Joint Meeting of Coronary Revascularization 8th to 9th December 2017

The Utility of NOACs Trough Levels in Clinical Practice

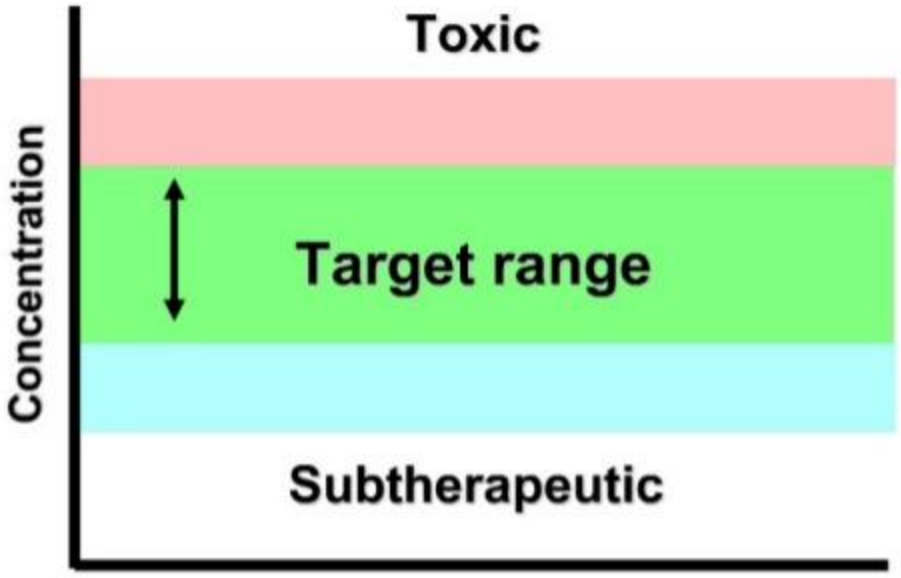
Tiong Lee Len

Senior Research Pharmacist

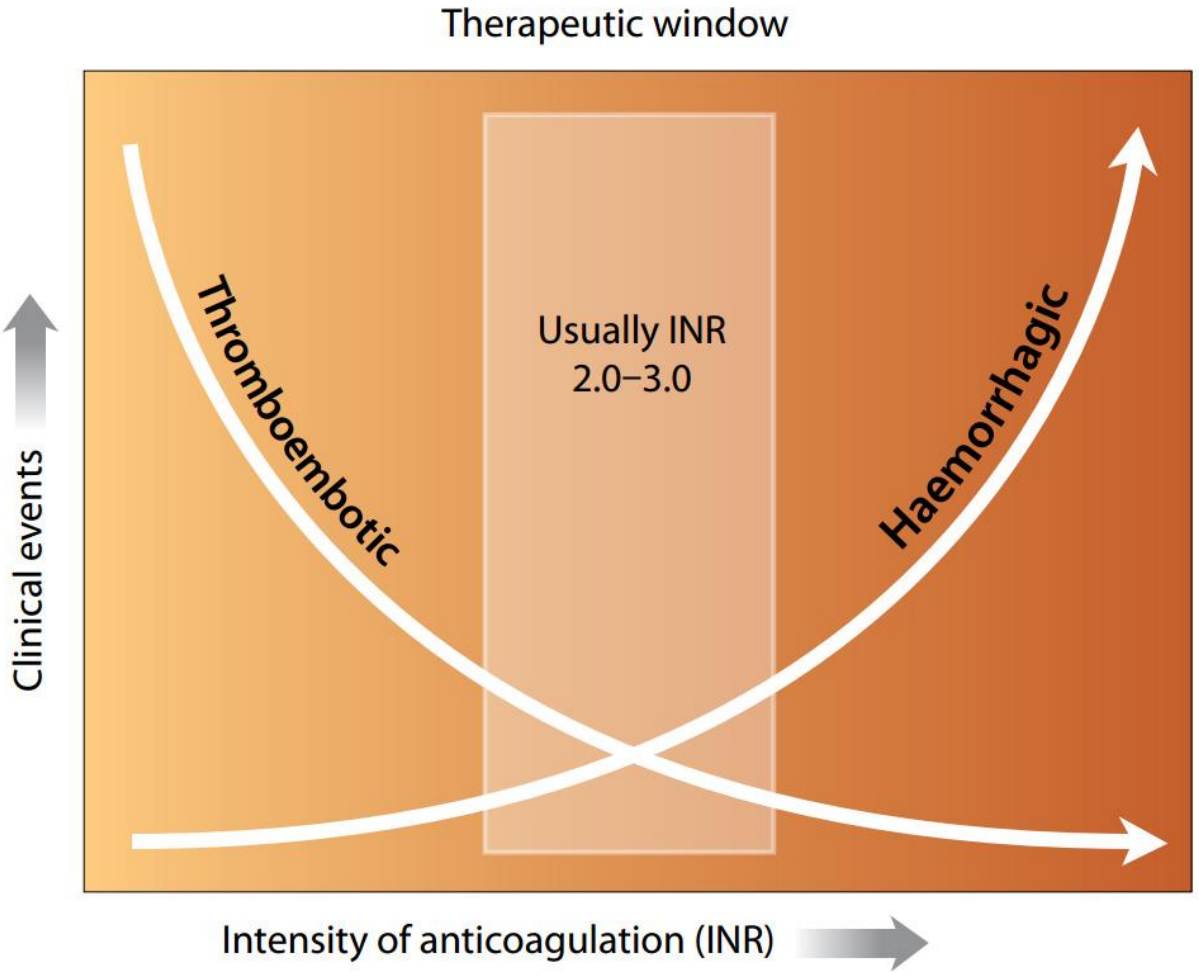
Clinical Research Center

Sarawak General Hospital

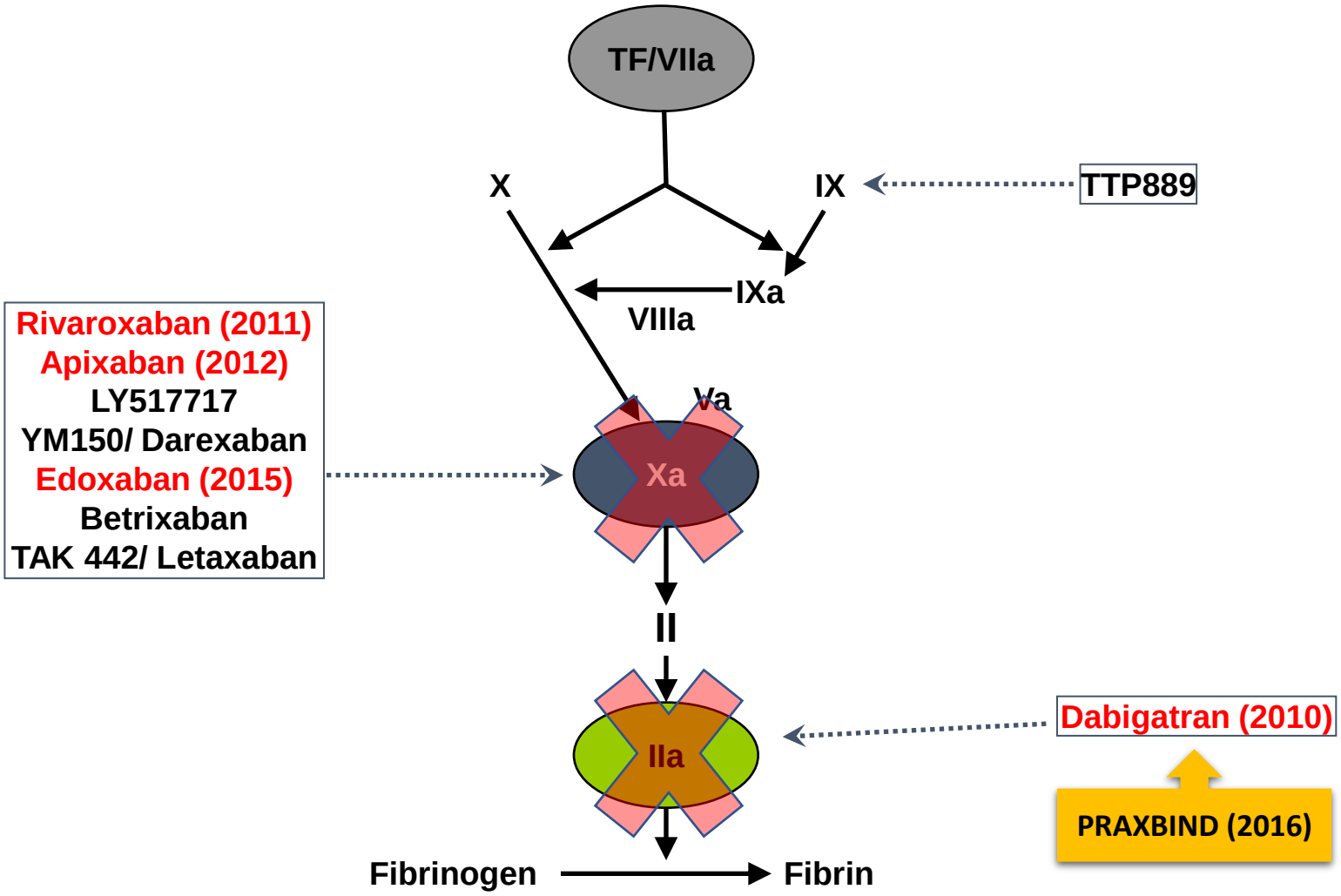
Therapeutic Drug Monitoring



Traditionally with Warfarin….

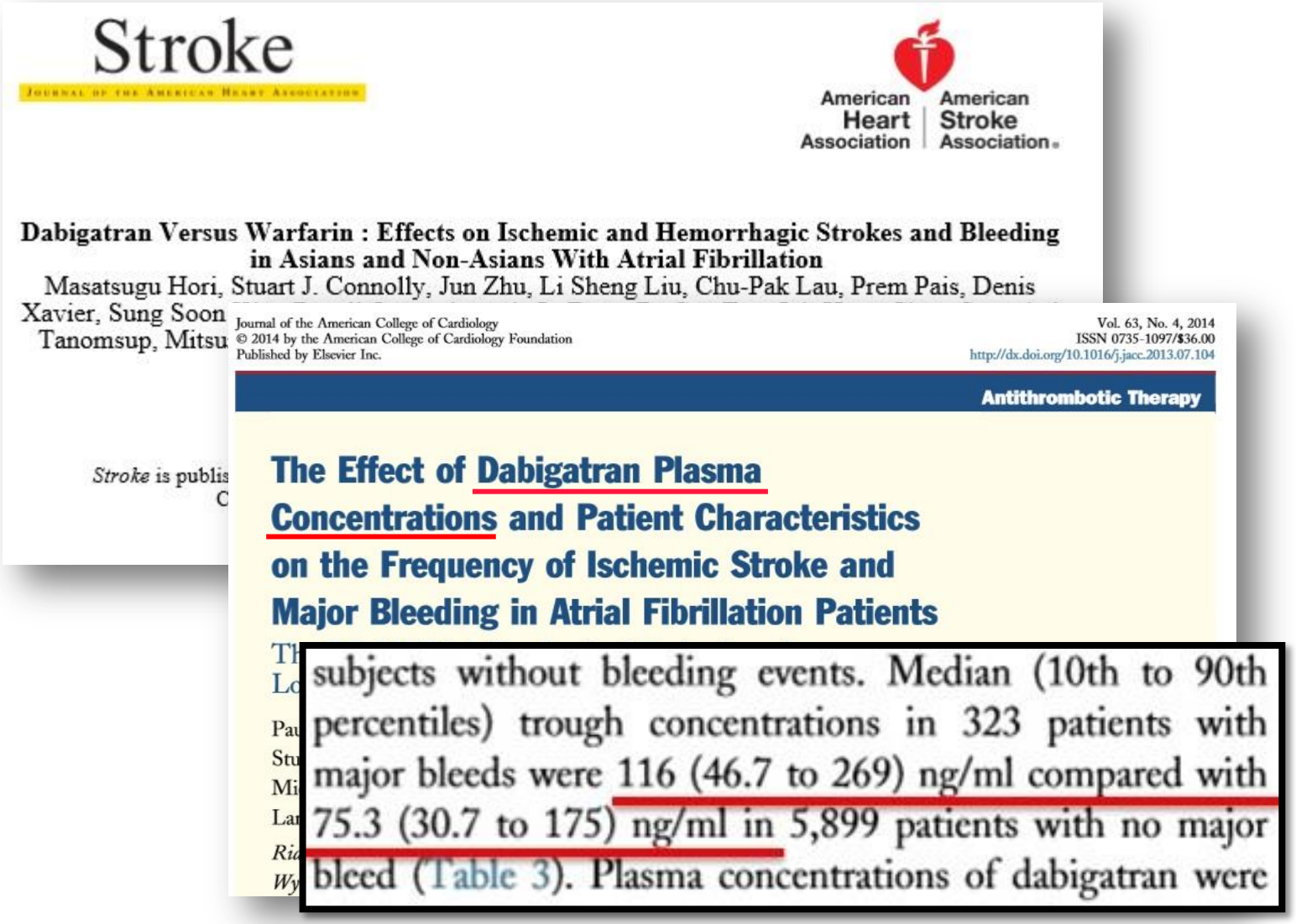


Novel Oral Anticoagulants



Adapted from Weitz & Bates, *J Thromb Haemost* 2007

Dabigatran Etexilate



Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association | American Stroke Association

Dabigatran Versus Warfarin : Effects on Ischemic and Hemorrhagic Strokes and Bleeding in Asians and Non-Asians With Atrial Fibrillation

Masatsugu Hori, Stuart J. Connolly, Jun Zhu, Li Sheng Liu, Chu-Pak Lau, Prem Pais, Denis Xavier, Sung Soon Tanomsup, Mitsu

