APTT vs Anti-Xa for Unfractionated Heparin Anticoagulation Monitoring

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Objectives

- Review clinical indications and considerations for unfractionated heparin (UFH) anticoagulation
- Understand the current laboratory methods and practices used to guide UFH anticoagulation
- Discuss the limitations of these assays and discuss implementation of alternative strategies and hurdles associated with same.

UFH citations

- **Clinical**: Smythe, MA et al. J Thromb Thrombolysis. 2016; 41:165-86.
- **Laboratory**:
  - Controversies: Zehnder J, et al Am J Hematol 2012; S137-140.
  - Monitoring: Marlar RA, et al Sem Thromb Hemost 2017; 43:253-60.
  - Anti-Xa discordance: Price EA, et al. Ann Pharmacotherapy 2013; 47:151-58.

UFH: What does it do

Sulfated glycosaminoglycan which complexes with antithrombin (AT)

- Kinetically enhances AT activity
- AT is a serine protease inhibitor
  - Serine proteases:
    - XIIa, XIa, Xa, IXa, Thrombin
- Non-specific UFH binding
  - monocytes, endothelium, circulating proteins

UFH Anticoagulation - Clinical

- Indications
  - Treatment (e.g. VTE, ACS)
  - Prophylaxis (e.g. trauma)
  - Other (e.g. ECLS)
- Infusion dose
  - Weight based (total vs ideal vs adjusted)
  - To bolus or not
  - Maximum infusion rate

UFH Anticoagulation - Clinical

- Weight
- Laboratory Testing – baseline
  - CBC
  - PT and APTT
- Monitoring
  - Infusions vs subcutaneous
  - Guideline driven (e.g. CHEST)
  - Institution specific
  - Others (e.g. JCAHO)

UFH Anticoagulation – Clinical

- Although in place for ~60 years, the supporting evidence for current practices:
  - Weight based: weak
  - Monitoring frequency: weak
  - Monitoring methods (APTT vs anti-Xa): weak
  - Therapeutic targets:
    - APTT: very weak
    - Anti-Xa: very weak

Smythe, et al J Thromb Thrombolysis 2016; 41: 165-86.

UFH Anticoagulation – Laboratory

- Majority clinical laboratories use APTT
  - Reporting methods
    - Seconds
    - Ratios – historical, not recommended
  - Heparin Therapeutic Range (HTR)
- Alternatives:
  - When baseline APTT is elevated
  - When there is UFH “resistance”

UFH Anticoagulation – Laboratory

- Guidance
  - College of American Pathologists (CAP)
    - Checklist requirements
  - Publications
    - CAP Olson JD, et al Arch Pathol Lab Med 1998; 122:782-798
    - CLSI H47-A2 Approved Guideline 2008
  - Brill-Edwards P, et al Ann Intern Med 1993; 119:104-109.
    - Described Anti-Xa (protamine) vs APTT HTR (ratios 1.5-2.5)

CAP Recommendations for UFH monitoring

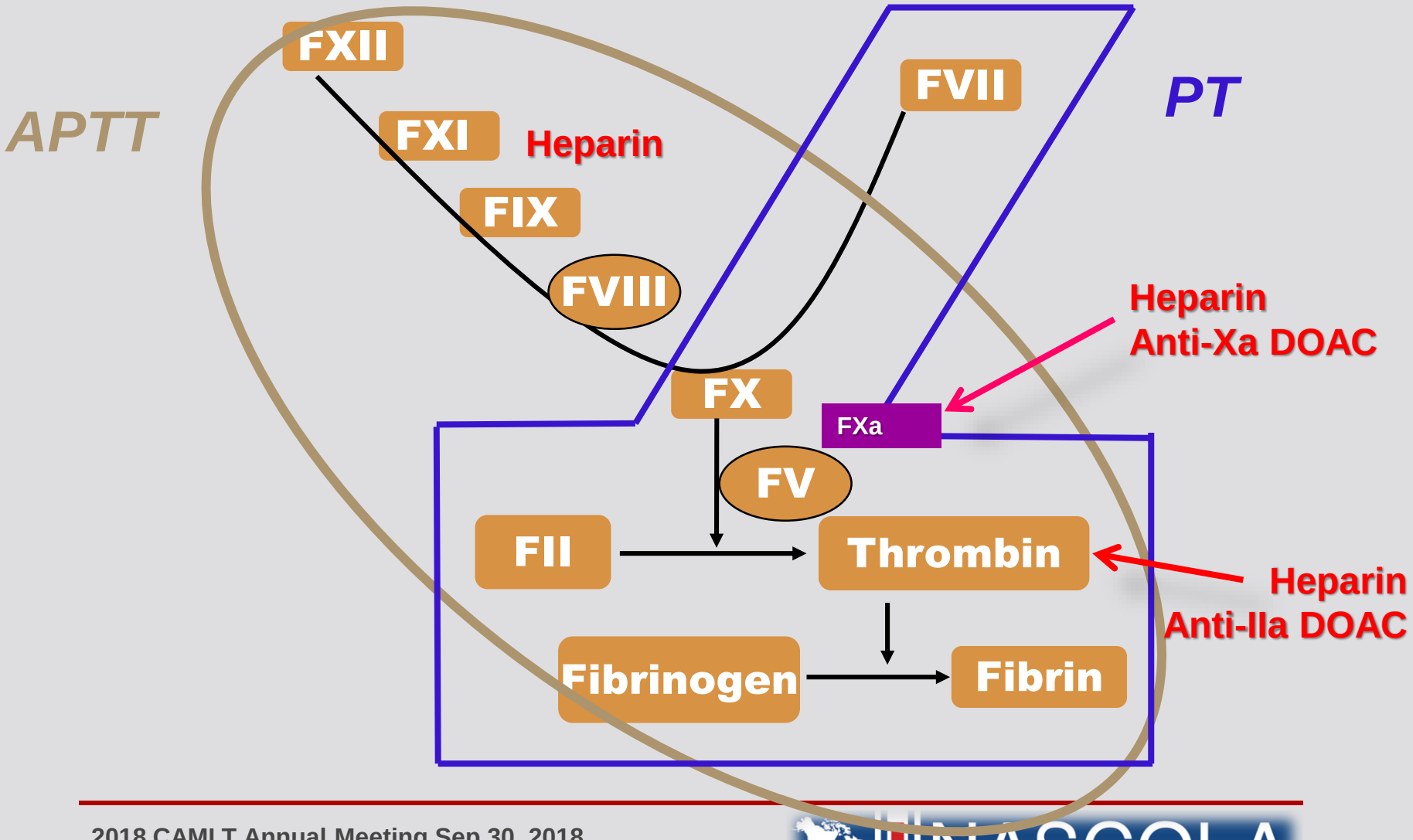
- Adjusted and therapeutic doses requires monitoring
- Monitoring to occur at 6 hour intervals until desired response reached.
  - For IV: daily monitoring thereafter, pref. before 1000
- Phlebotomy opposite extremity of infusion site
- Provide method and therapeutic range

