

# DOAC Assessment at UCDHS:

## What's important

CRDH Public Workshop

IVD Testing for DOACs

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# Disclosures

Consultant

Instrumentation Laboratory, Inc

North American Advisory Committee

Sekisui Diagnostics, Inc

# Outline

- Introduction of concern
- What do we use at UCDHS?
- How did we validate it?
  - Challenges to validating
    - Accuracy assessment
- When do we use it?
- Concluding problems or concerns
  - Screening tests
  - Recommendations
  - Other

# New method verification of performance

- Imprecision
- Accuracy
- Carryover
- Linearity (reportable range)
- Reference range
  - where applicable, but not for DOAC testing
- Other

# DOAC Assessment at UCDHS

- Dabigatran
  - Implemented ECA testing in 2011
    - Chromogenic ecarin test
    - Hyphen Biomedical calibrators and controls
- Rivaroxaban
  - Implemented drug calibrated anti-Xa in 2013
    - Techniclone and Hyphen Biomedical calibrators and controls
- Apixaban
  - Implemented drug calibrated anti-Xa in early 2015
    - Stago and Hyphen Biomedical calibrators and controls

# Pradaxa prescribing information packet

## Section 2.4 Surgery and Interventions

If surgery cannot be delayed, there is an increased risk of bleeding [*see Warnings and Precautions (5.1)*]. This risk of bleeding should be weighed against the urgency of intervention [*see Warnings and Precautions (5.1)*]. **Bleeding risk can be assessed by the ecarin clotting time (ECT).** This test is a better marker of the anticoagulant activity of dabigatran than activated partial thromboplastin time (aPTT) or thrombin time (TT).

Copyright 2011, Boehringer Ingelheim Pharmaceuticals, Inc.

# DOAC test verification of performance

- Dabigatran
  - With ECA:
    - Drug obtained from Boehringer Ingelheim
    - Collaborative study – drug enriched plasma US+ labs
    - Collaborative study with UNC – patient samples
    - LC-MS/MS data provided by Boehringer Ingelheim
  - With ECA II
    - Comparison between ECA and ECA II
    - Commercial samples provided by sponsor

# Dabigatran ECA performance verification

## Within run imprecision

Mean, ng/ml	0	23	166
SD	0.4	0.5	16.0
CV	223.6%	2.3%	9.6%

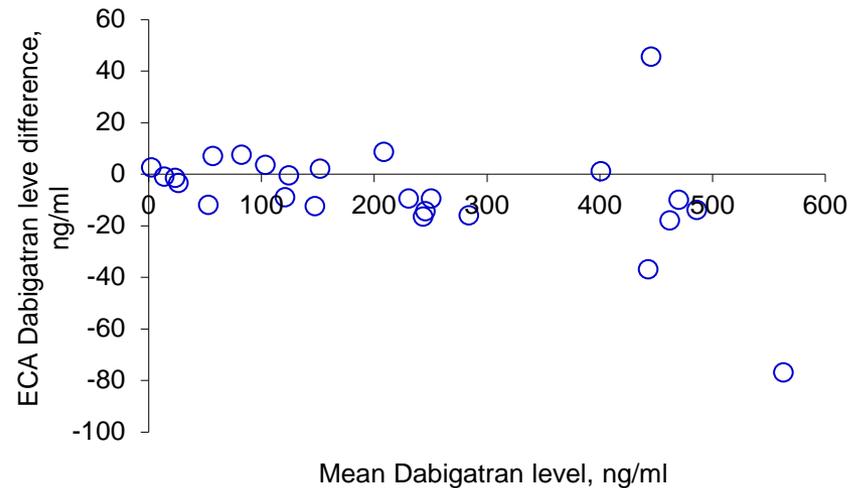
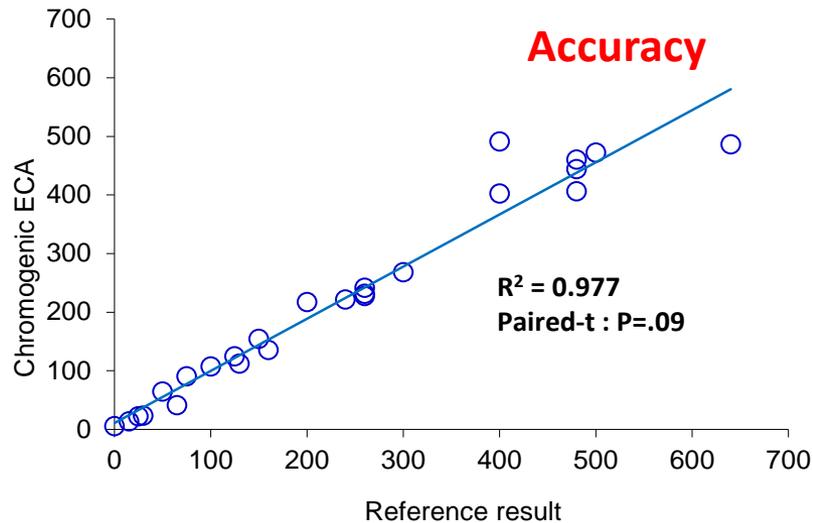
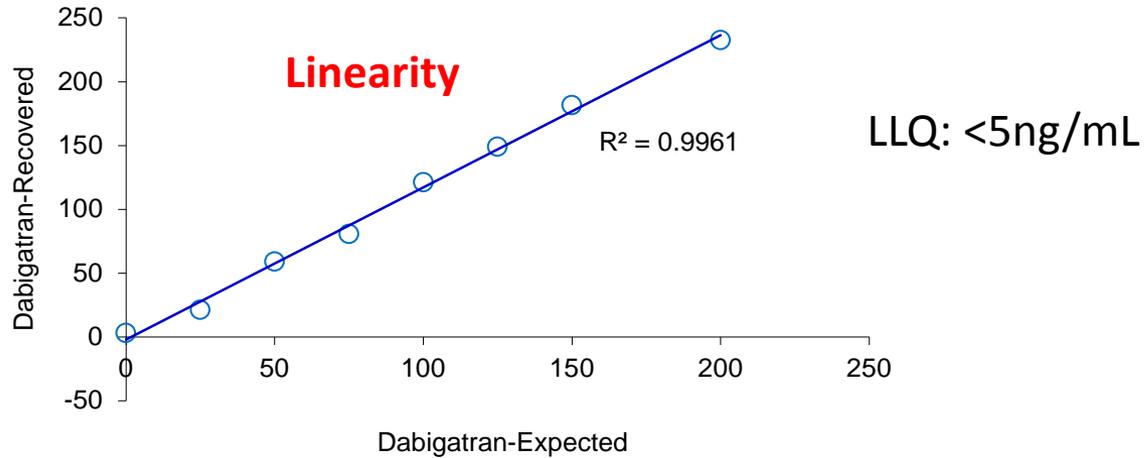
## Day-to-Day imprecision

