advantages

Discuss the advantages of conversion to Heparin Anti-Xa

- Improved patient outcomes
- Overall system efficiency
- Direct measurement of patient's heparin level
- Consistent therapeutic range

Training on New Heparin Protocols

Lab Personnel

- Use of reagents and anti-Xa application.

Nursing, Pharmacy and Physicians

- Explain the benefits to anti-Xa monitoring and improved outcomes.
- Educate on value interpretation and patient treatment.

Set the Stage for Anti-Xa Testing

- **Set up orderable anti-Xa assay(s)**
  - ✓ IT and catalogue of requirements.
  - ✓ List the most commonly used UFH and LMWH drugs from your hospital.
  - ✓ Include therapeutic ranges for both UFH and LMWH.
- **Set up heparin protocol(s) based on anti-Xa monitoring.**
- **Inform all personnel affected by the change.**

Challenges to Acceptance

- Increased lab costs for reagents; however, reduced overall costs for the medical center
- Change in existing processes
- Time to get familiar with new method

Move beyond a departmental budget and focus on improving patient care.

Heparin: Monitor with Confidence
INNOVANCE Heparin

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- Available 24/7

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QUESTIONS?