CAP Recommendations for UFH monitoring

- Baseline aPTT and platelet count
- Therapeutic range for each lot aPTT reagent assessed by ex-vivo samples using:
  - Comparisons with heparin level
    - Anti-Xa or protamine titration
  - Comparisons with previously validated reagents
- Does not advocate in-vitro spiking for determining HTR

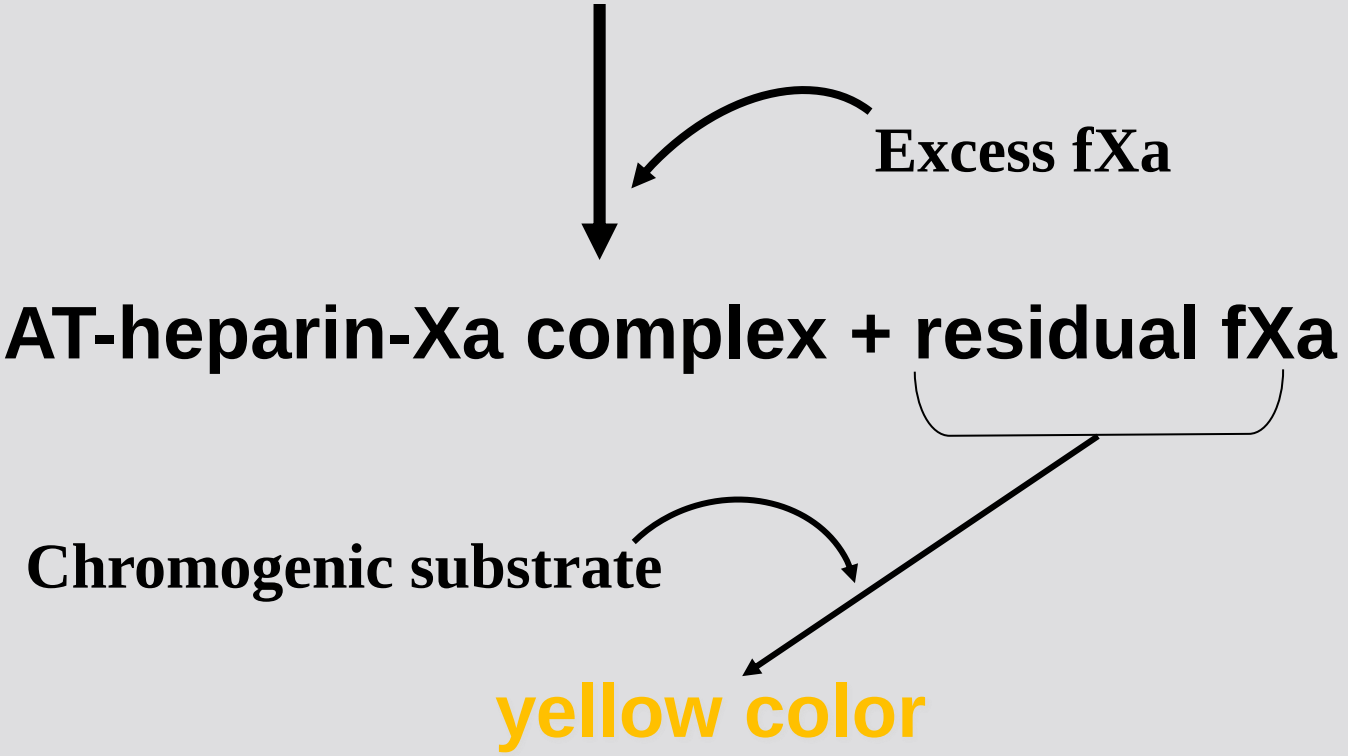
Reminders…

“Waterfall” Coagulation Cascade:



Anti-Xa activity

plasma [heparin] + (exogenous antithrombin)



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APTT vs Anti-Xa

APTT

- Diagnostic test
  - Factor deficiency
  - Inhibitor assessment
    - Factor
    - Lupus anticoagulant
- Monitoring test
  - UFH
  - DOAC assessment
  - Measure of Rx efficacy
    - FFP/Cryo therapy
    - Factor replacement

Anti-Xa

- Monitoring test only
  - UFH
  - LMWH
  - Pentasaccharide
  - DOAC
    - Xarelto (rivaroxaban)
    - Eliquis (apixaban)
    - Saveysa (edoxaban)
    - Bevyxxa (betrixaban)

Limitations of Testing

APTT

- Pre-analytical:
  - Sample stability, temperature, tourniquet time, site selection, citrate:blood ratio, etc.
- Analytical:
  - factor levels (high or low), inhibitors, anticoagulants, antibiotics, physiology, different lot sensitivity to factors and anticoagulants