Stroke is publis

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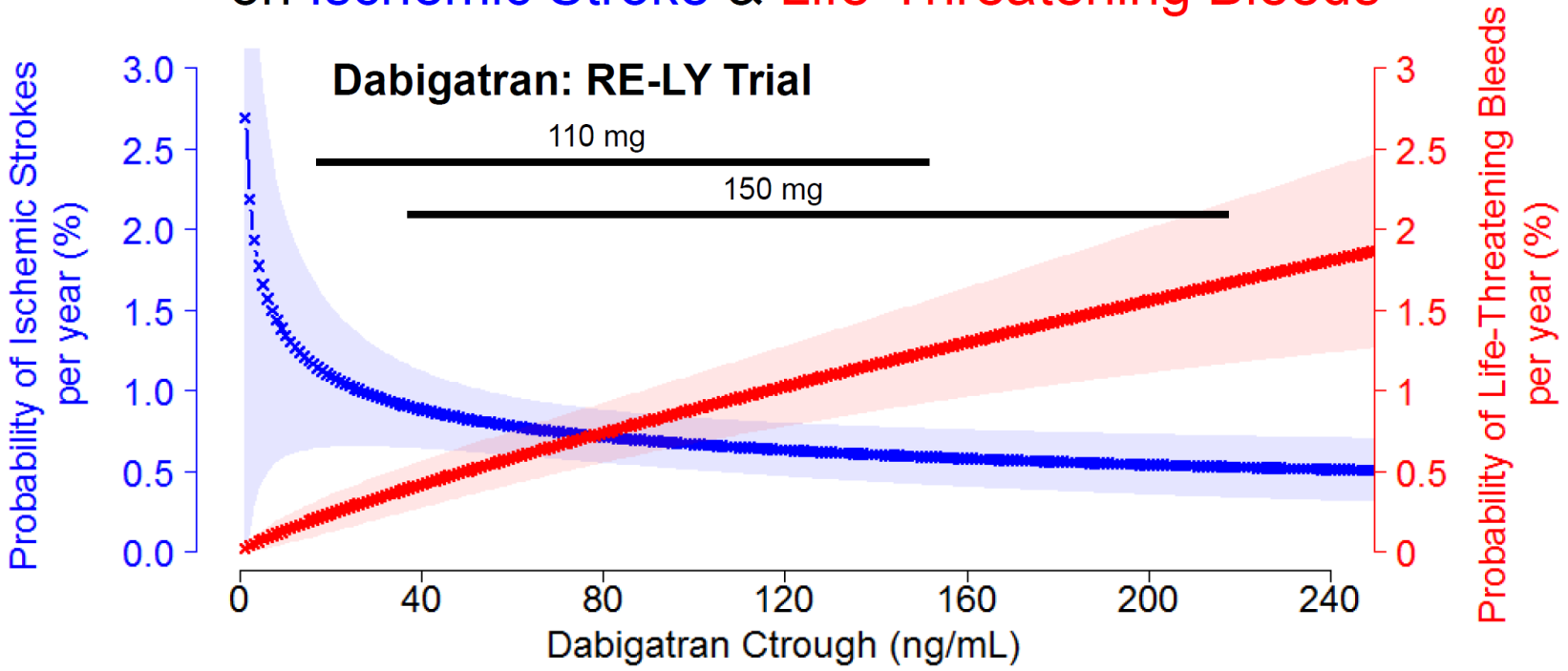
http://dx.doi.org/10.1016/j.jacc.2013.07.104

Antithrombotic Therapy

The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients

subjects without bleeding events. Median (10th to 90th percentiles) trough concentrations in 323 patients with major bleeds were 116 (46.7 to 269) ng/ml compared with 75.3 (30.7 to 175) ng/ml in 5,899 patients with no major bleed (Table 3). Plasma concentrations of dabigatran were

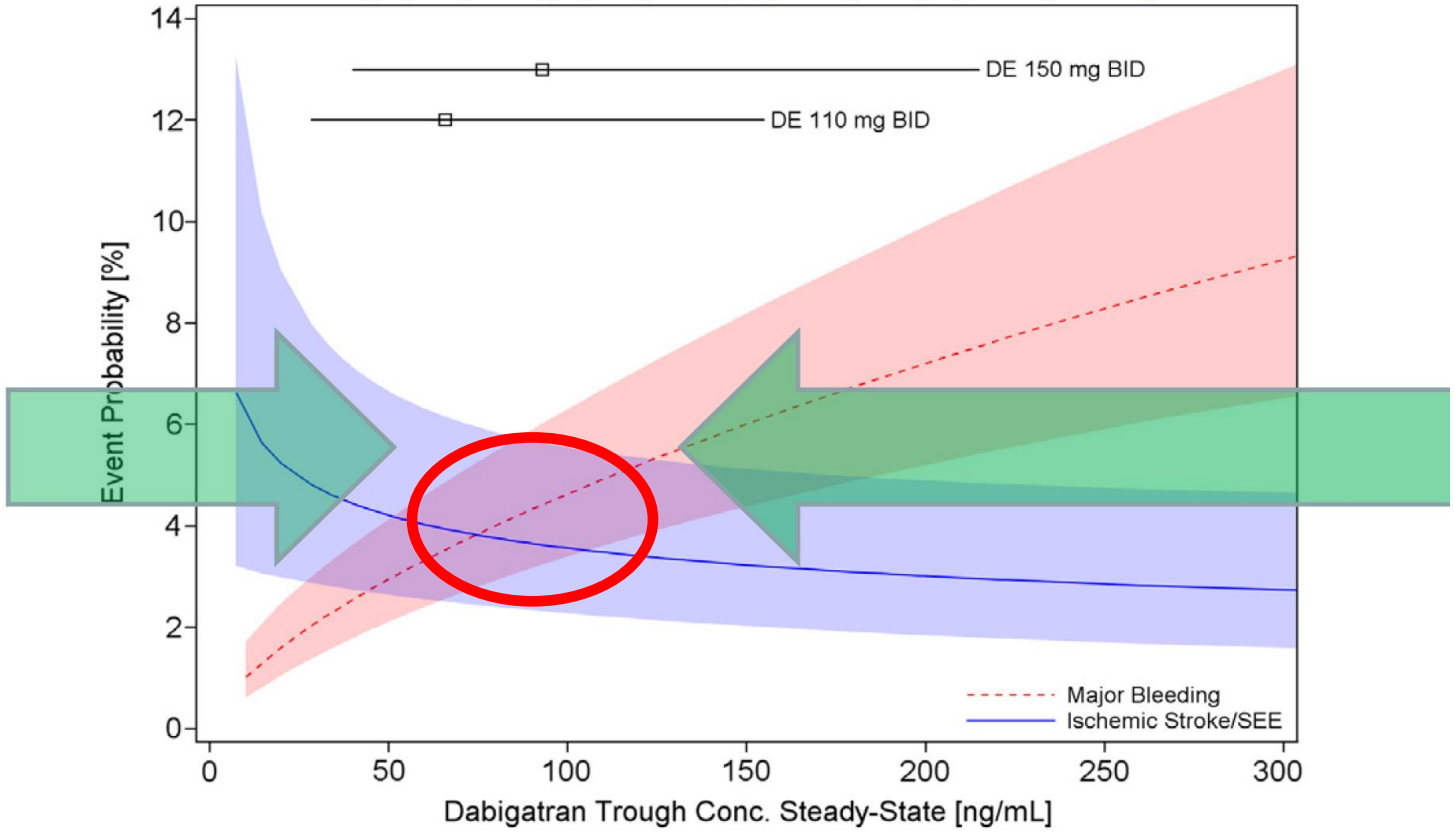
Dabigatran Exhibits Concentration Dependent Relationship on Ischemic Stroke & Life-Threatening Bleeds



- Warfarin also has a similar relationship based on INR

Adapted form FDA's Correlation of Drug Levels and Outcomes in Phase III NOAC Trials, slide 8

Selection of a target window based on balance of benefit and risk



Adapted form FDA's Correlation of Drug Levels and Outcomes in Phase III NOAC Trials, slide 19 (from Reilly *et. al.* 2014)

Rivaroxaban

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Pate
Werner Hacl
Jonathan P. P

Heartwire from Medscape

ROCKET AF Reveals Higher GI Bleeding Rates With Rivaroxaban

Pam Harrison

November 30, 2015

10 comments Print

REL

It does seem as i higher doses, higher plasma levels, and higher GI exposure of the factor Xa inhibitors are associated with an increased risk of GI bleeding compared with warfarin, observed Prof Lars Wallentin (Uppsala Clinical Research Center, Sweden) for **heartwire**.