Count	12	13
Mean, ng/ml	121	326
SD	9.0	26.8
CV	7.4%	8.2%

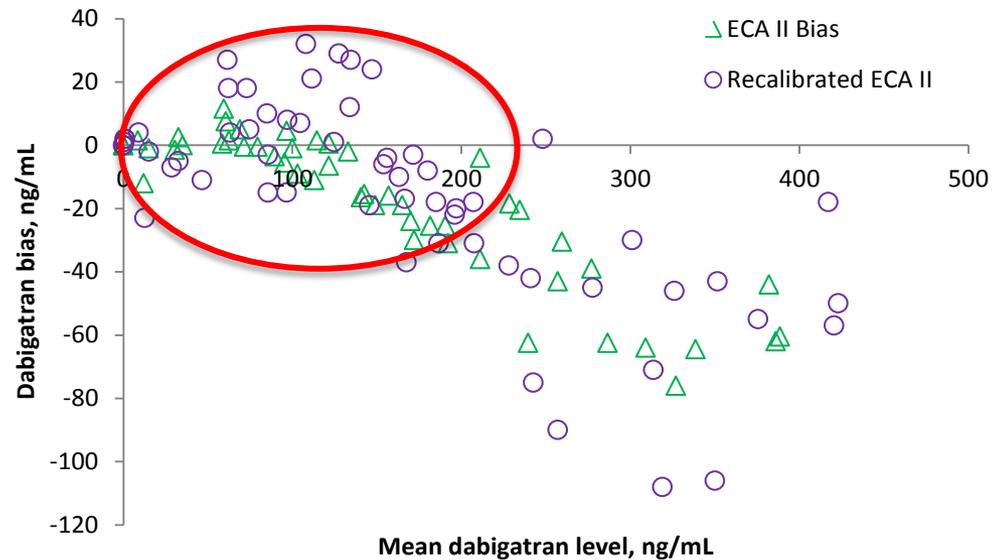
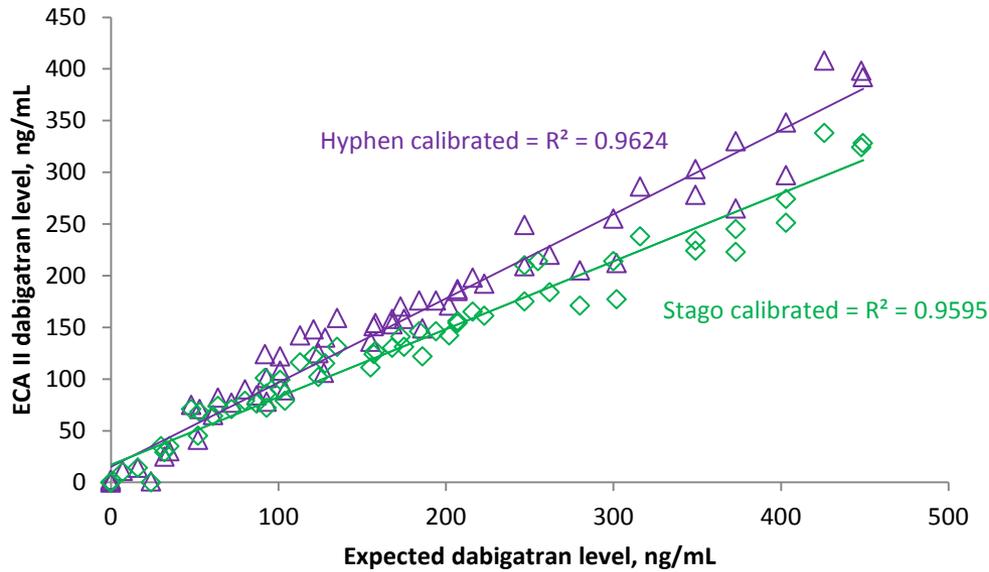
## Carryover

Sample	ECA
Dabi-0ng/ml	0
Dabi-480,ng/ml	472
Dabi-0, ng/ml	0

# Dabigatran ECA performance verification



# Dabigatran ECA II performance verification



# Post-Analytical

Comment with each result – P&T subcommittee

*Although a therapeutic range has not been established, in a prospective clinical trial of patients with atrial fibrillation, the range of trough dabigatran levels receiving 150mg b.i.d. was 40-240ng/ml.*

# FXa DOAC test verification of performance

- Rivaroxaban
  - Collaborative study with UNC – patient samples
  - LC-MS/MS provided by Lab Corp
  - Drug obtained from Janssen Pharmaceutical Inc
    - Enriched plasma studies
- Apixaban
  - Drug obtained from pharmacy
    - Enriched plasma studies
  - Multiple manufacturers – controls/calibrator material
    - Variable reconstitution of commercial material
- Edoxaban
  - Drug obtained from Daiichi Sankyo Inc
    - Drug enriched plasma studies
  - LC-MS/MS provided by Lab Corp