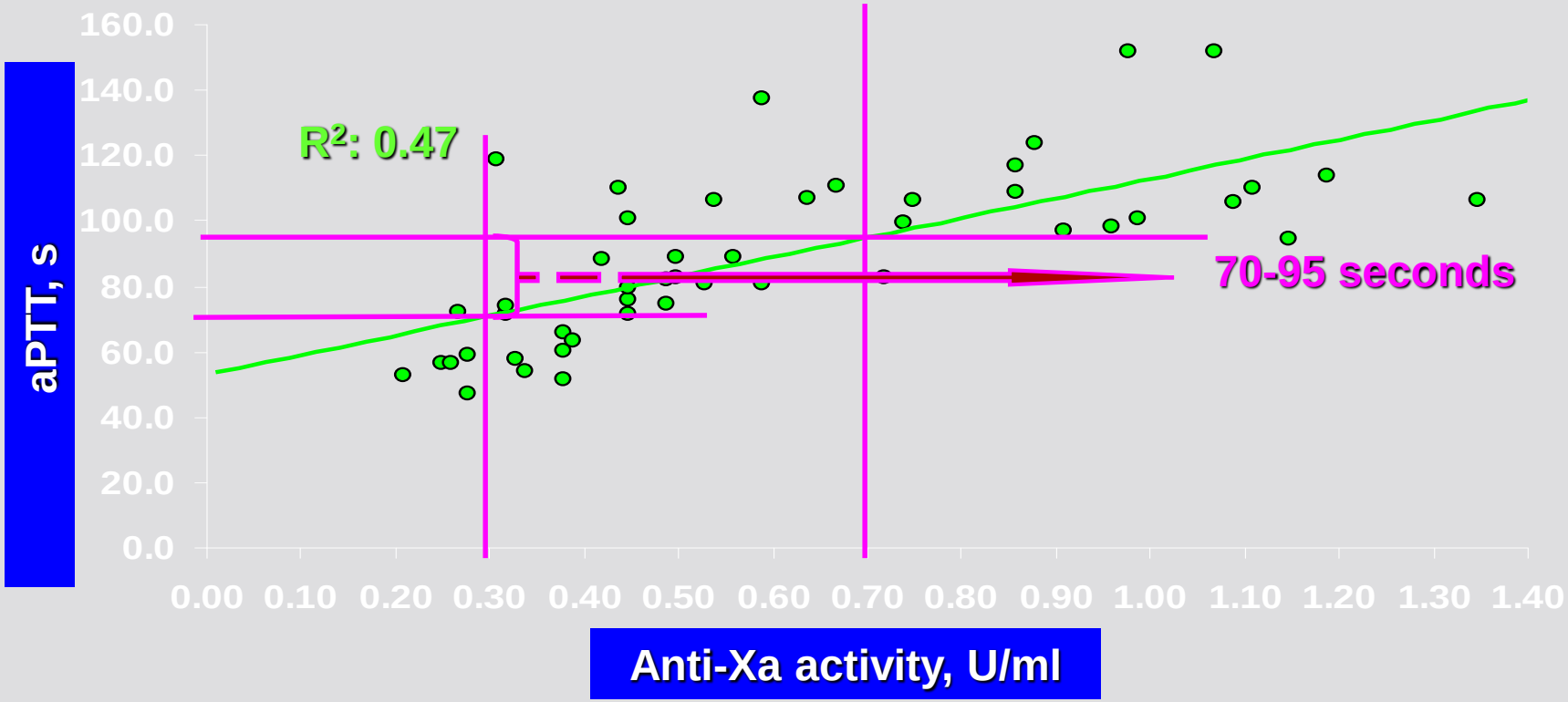
Anti – Xa

- Pre-analytical:
  - Timing of sample
  - Sample stability
  - Site selection
  - Processing
- Analytical:
  - Cannot differentiate between anti-Xa drugs
  - Possible challenges with icterus and lipemia
  - Calibration

CAP Recommendations for UFH monitoring

- Therapeutic range for each lot aPTT reagent assessed by ex-vivo samples using:
  - Comparisons with heparin level
    - Anti-Xa or protamine titration really?
  - Comparisons with previously validated reagents
- Does not advocate in-vitro spiking for determining HTR

UFH Therapeutic range (HTR)



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Heparin Therapeutic Range (HTR)

Modified Brill-Edwards method

- VTE Rx patients only
- Comparison between APTT and Anti-Xa
- APTT HTR corresponding to 0.3 – 0.7 in treated patients

- R^2 ranges between 0.35-0.70 **(never come close to 0.70)**
- Recheck with every APTT reagent lot change

CAP Recommendations for UFH monitoring

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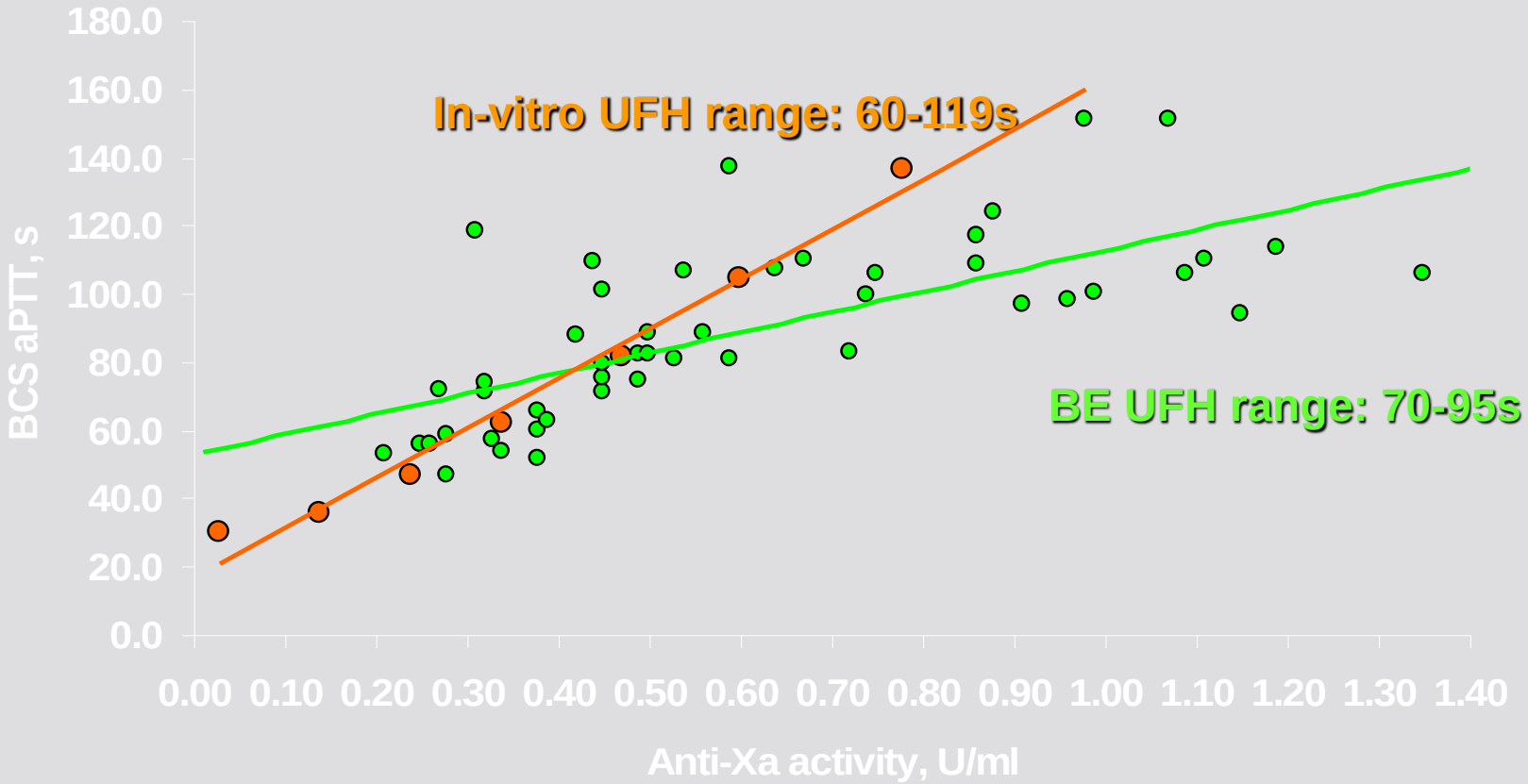
In-vitro addition vs Brill-Edwards HTR