Apixaban

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 15, 2011 VOL. 365 NO. 11

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

Edoxaban

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

Robert
Sabina
Albert
James

Lancet. 2015 Jun 6;385(9984):2288-95. doi: 10.1016/S0140-6736(14)61943-7. Epub 2015 Mar 11.

Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial.

Ruff CT[1], Giugliano RP[2], Braunwald E[2], Morrow DA[2], Murphy SA[2], Kuder JF[2], Deenadayalu N[2], Jarolim P[2], Betcher J[3], Shi M[4], Brown K[4], Patel I[4], Mercuri M[4], Antman EM[2].

Author information

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2 Brigham and Women's Hospital and Harvard Medical School,
3 Quintiles Inc, Research Triangle Park, NC, USA.
4 Daiichi-Sankyo Pharma Development, Edison, NJ, USA.

Abstract

BACKGROUND: New oral anticoagulants for stroke prevention i
for the routine monitoring that has hindered usage and acceptan
measurement of drug concentration or anticoagulant activity mig
increase bleeding risk. In the ENGAGE AF-TIMI 48 trial, higher-d
atrial fibrillation. Each regimen incorporated a 50% dose reductio
exposure. We aim to assess whether adjustment of edoxaban do
events.

METHODS: We analysed data from the randomised, double-blin
concentration, and anti-Factor Xa (FXa) activity and compared e
Patients with atrial fibrillation and at moderate to high risk of stro
to an international normalised ratio of 2·0-3·0, higher-dose edoxa
Randomisation was done with use of a central, 24 h, interactive,
measured using an encrypted point-of-care device. To maintain masking, sham international normalised ratio values were generated for patients assigned to edoxaban. Edoxaban (or placebo-edoxaban in warfarin group) doses were halved at randomisation or during the trial if patients had creatinine clearance 30-50 mL/min, bodyweight 60 kg or less, or concomitant medication with potent P-glycoprotein interaction.

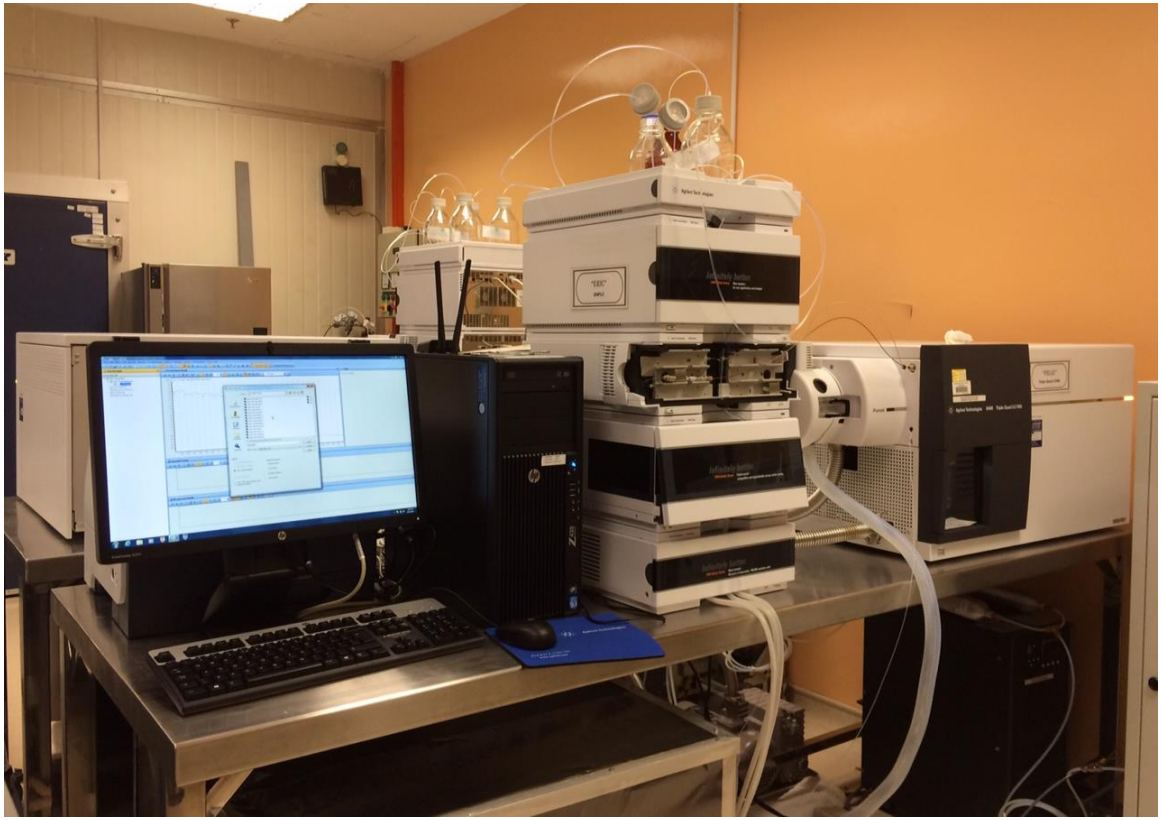
- Reported a mean trough plasma concentrations range of 16.0 - 48.5ng/mL.
- Significant inter-individual variability in trough plasma drug levels was again observed among all doses of Edoxaban tested.
- Higher plasma levels with increased risk of major bleed.

Avail ate
Pl e
Dete of

Test	Molecule(s)	Utility	Sensitivity/ Specificity	Dependence of the reagent	External quality control	Cut-off for a risk of bleeding (Unit(s) of expression)
LC-MS/MS	Dabigatran/ Rivaroxaban / Apixaban / Edoxaban	Proven: Accurately estimates the plasma concentrations—results expressed in ng/mL	LoD and LoQ around 1 and 3 ng/mL	Not applicable	No	Yes: Depends on the indication (ng/mL) for dabigatran (i.e. 200 ng/m at trough in AF) Not established for direct factor Xa inhibitors
APTT	Dabigatran	Limited: Poorly reflect the intensity of anticoagulation	±100 ng/mL / No	Yes	Yes	Yes: Depends on the indication and the reagent (specific values are not presented since they depend on the reagent)
TT	Dabigatran	Limited: Only to exclude the presence of dabigatran. Useful in the peri-operative setting	Too sensitive (lower LoD below 0.025 ng/mL with some methodologies) / No	Yes	Yes	Not established
dTT	Dabigatran	Proven: Accurately estimates the plasma concentrations—results expressed in ng/mL	±10 ng/mL / No	No	Yes	Yes: Depends on the indication (ng/mL)
ECT	Dabigatran	Limited: Standardization and validation required	±15 ng/mL / No	Probably not but an inter-lot variability has been reported	No	Yes: Depends on the indication (ratio: 3xULN and seconds: >103 seconds)
ECA	Dabigatran	Proven: Accurately estimates the plasma concentrations—results expressed in ng/mL	±10 ng/mL / No	No	Yes	Yes: Depends on the indication (ng/mL) (i.e. 200 ng/m at trough in AF)
PT	Rivaroxaban/ (Edoxaban)	Limited: Poorly reflect the intensity of anticoagulation	from ± 100 to > 500 ng/mL (depending on the reagent) / No	Yes	Yes	Not established
Chromogenic anti-Xa assays	Rivaroxaban / Apixaban / Edoxaban	Proven: Accurately estimates the plasma concentrations—results expresses in ng/mL	± 10 ng/mL / Yes–No (depend on the anti-Xa assay)	No	Yes	Not established

[a]Based on presentations and discussions during the workshop, and information summarized in[7,15] of this article.
[b]None of these tests are able to discriminate between therapies. Thrombin specific tests can easily identify dabigatran but other direct thrombin inhibitors such as argatroban or hirudin can influence them. For direct factor Xa inhibitors, only the Biophen® Direct Factor Xa Inhibitor can discriminate between heparins and direct FXa inhibitors but fail to differentiate between direct FXa inhibitors.
LoD, limit of detection; LoQ, limit of quantification; ULN, upper limit of normal.