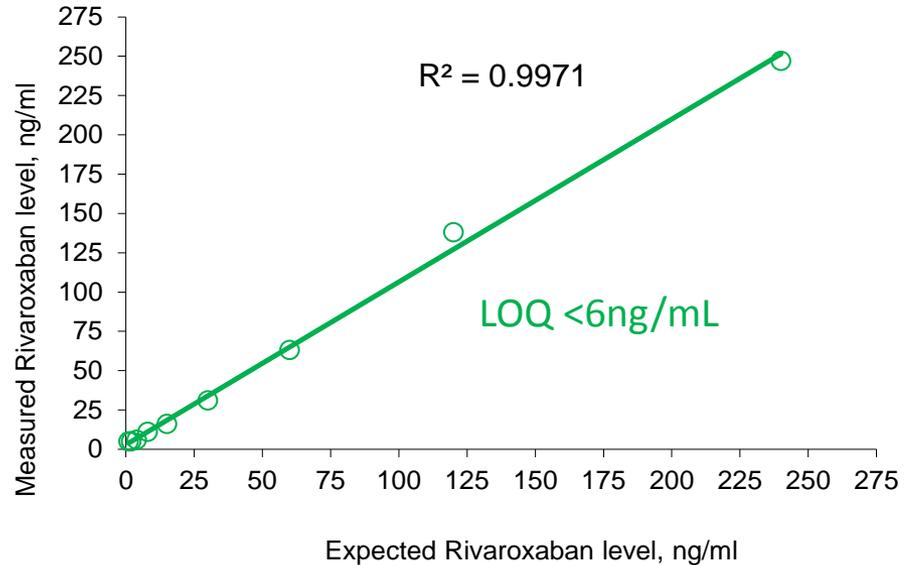
## Imprecision

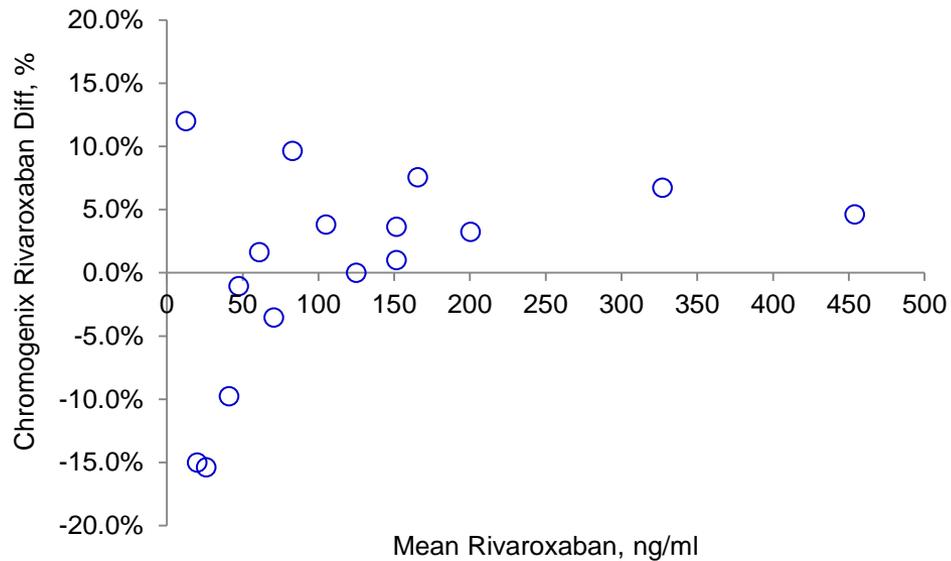
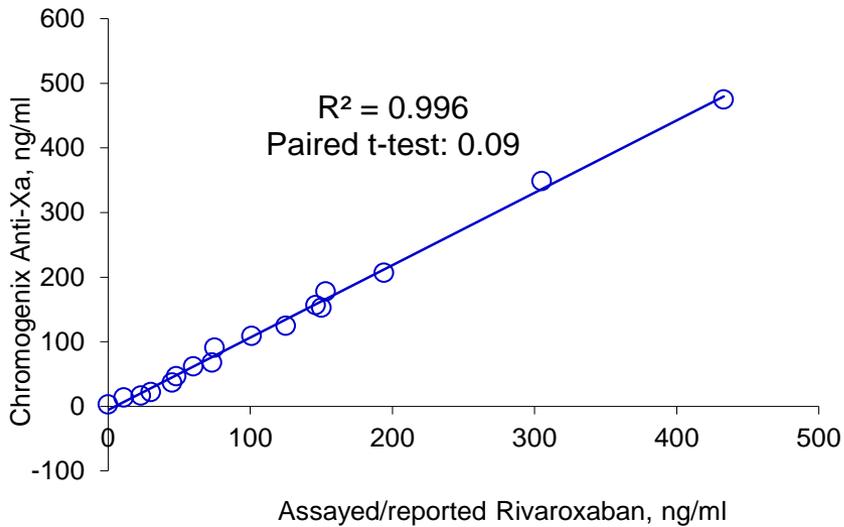
Within-run	N=10	N=10	Day-to-Day	N=12	N=12
Mean	99	292	Mean	107	317
SD	3	4	SD	7	18
CV	3.2%	1.4%	CV	6.1%	5.8%