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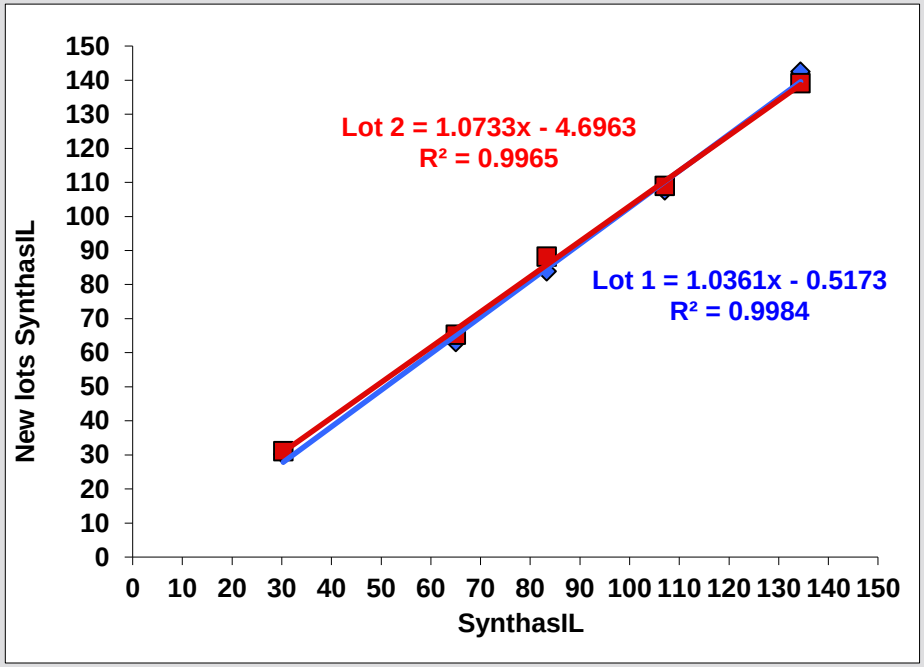
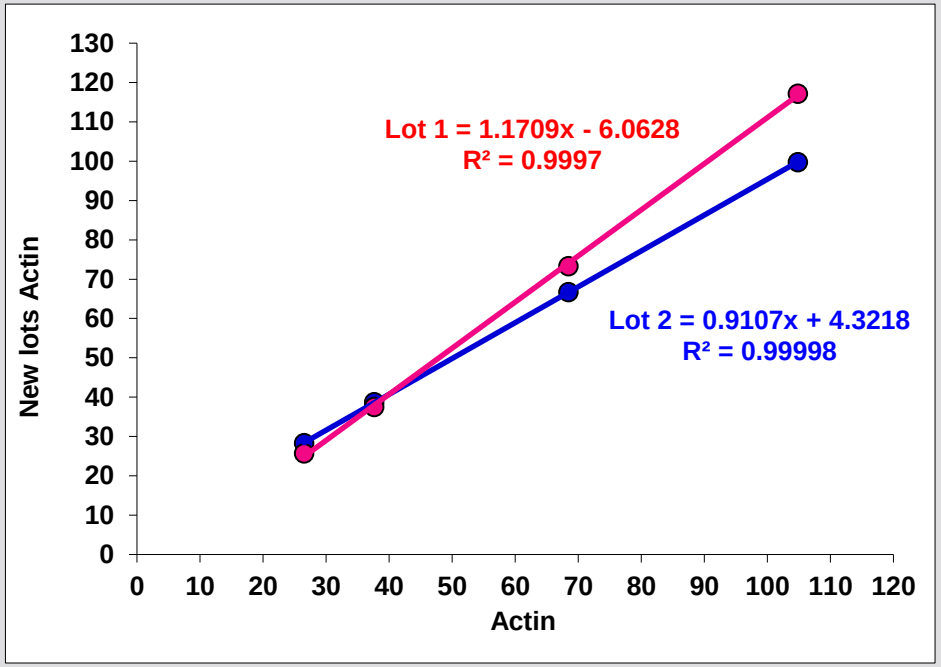
Proposed Alternative HTR Assessment for New lot APTT reagents

*** Comparing of commercial or UFH enriched NPP on current and new lot reagents**

*** Limits: slope? or intercept? or R^2? of combination thereof…**





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CAP Appendix to guidelines

- **Validation of UF heparin sensitivity of aPTT: Comparison with existing, validated reagent**
  - **Accumulating samples and freezing**
    - **NO minimum number detailed (Brill-Edwards: N=30)**
    - **Platelet-poor**
    - **No 2 samples on a given patient**
  - **Select reagent with comparable sensitivity**
  - **Comparison testing**
    - **old "x" axis vs new "y" axis**
  - **Cumulative summation of differences**
    - **Mean of new and old reagents**
    - **Difference between new – old**
    - **Cumulative difference over lots**
      - <5sec: **NS**; 5-7sec: **concern**; >7sec: **action**