Measuring NOACs Concentrations



LC-MS/MS

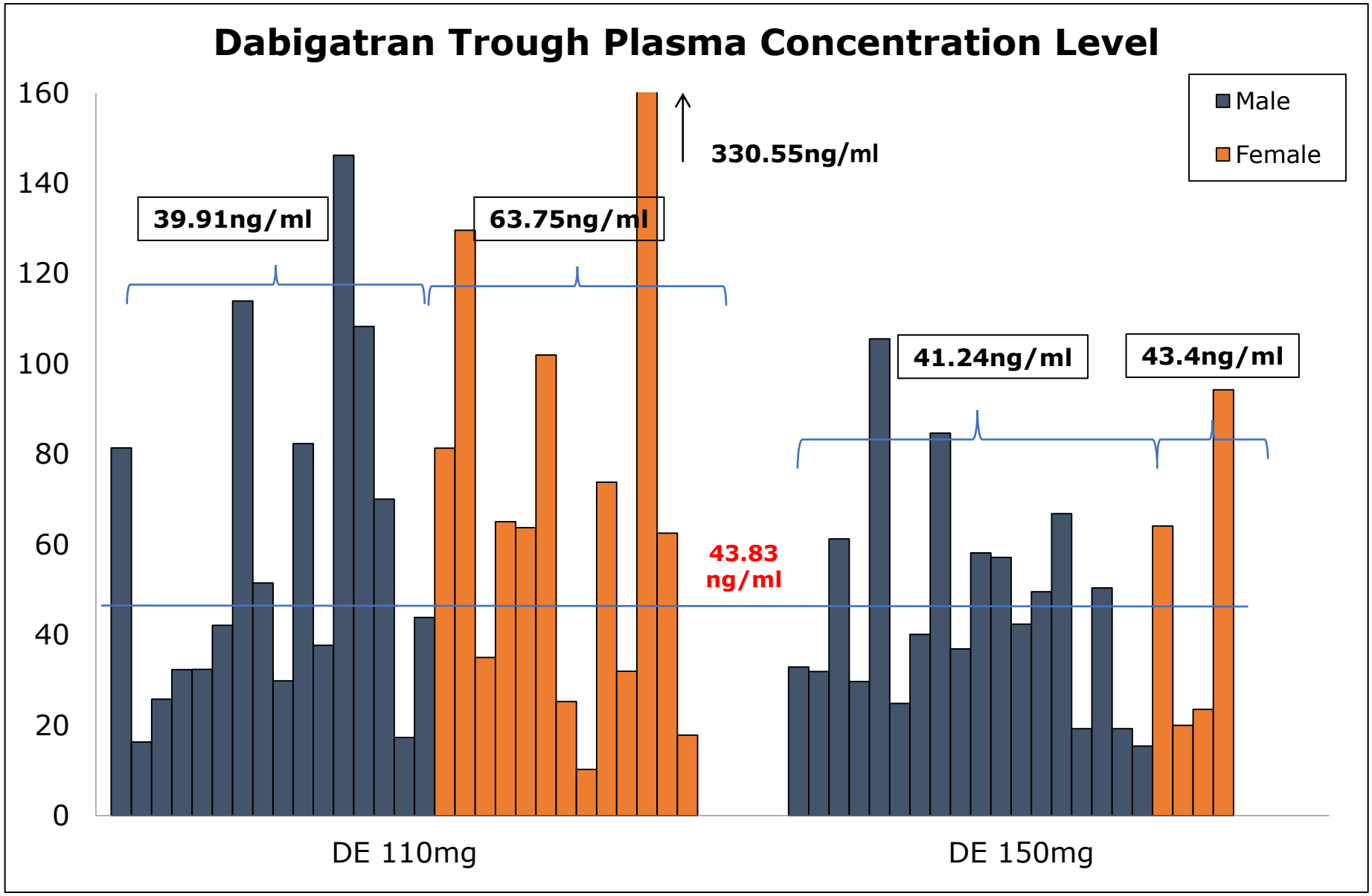
Data from our cohort…

Demographics

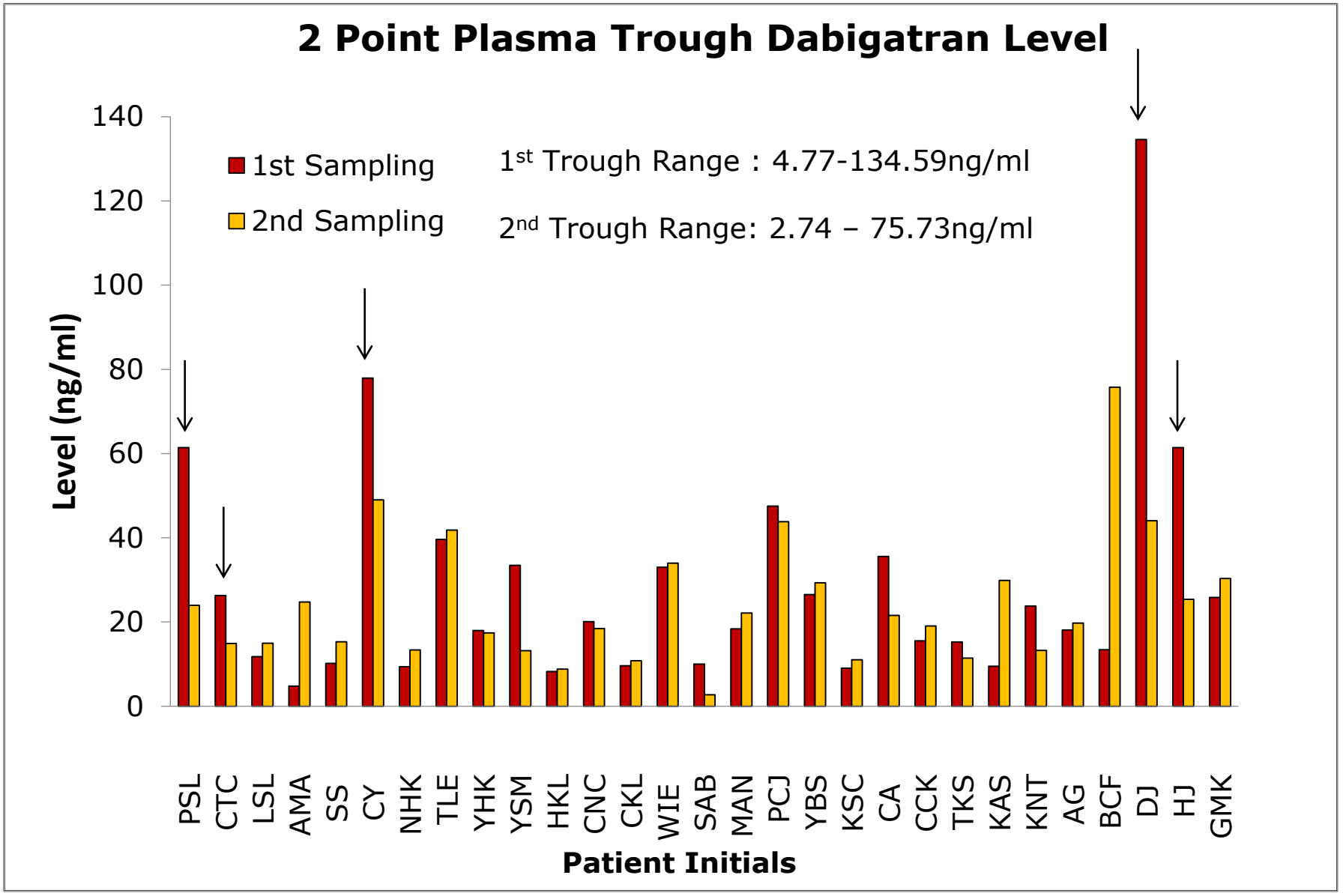
Variable	Dabigatran Etexilate	Rivaroxaban	Apixaban	Overall
Age(yr)*	70.17(7.58)	62.25(9.75)	80.25(4.57)	68.96(9.31)
Gender$^{\delta}$ Male Female	 17(58.6%) 12(41.4%)	 10(83.3%) 2(16.7%)	 1(25.0%) 3(75.0%)	 28(62.2%) 17(37.8%)
AF$^{\delta}$ Paroxysmal Persistent Permanent	 11(37.9%) 3(10.3%) 15(51.7%)	 2(16.7%) 2(16.7%) 8(66.7%)	 2(50.0%) - 2(50.0%)	 15(33.3%) 5(11.1%) 25(55.6%)
Weight, kg*	60.96(9.85)	79.71(17.69)	61.93(22.90)	66.19(15.51)
CrCl, ml/min*	58.72(17.7)	89.65(35.6)	35.62(9.88)	64.53(27.52)
CHA_2DS_2-VASc*	3.76(1.41)	2.83(1.27)	4.20(1.30)	3.58(1.42)
HAS-BLED*	1.41(0.68)	0.75(0.45)	1.25(0.50)	1.22(0.67)