Sample ID	Rivaroxaban Level
GK-NPP	2
Rivaroxaban - 480	475
GK-NPP	2

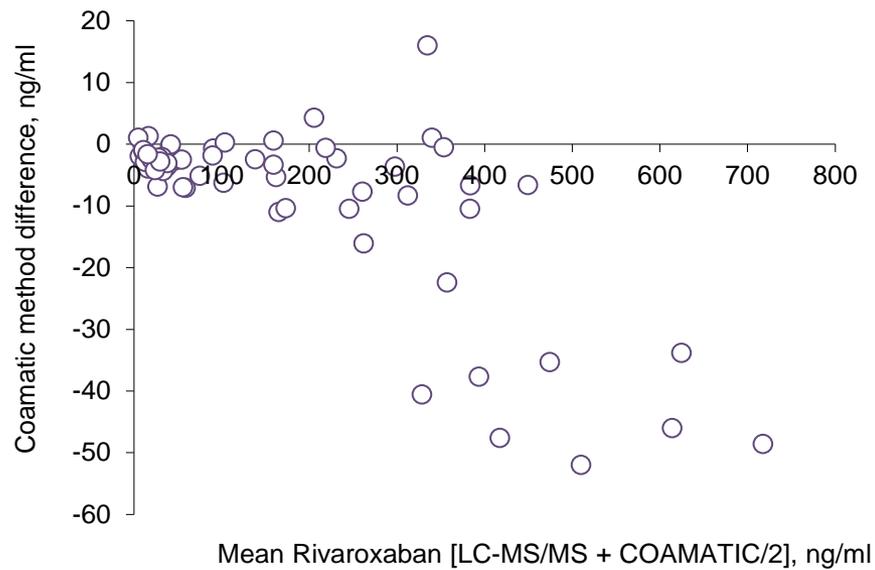
## Carryover

## Linearity



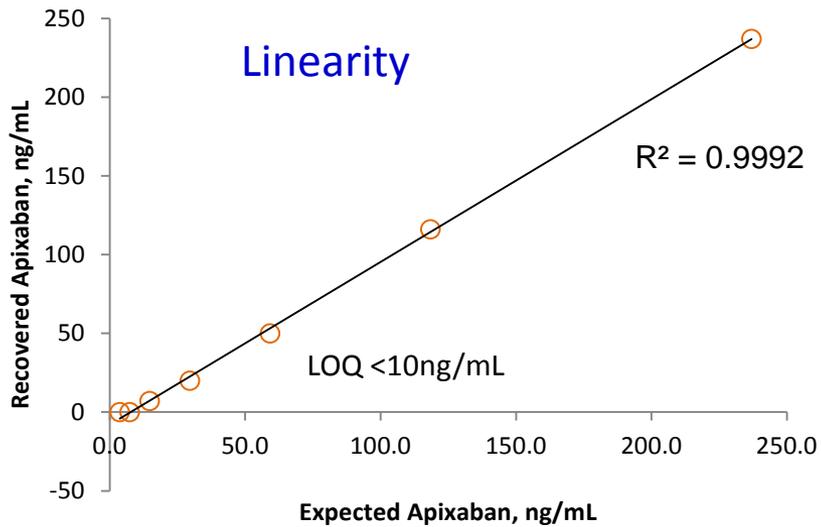
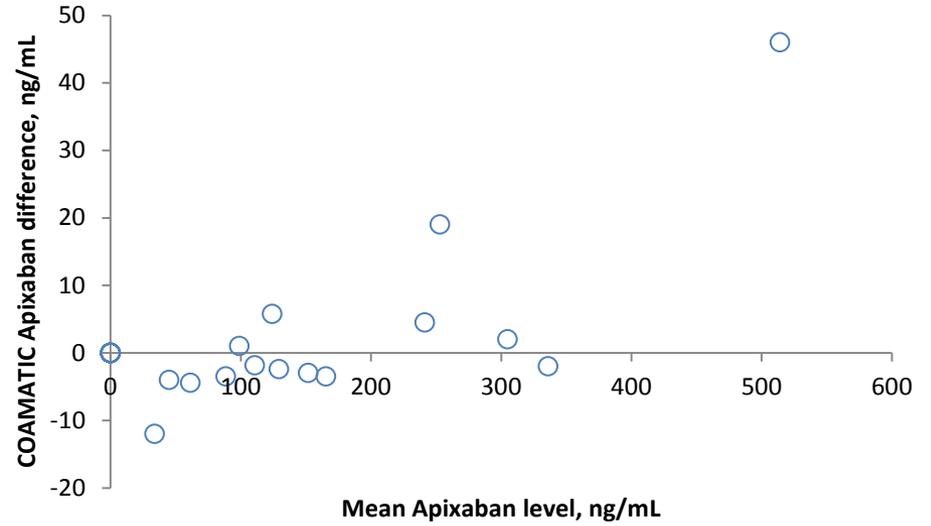
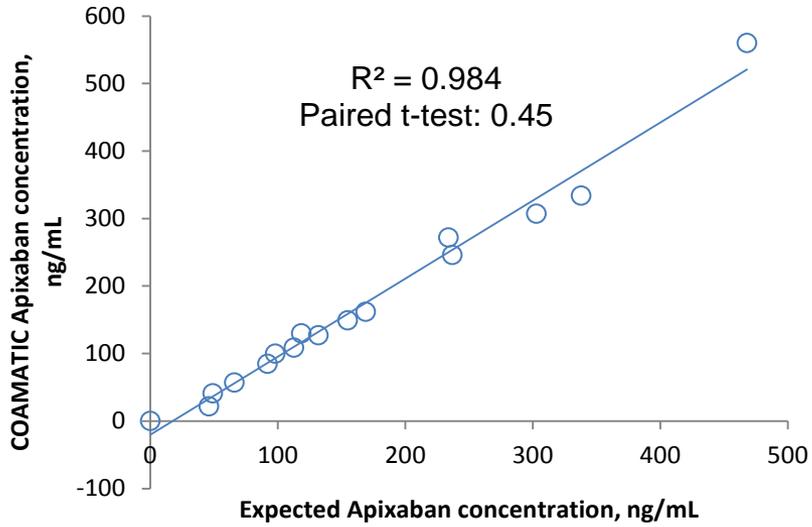


UNC Study



$R^2 = 0.988$   
Paired t-test: 0.60

## Accuracy



## Imprecision

N=11	QC1	QC2
Mean	85	302
SD	4.7	12.0
CV	5.6%	4.0%

## Carryover test

Sample ID	Apixaban level
Cal 1- 0ng/ml	0
CH - 338ng/ml	336
Cal 1- 0ng/ml	0

# Comment with each result:

## Rivaroxaban:

*Routine monitoring of Rivaroxaban (Xarelto) serum levels is not currently recommended with only limited data available for use patients receiving this drug. Results can vary depending on selected factors such as indication, renal function, daily dose and frequency of administration, with or without food etc. In the Einstein-DVT-Dose-Ranging Study (Blood 2008;112:2242-2247), patients receiving 20mg rivaroxaban once daily for continued DVT treatment had median trough drug levels of 32ng/mL (19-60ng/mL interquartile range) . For further assistance regarding Rivaroxaban plasma levels please contact anticoagulation pharmacists*

## Apixaban:

*There is no established therapeutic range for Apixaban. The 5mg bid dose used for stroke prevention in non-valvular atrial fibrillation has a predicted trough drug concentration of 41-230 ng/mL. (from [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_Product\\_Information/human/002148/WC500107728.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/002148/WC500107728.pdf).)*

Availability: M-F dayshift, call-in if STAT

– presence vs quantitation

Recommend trough collection (if timed)

Proficiency programs:

ECAT/NASCOLA : Dabi, Riva, Apix

CAP: Dabi, Riva

Surveillance:

Since inception:

~100 dabigatran levels (started 2011)

~60 rivaroxaban levels (started 2013)

~12 apixaban levels (started 2015)

The clinical laboratory establishing and offering a DOAC measurement test:

**What's important?**

What is the question that is being asked?

# DOAC assessment: The scenarios at UCDHS

- Known medications: Is it still there?
  - Pre-operative/procedure
  - Regional anesthesia
- Known medications: How much is there?
  - Bleeding and reversal
  - Not bleeding but elderly or renal dysfunction
  - Not bleeding with high values
- Unknown medications: What is there?