Evidence supporting CAP summation of differences recommendations for UFH HTR assessment

Concept from S Moll, UNC

Heparin Therapeutic Range (HTR)

- Problems for new lot HTR assessment:
  - No recommended sample size
  - No more than 2 samples per patient
  - CAP recommendations (vague)
  - Not reproducible (beginning vs end)
  - Poor sample handling for Anti-Xa testing
  - Occurs every 12-14 mos
  - HTR changes to dosing order sets

UFH Monitoring: Recommendations

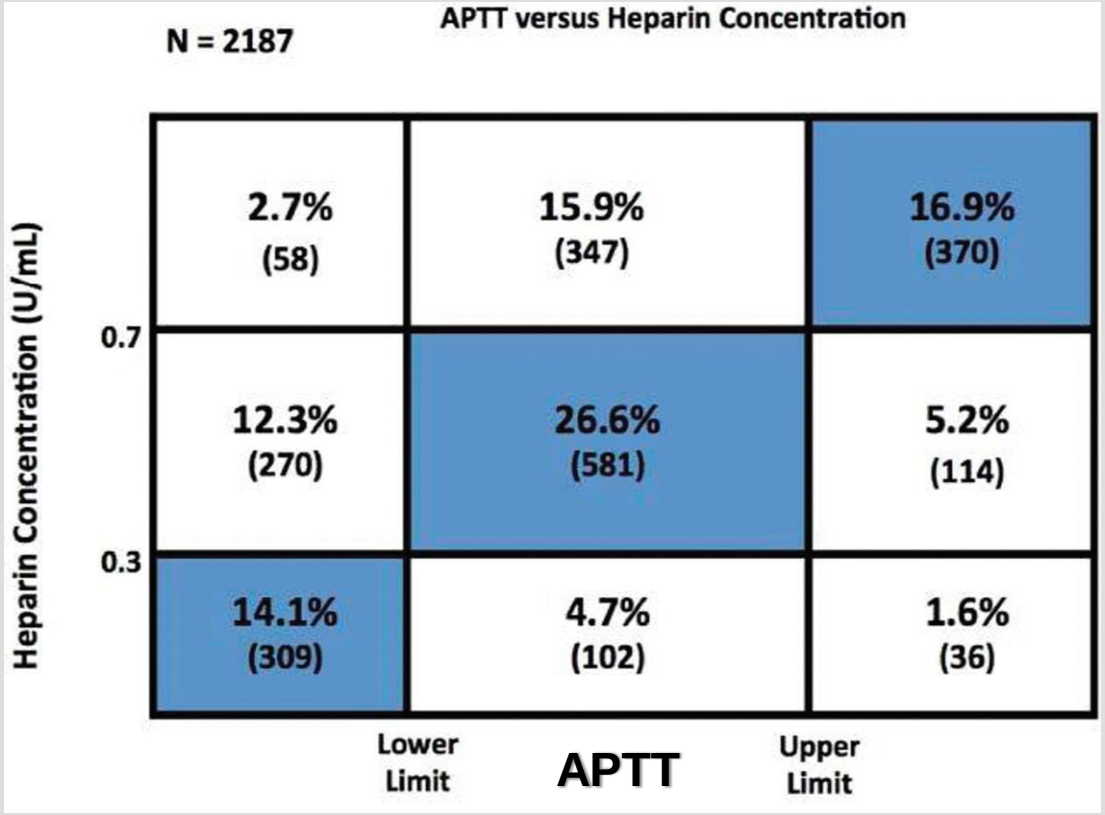
Acceptable HTR methods:

- **>20 samples (preferred N=30-50)**
- **<10% from same patient**
- **Samples with INR <1.3**
- **Frozen samples acceptable if demonstrated equivalence between fresh and frozen results**
- **Must be determined on all instruments in use**
- **Cannot use single instrument for multiple labs/sites/instruments**

Marlar RA, et al Sem Thromb Hemost 2017; 43: 253-60.

UFH Monitoring: Recommendations

Linearity between APTT and Anti-Xa measurements



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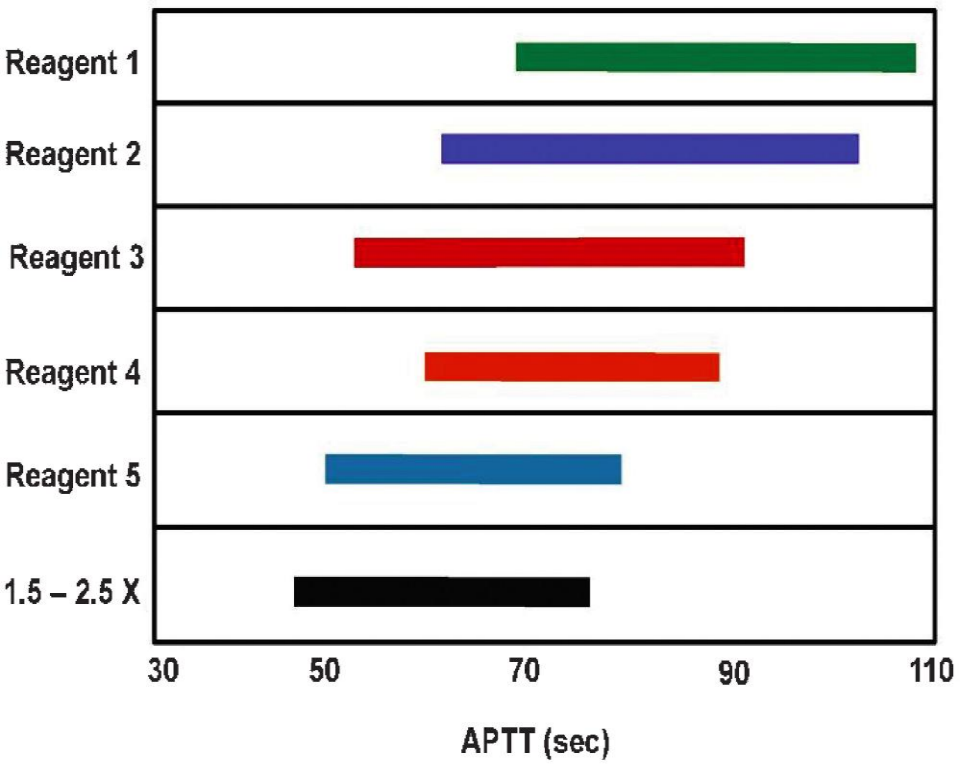
UFH Monitoring: Why not ratios

APTT ratios are not optimal



Marlar RA, et al Sem Thromb Hemost 2017; 43: 253-60.