**All data presented as Mean(SD) with 95% Confidence Interval*
$^{\delta}$All data presented as percentage

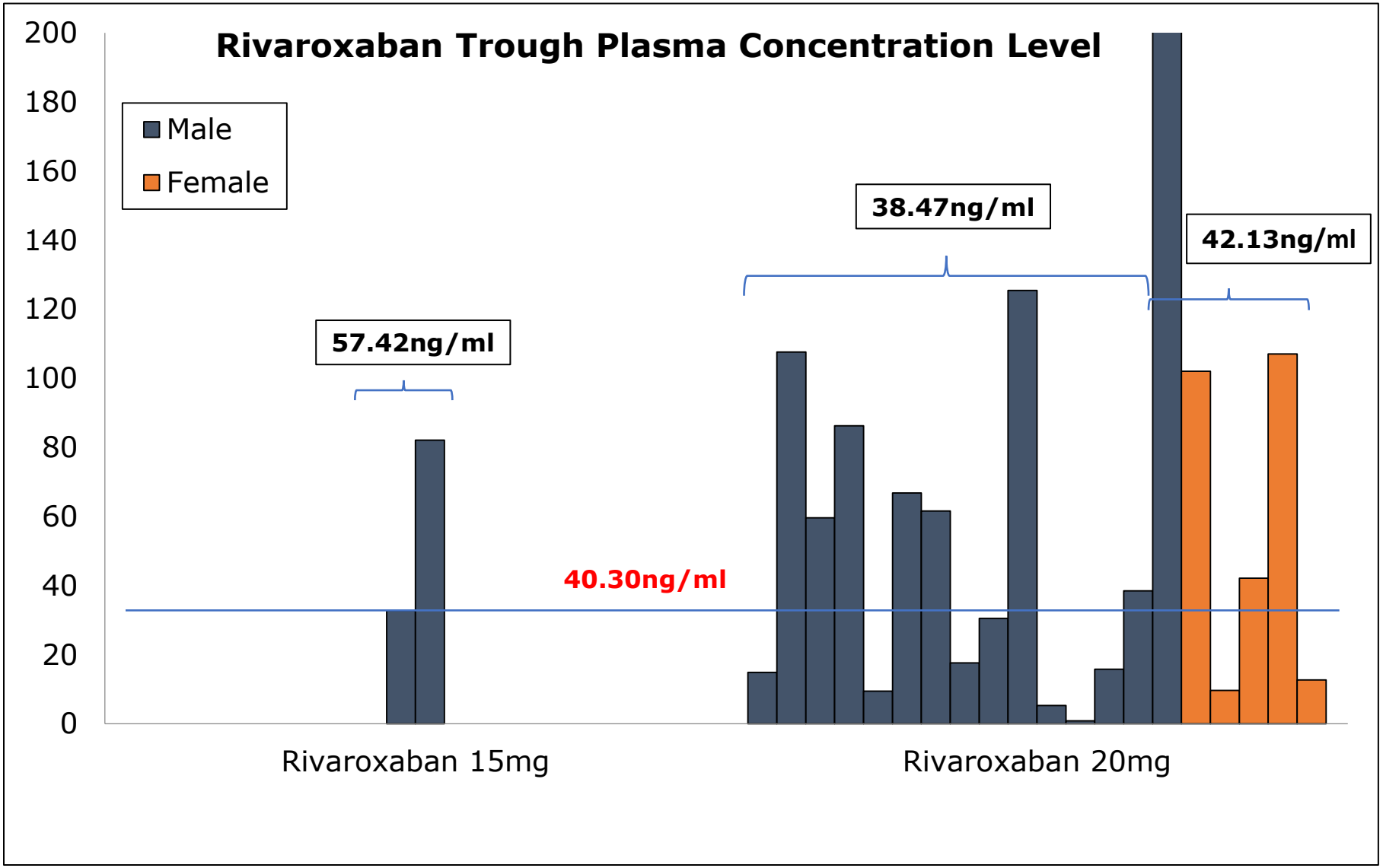
Dabigatran Trough Levels



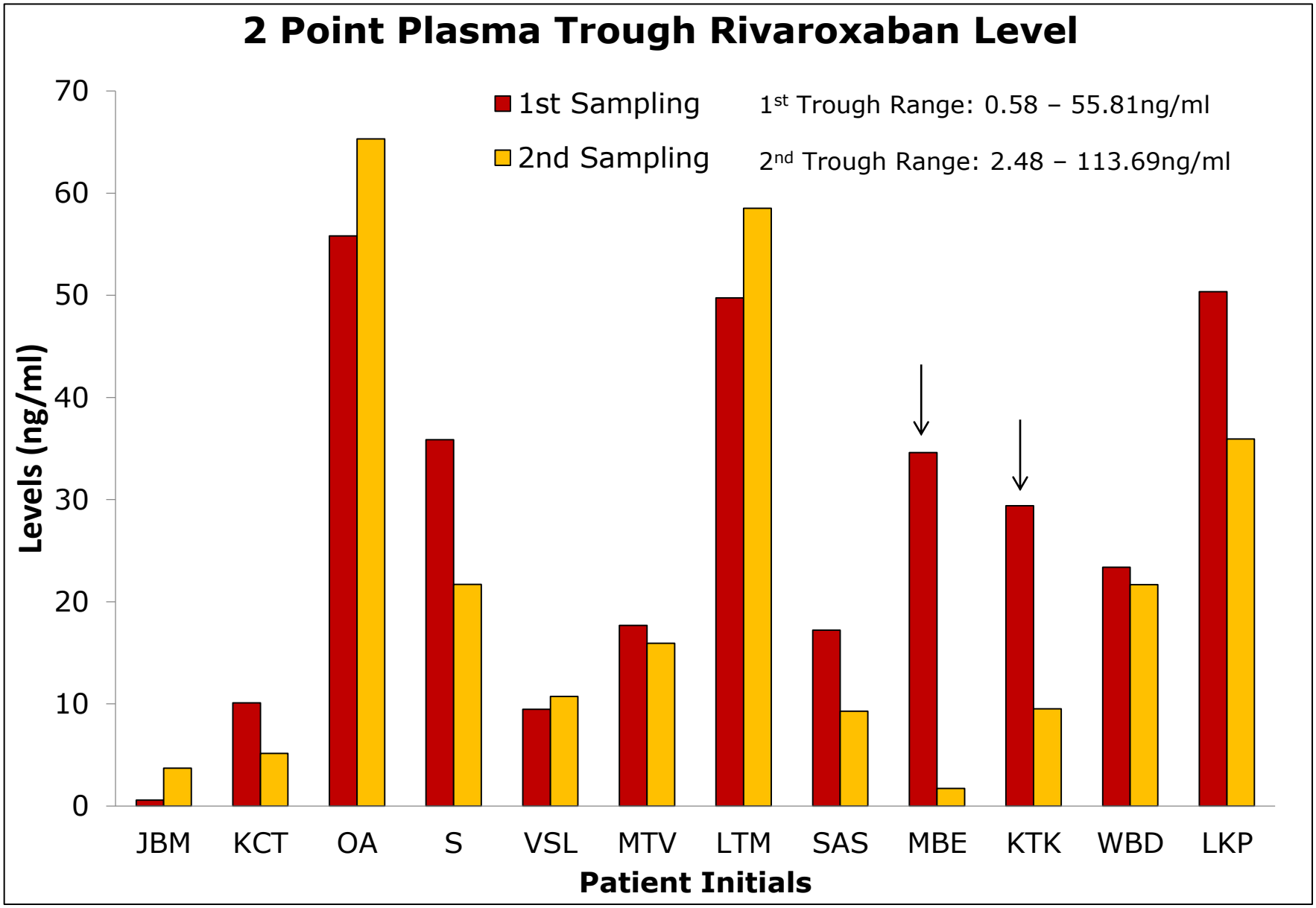
Dabigatran Trough Levels (2)