# DOAC – Is it there?

- Dabigatran
  - Thrombin time (not dilute thrombin time) is highly sensitive
    - Offered 24/7
  - Can quantify as well
    - Ecarin chromogenic assay
    - M-F dayshift, call in if emergent
- Factor Xa DOACs (FXa DOACs)
  - Rivaroxaban, apixaban
  - Drug calibrated anti-Xa
    - LLQ is ~10ng/mL
  - M-F dayshift, call in if emergent

# DOAC – How much is there?

- Dabigatran
  - Ecarin based assay
    - ECA – dist by Diagnostica Stago
    - ECA II – Diagnostica Stago
  - Adapted to BCSXP (Siemens Healthcare Diagnostics)
  - Calibrators and controls – (Hyphen Biomedical)
    - Stago calibrators and controls
- Factor Xa DOAC
  - Drug calibrated anti-Xa
  - Calibrators and controls
    - Diagnostica Stago
    - Techniclone
    - Hyphen Biomedical
    - Similar raw data values with rivaroxaban and apixaban

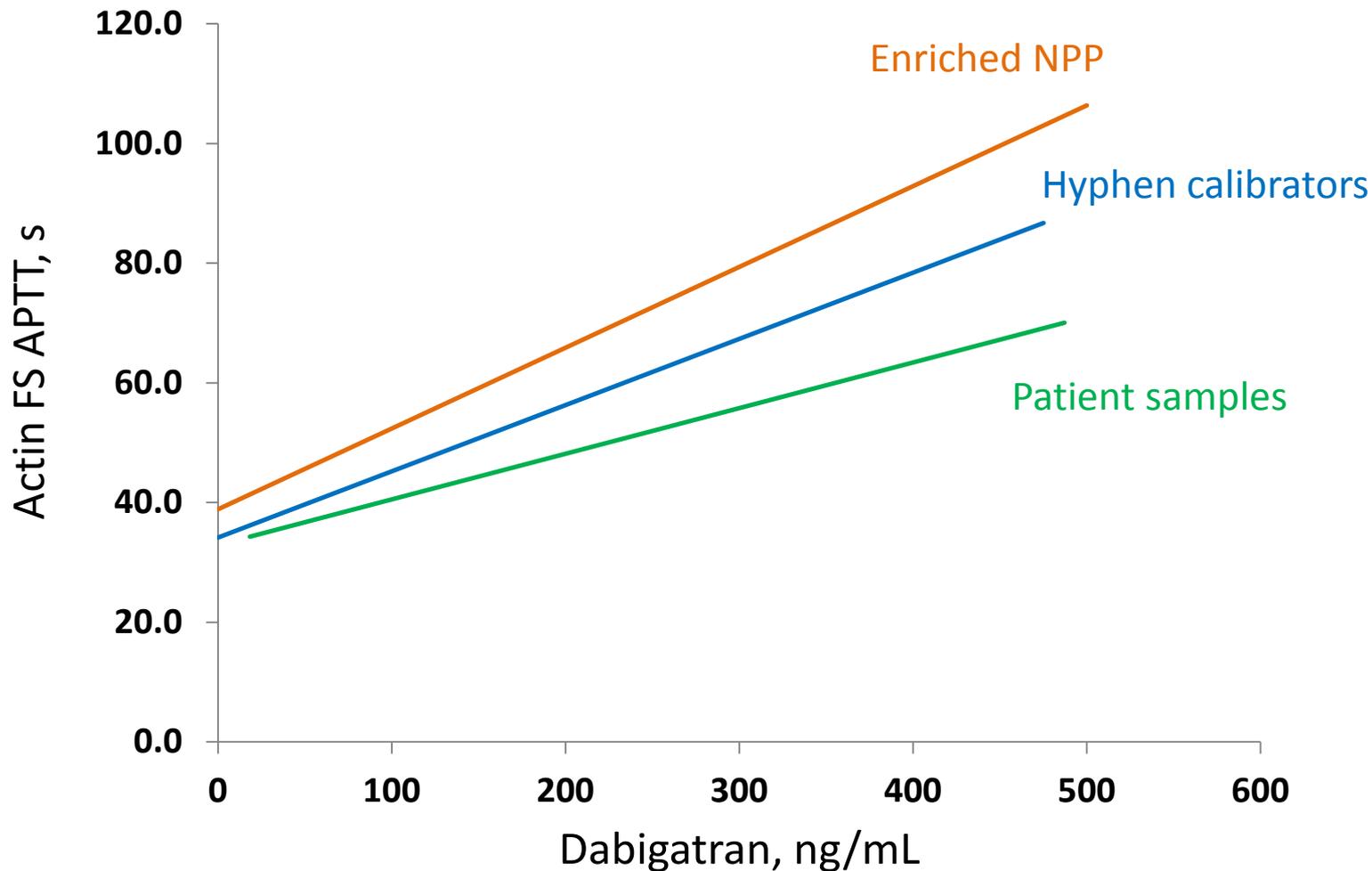
# DOAC Assessment in the US

- Based on recent College of American Pathologists proficiency survey:
  - ~4,500 laboratories report PT and APTT
  - ~400 laboratories report Anti-Xa measurements
    - UFH, LMWH, Hybrid
  - ~ 20 laboratories report measurement of DOAC
    - 19 Anti-IIa
    - 21 Anti-Xa
      - Only rivaroxaban?