Heparin “resistance”

Failure to achieve a therapeutic aPTT despite adequate or maximal dosing:

- **Elevated fibrinogen**
- **Elevated factor VIII**
  - **Depressed antithrombin**
  - **Drug not given**
  - **Wrong patient**

Heparin “resistance”

Alternative strategies:

- Most likely available, but not often utilized:
  - Thrombin time
    - Linear
    - TR can be created using UFH enriched normal pooled plasma
- May be available:
  - Anti-Xa

Anti-Xa measurements

Two types chromogenic methods:

- **With or without Antithrombin (AT)**
- **Without AT supplementing**

<50% AT = ↓Anti-Xa

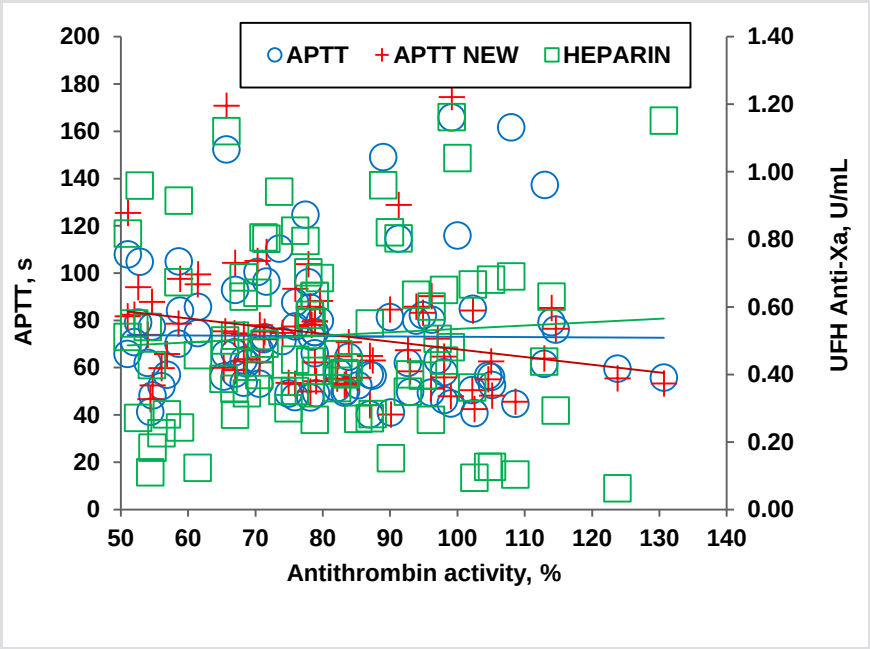
Sample mixing with NPP

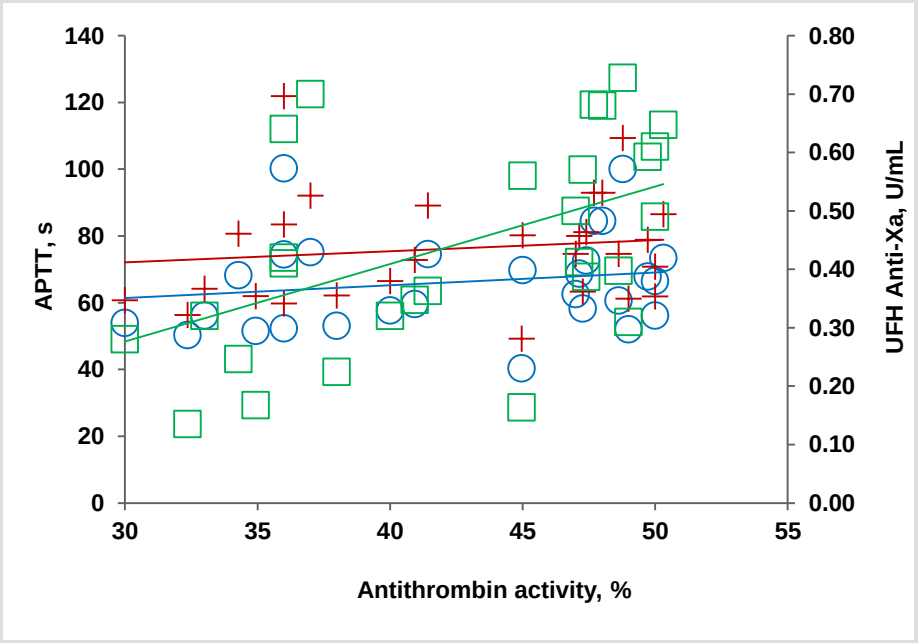
Calibration – variable

UFH, LMWH, Hybrid

Commercial vs In-house preparation

Anti-Xa activity: AT influence