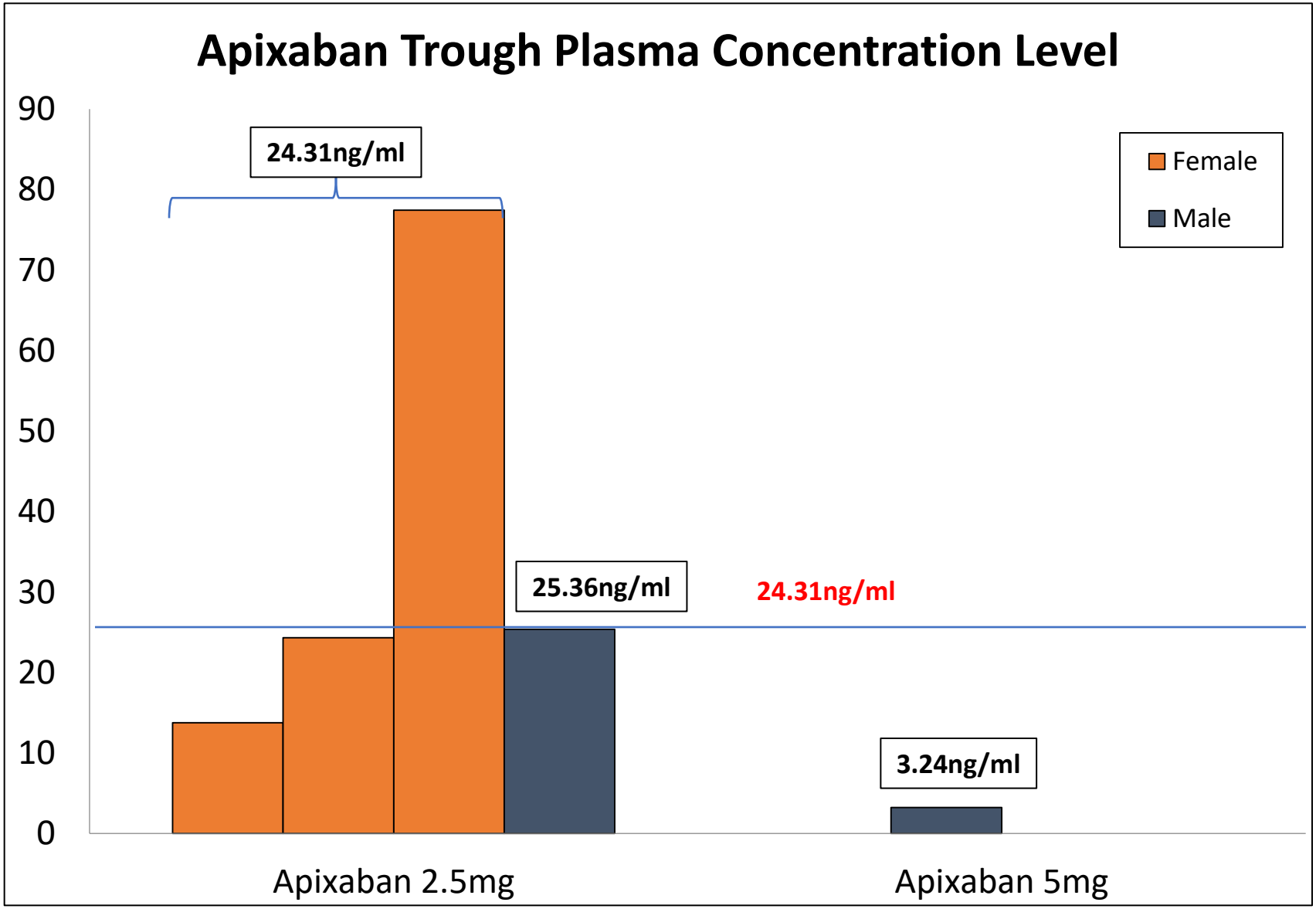
Rivaroxaban Trough Levels



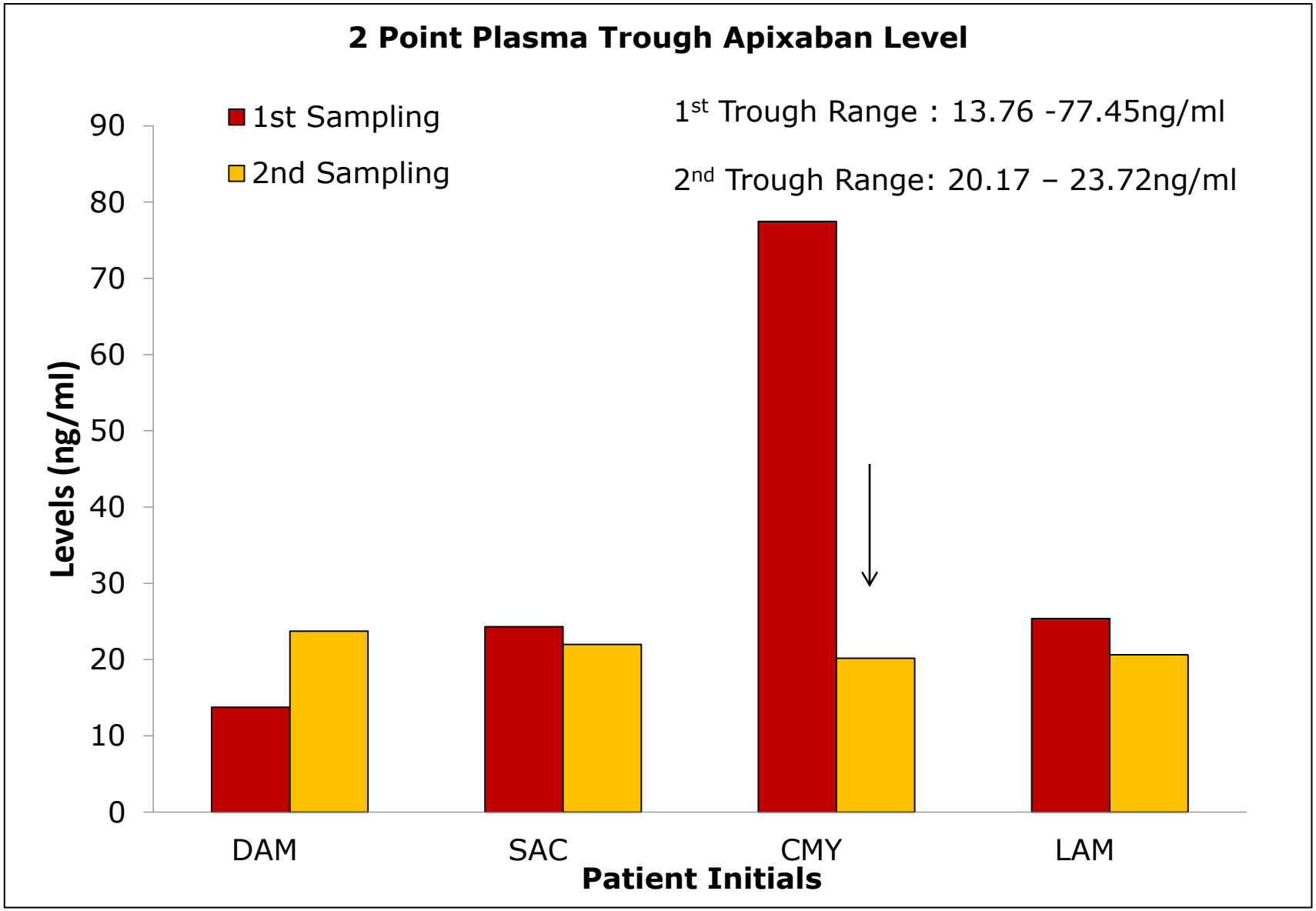
Rivaroxaban Trough Levels(2)



Apixaban Trough Levels



Apixaban Trough Levels (2)



In our Cohort….

- Wide range of plasma NOAC trough levels.
- Median trough level for Dabigatran, Rivaroxaban and Apixaban is **43.83ng/mL**, **40.30ng/mL** and **24.31ng/mL**; respectively.
- Plasma NOAC trough levels are consistent within individual but **VARY** between individuals.

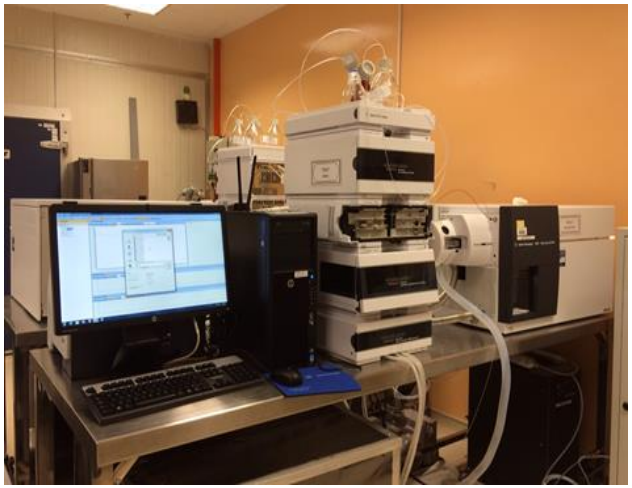
Clinical Utility

- Treatment failure (i.e. recurrence of thrombosis)
- Before invasive procedure or surgery
- In elderly patients (>75 years of age)
- In patients with extreme body weight (< 50kg or > 110kg)
- In patients with renal and/ or hepatic impairment
- Monitor compliance