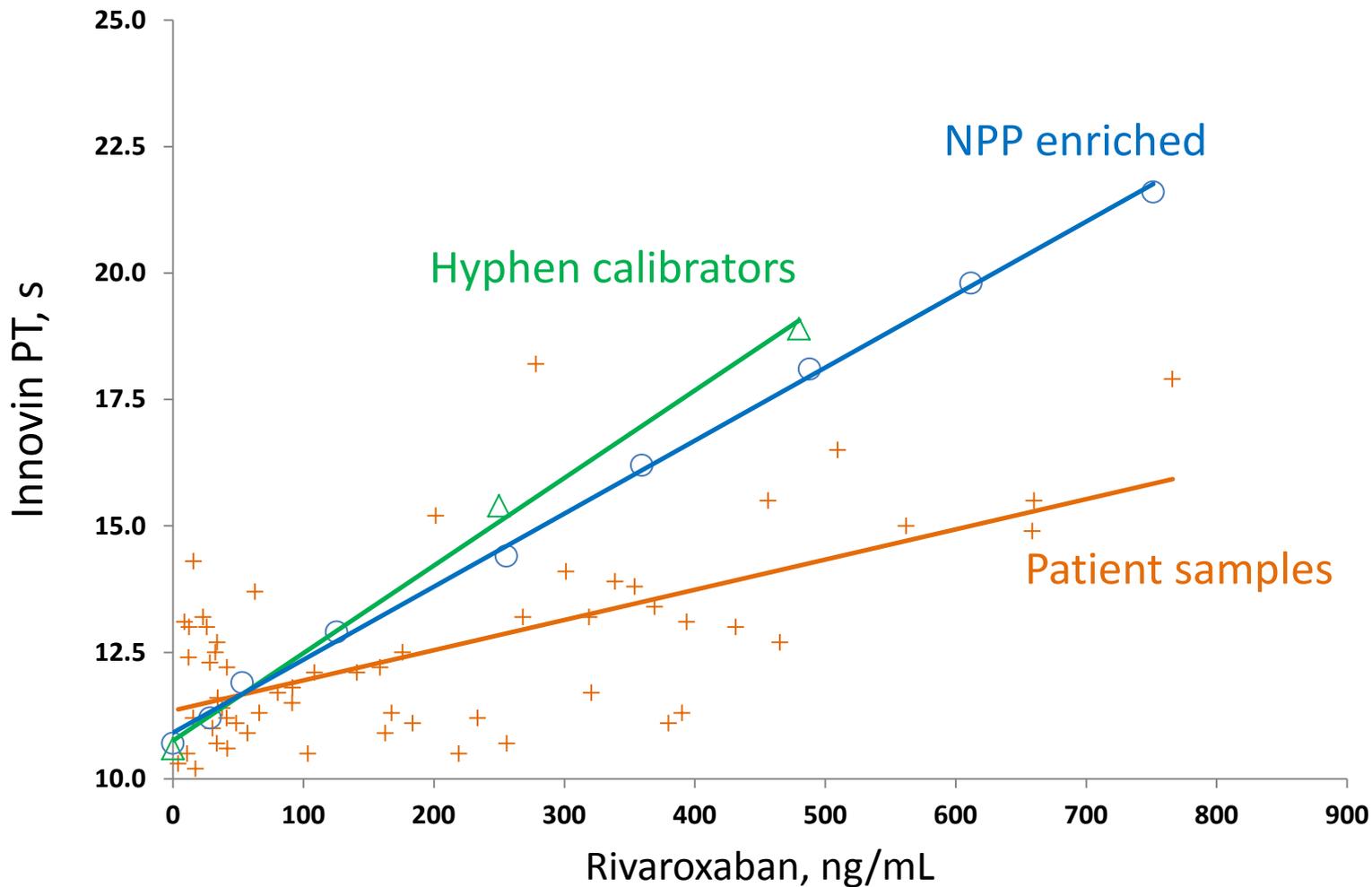
# The DOAC Generals in the US:

- With so few laboratories performing any quantitative measurement of DOAC,
  - **General** Assumption about reagents - guidelines
  - **General** Assumption about sensitivity - guidelines
  - **General** Assumption nothing is required -
  - **General** reluctance about performing any test in the absence of FDA approved material

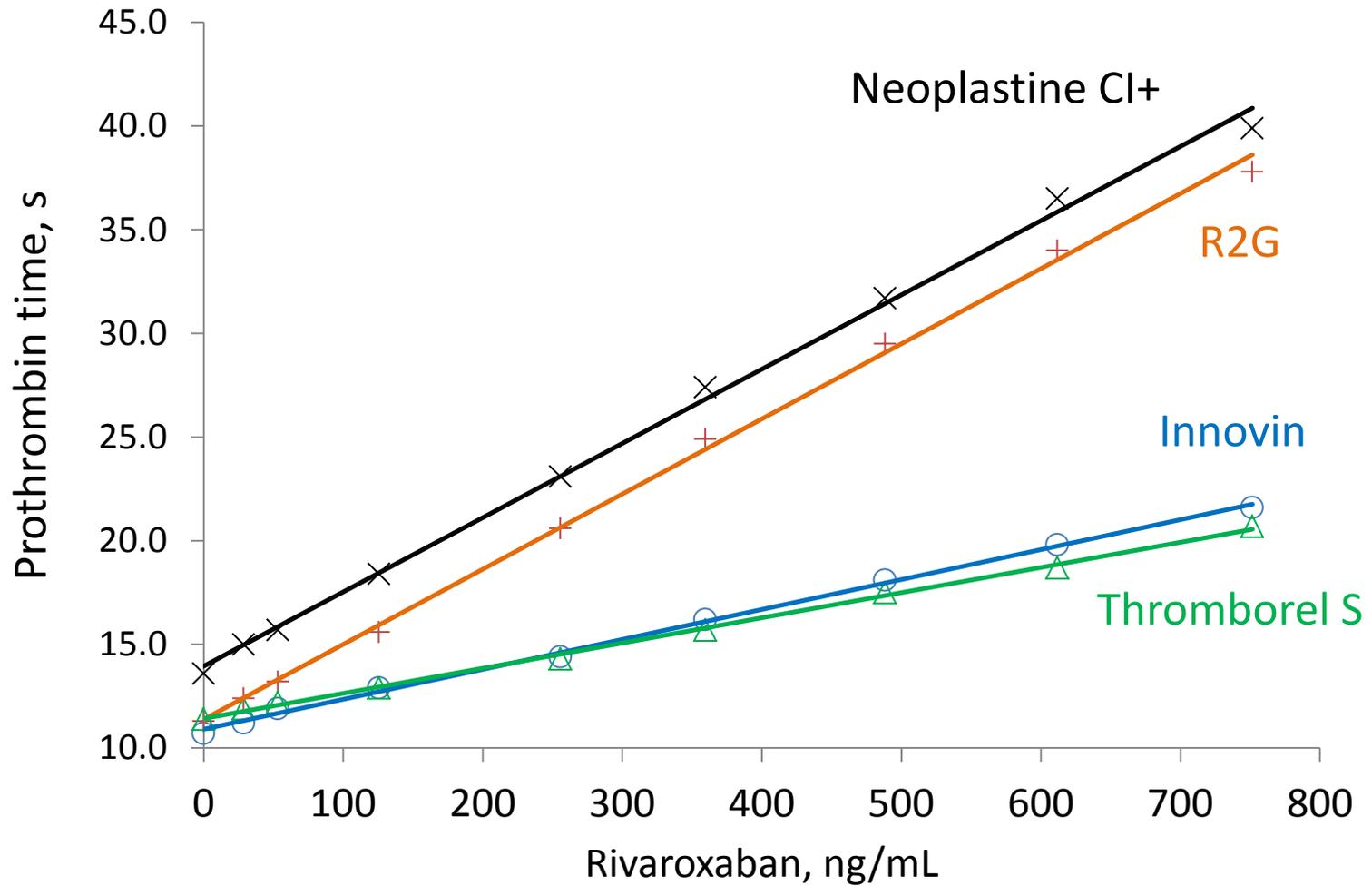
# In-vitro enrichment vs. commercial calibrators vs. patient samples