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UFH via HTR monitoring

We know the APTT is dismal

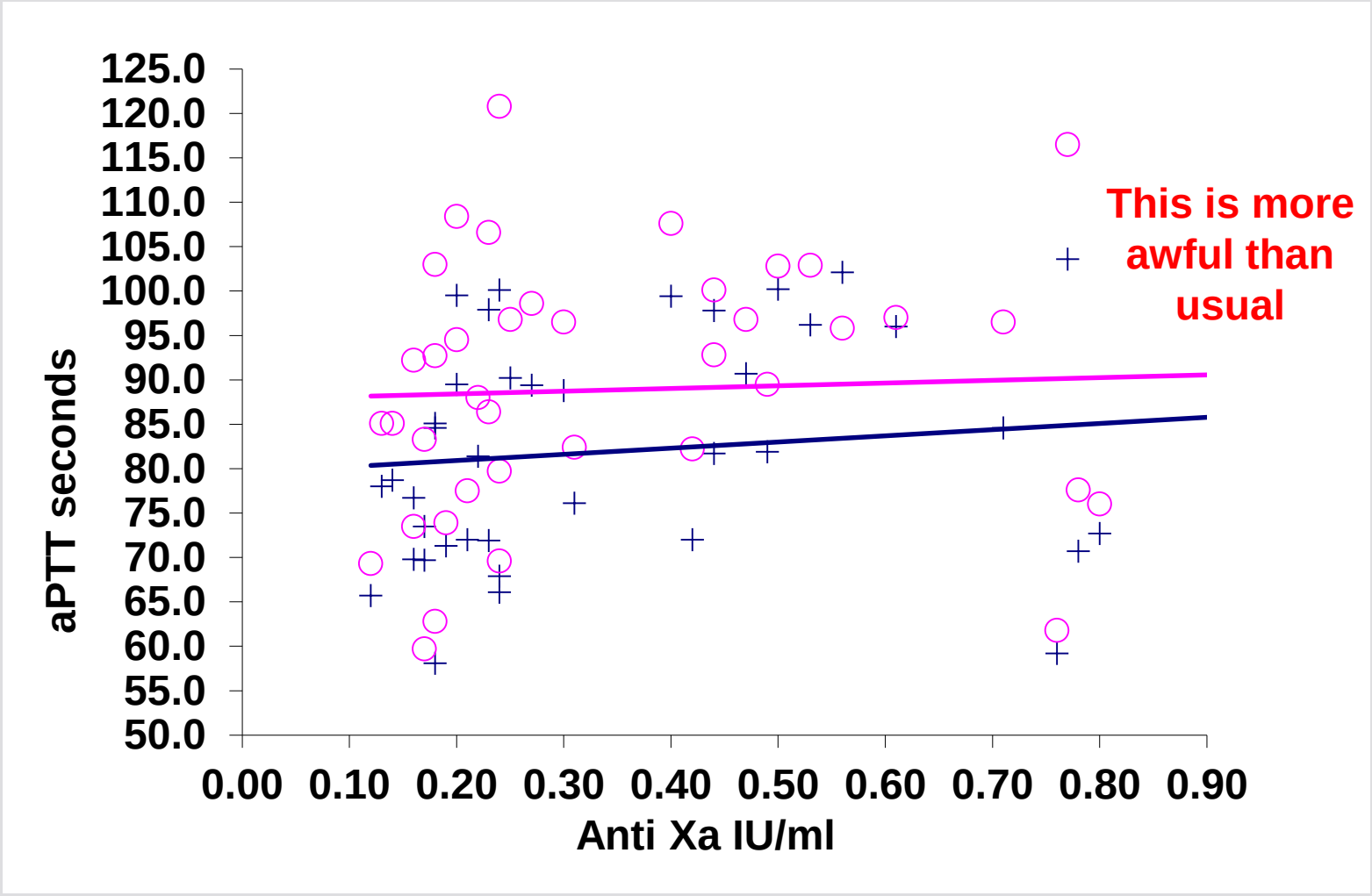
- Challenges with determining HTR
  - Guidelines - CAP
  - Feasibility – smaller labs
- Analytical – Pre-analytical variables
  - Quality of sample, time delays, other existing conditions, etc

Some labs opting for Anti- Xa testing

UCDHS UFH-HTR Challenges

- Historical:
  - Poor communication between laboratory and end-users
  - Implementing embedded comments within APTT result
  - HTR at beginning of lot does not reproduce at end of lot use
  - Timing and dosing order set changes
    - Easy for the lab, more challenging for the pharmacy
  - The straw…

2016: New lot APTT evaluation



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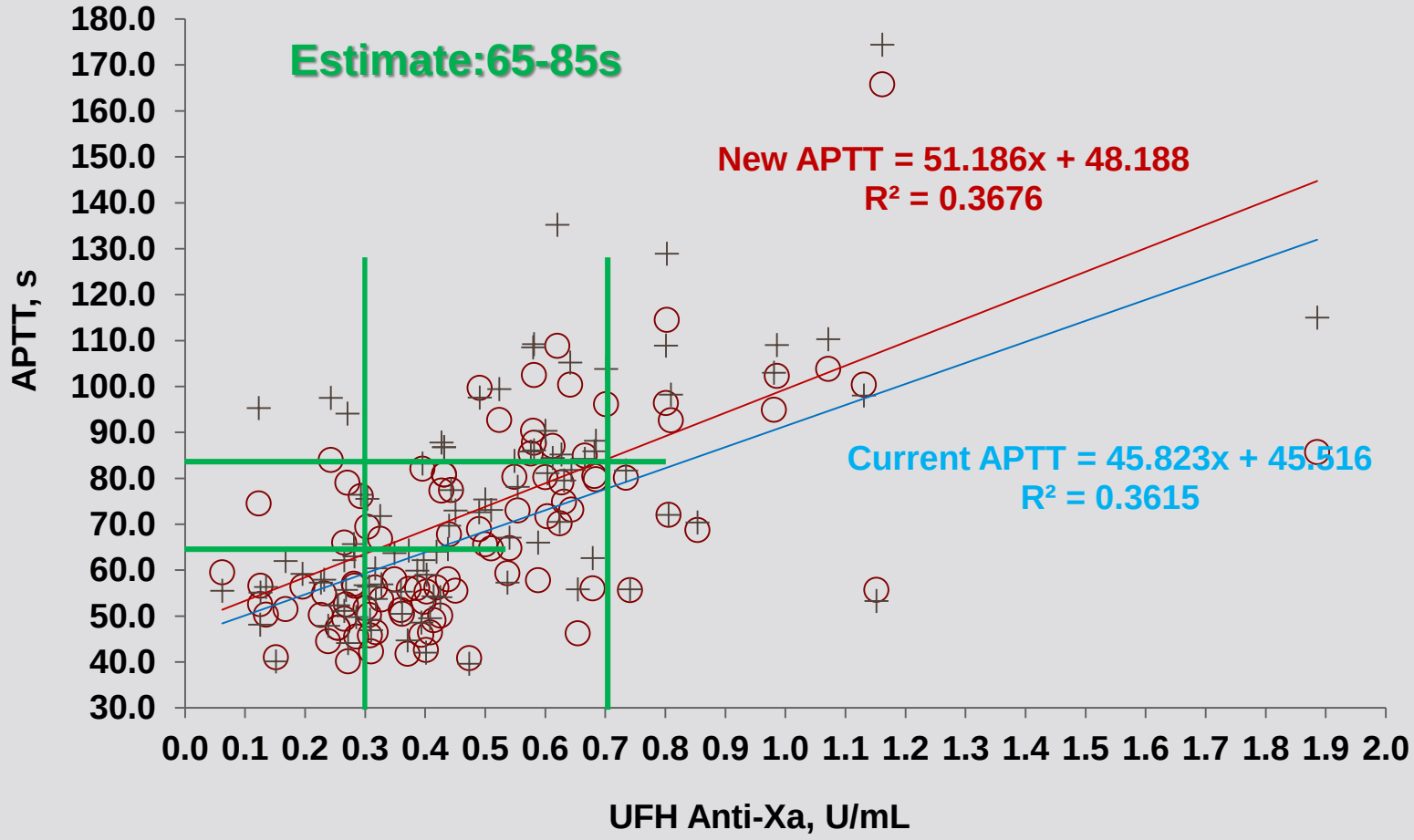
2016: New lot APTT evaluation