- Suspected drug-drug interactions
- Suspected overdose
- In patients with genetic mutations (i.e., rs2244613 minor allele carriers for dabigatran - no mutations are currently known for the other NOACs)

Case Scenario

- 71 y/o Chinese, Male
- History of single vessel disease and paroxysmal atrial fibrillation
- On Aspirin 100mg OD and Dabigatran 110mg BD
- Intracranial hematoma secondary to fall
- Decision for neurological intervention

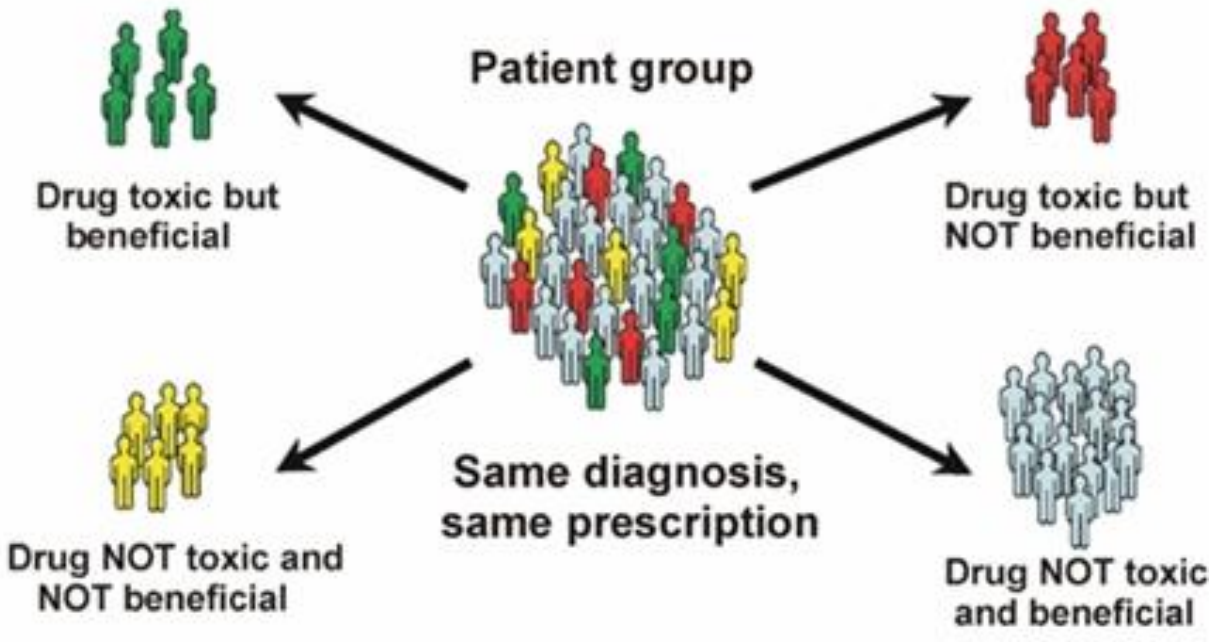
Tools Aided Therapy



102 AU*min

2.1ng/mL

Personalized Drug Therapy



"Tonight I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes.

And to give us all access to the personalized information we need to keep ourselves and our families healthier."

President Barack Obama
2015 State of the Union Address | January 20, 2015


THANK YOU