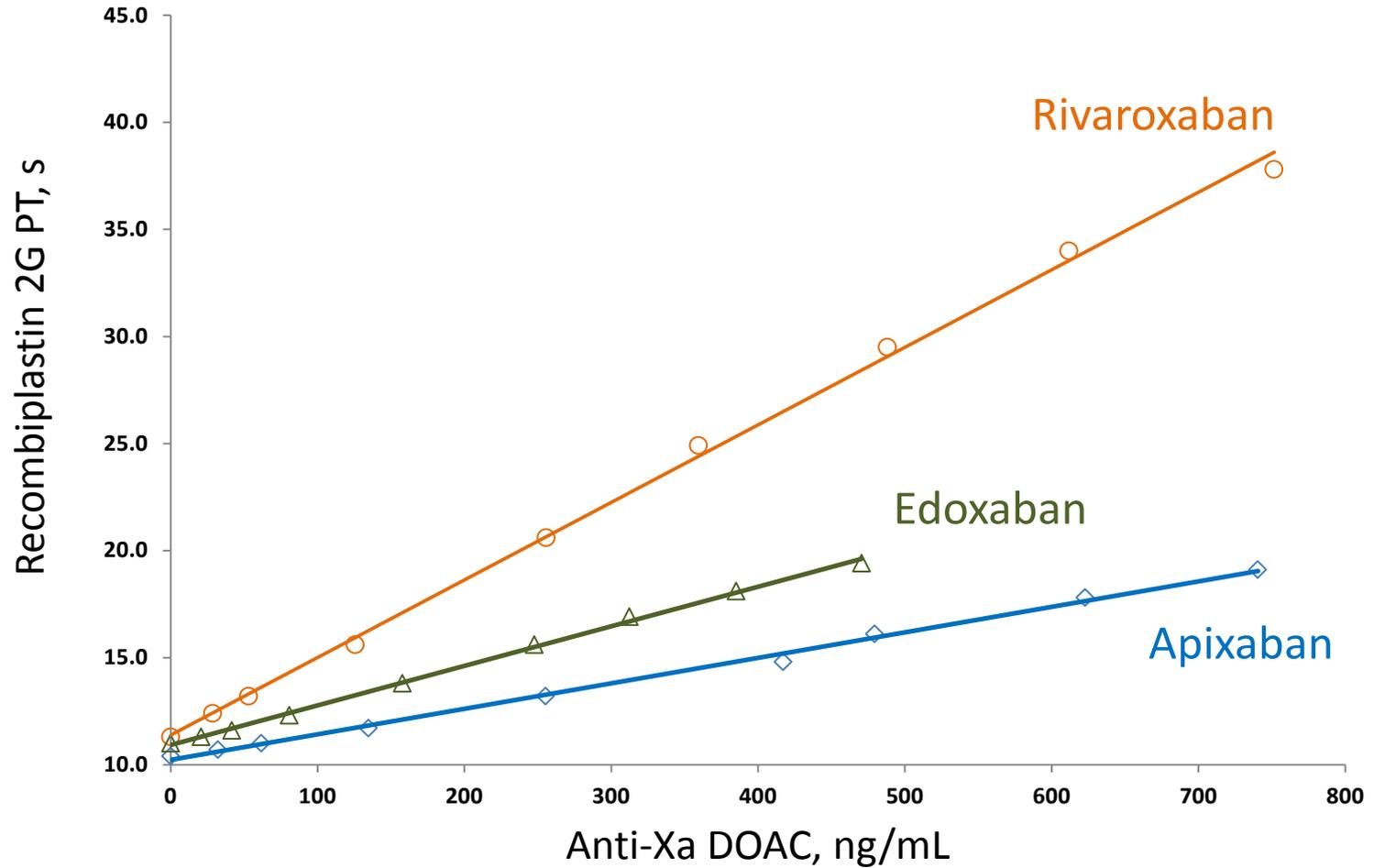
# In-vitro enrichment vs. commercial calibrators vs. patient samples