- APTT run on fresh samples
  - Auto-program run any elevated APTT with INR <1.19
  - Samples meeting criteria were saved:
    - Allegedly within 2 hours of collection
    - Allegedly after double centrifugation
    - Frozen at -70^{o}C
- Recommendation to run concurrent fresh APTT and anti-Xa activity

2016: New lot APTT evaluation



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2016 UCDHS UFH Monitoring

- Presented data to Thrombosis Subcommittee
  - Concerns about initial data and subsequent data
    - Most likely poor processing before freezing
  - Concerns about lot changes and failure to reproduce HTR
  - Recommendations made by laboratory to consider switching to anti-Xa measurements
    - Paradigm shift in practice
    - Similar shift to when we implemented INR reporting

UFH Anti-Xa monitoring: Education

- Rationale for monitoring change
- Identify potential cost and labor savings
- Identify potential putative benefits of 24/7 anti-Xa testing
  - Current practice is once daily anti-Xa testing

Education: APTT vs Anti-Xa Rationale for change

APTT

- Influenced by 8 Fx levels
- Poor specificity
- Diagnostic test
  - Screen for Fx deficiency
  - Screen for Inhibitor
- Monitoring test
  - UFH, DTI, DOAC
  - Post Fx Rx

Anti-Xa

- Monitoring test only
  - UFH, Anti-Xa DOAC

Monitoring UFH with Anti-Xa Rationale for change – Cost?

- Shorter time to therapeutic target (TTT)
  - Within 6 hours (54% Anti-Xa vs 27% APTT)
  - Within 24 hours (74% Anti-Xa vs 63% APTT)
- Less dosing changes with 24 hours
  - Average 1.7 for APTT
  - Average 1.0 for Anti-Xa

Fruge, et al Am J Health-Sys Pharm 2015; 72 (Suppl 2) 590-7.

Monitoring UFH with Anti-Xa Rationale for change – Cost vs Savings?

- TTT
  - Ave 28 Hrs with Anti-Xa vs 48 Hrs with APTT
- More test results within TT goal:
  - 66% for Anti-Xa vs 42% for APTT
- Less rate changes within 24 hours:
  - 0.8 for Anti-Xa vs 1.6 for APTT

Guervil, et al Ann Pharmacother 2011; 45:861-8

Monitoring UFH with Anti-Xa Rationale for change – Savings?

Less RBC transfusions associated with Anti-Xa UFH monitoring

UFH Indication	Odds ratio (95% CI)	Sample Size
ACS	0.16 (0.14 – 0.18)	14822
Stroke	0.41 (0.29 – 0.57)	1568
VTE	0.35 (0.26 – 0.48)	4414

UFH Indication	Bleed % Anti-Xa	Bleed % APTT
ACS	7.0%	24.6%
Stroke	13.8%	21.9%
VTE	3.9%	8.6%

Belk et al, J Thromb Haemost 2016, epub doi: 10.1111/jth.13476

Monitoring UFH with Anti-Xa Rationale for change – ?

- Stanford University hospital
- For ~ 9 years
- Discordant APTT vs Anti-Xa (higher APTT)
  - High 1-2 samples
  - Constant high >2 samples
  - Increased bleeding
  - Increased mortality
- Their practice: first 3 samples APTT + Anti-Xa

Price, et al Ann Pharmacother 2013;47:151-8

2016 UCDHS UFH Monitoring

Analyzing the data from UFH treated patients (N=243) :

	Current APTT	Anti-Xa (0.3-0.7)
No Rate Change	78	143
Rate reduced	61	53
Rate increased	78	47*

* Included 15 liver failure patient samples

Reasons (and benefits) to transition for Anti-Xa UFH monitoring

- TTT reached sooner
- Less dose changes
- Less testing
- 24/7 Anti-Xa testing
  - Putative benefit – Anti-Xa DOAC measurements
- No need for annual APTT reagent lot evaluation
  - Never change UFH dosing order sets again (?)
- Dwindling and exiting expertise in the field

UCDHS transition to Anti-Xa

1. What are the issues?
2. Did the transition happen?

UCDHS UFH Anti-Xa implementation

Identifying stakeholders

- Pharmacy, Surgery, ICU, GenMed, HemeOnc, ECLS
  - CMO meeting – on board
  - P&T committee – on board

Education

- Ownership
- Who takes lead and calls

- Lab logistical issues
  - Changing practice in laboratory
    - Staff?
    - Reagents?
  - Cost differential

Putative benefits for 24/7 Anti-Xa operation?

UCDHS transition to Anti-Xa

Transition to anti-Xa monitoring occurred

Difficulties associated with transition:

- Education process
- Dosing nomograms
- Concurrent therapy (e.g. apixaban when admitted)
- Interferences with testing (APTT or Anti-Xa)

Special recognition

- Faculty:
  - Richard White, MD
  - Adam Giermasz, MD
- Pharmacists:
  - William Dager, PharmD
  - Aaron “Josh” Roberts, PharmD
- Clinical laboratory scientists:
  - Leslie Freeman, CLS
  - Lisa Gandy, CLS

Thank you…

Any Questions?