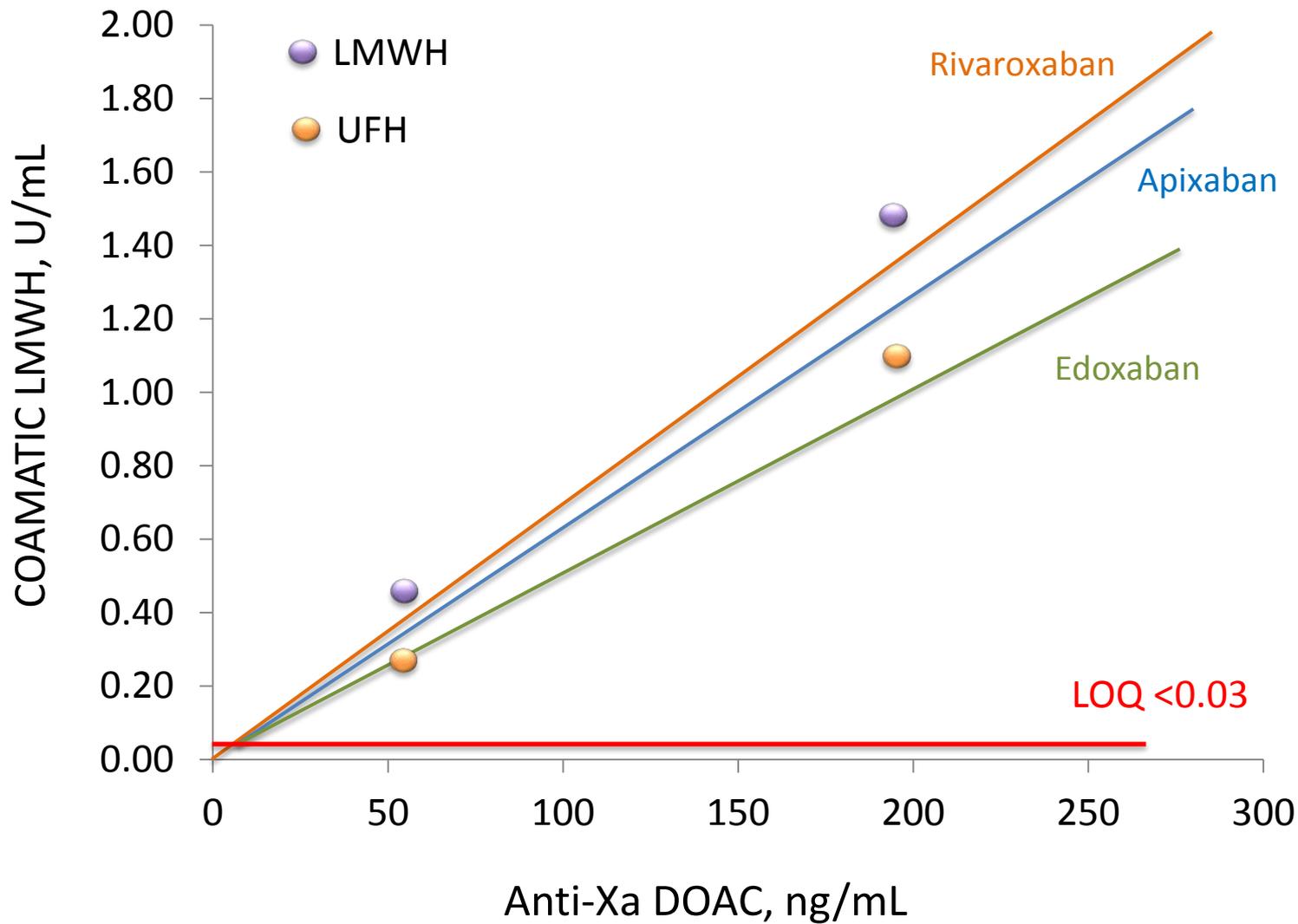


# Different PT reagent response to rivaroxaban



# Same PT reagent response to difference FXa DOACs





# Current concern: What is there?

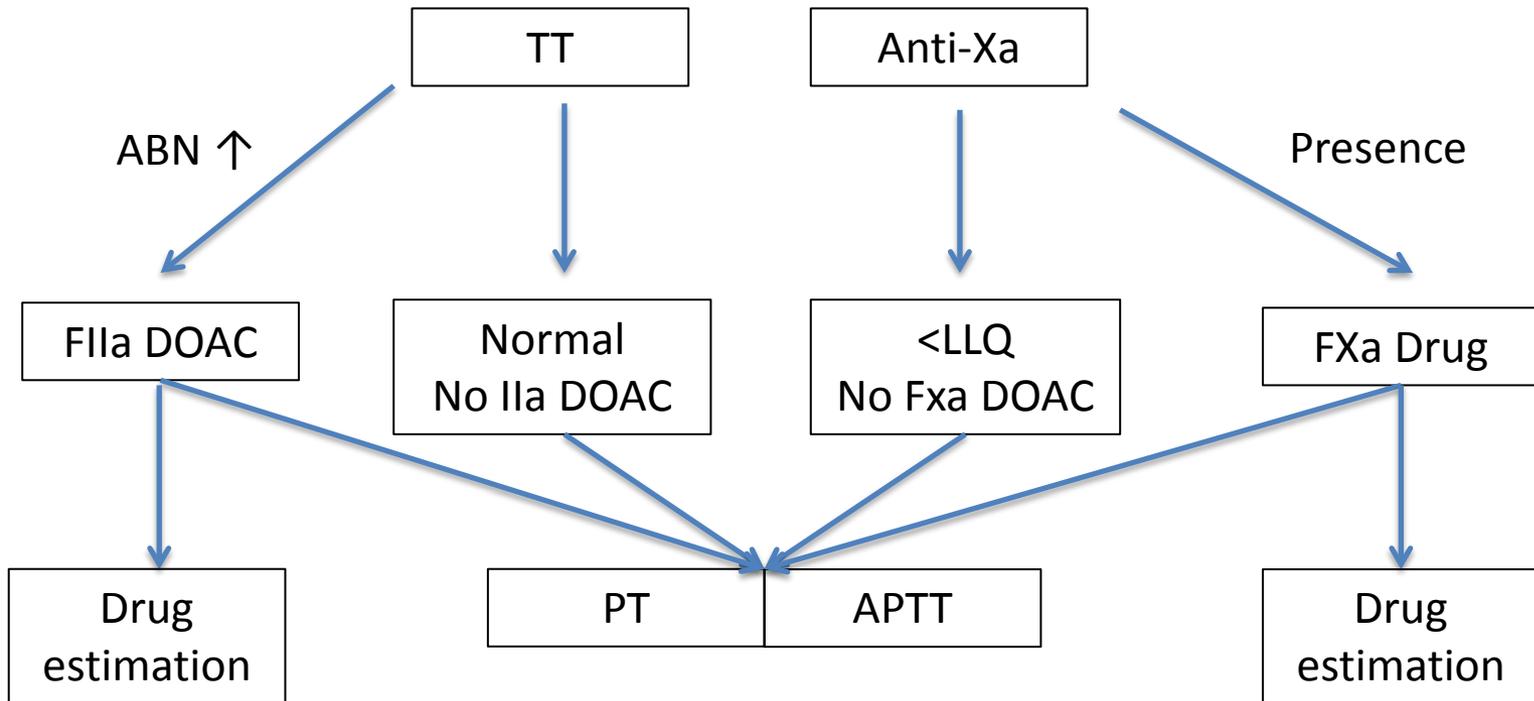
Situations where medication history is not available

- Trauma (UCDHS: level I trauma center)
- Stroke (UCDHS: advanced primary stroke center)
- Outta towners (Sacramento in between San Francisco or Napa and Lake Tahoe)

# Screening algorithms

- Current methods not reliable for DOAC assessment
- Underestimate presence of drug
  - Innovin
  - Apixaban

# Screening profile Unknown History



# Laboratory challenges

- No FDA approved methods, calibrators or controls
  - General reluctance
  - LDT?
- Compliance with CLIA requirements for method validation
  - Imprecision – easy
  - Carry-over – easy
  - Accuracy – difficult
- Publications and guideline recommendations
  - In-vitro vs patient samples
  - Commercial material vs patient samples