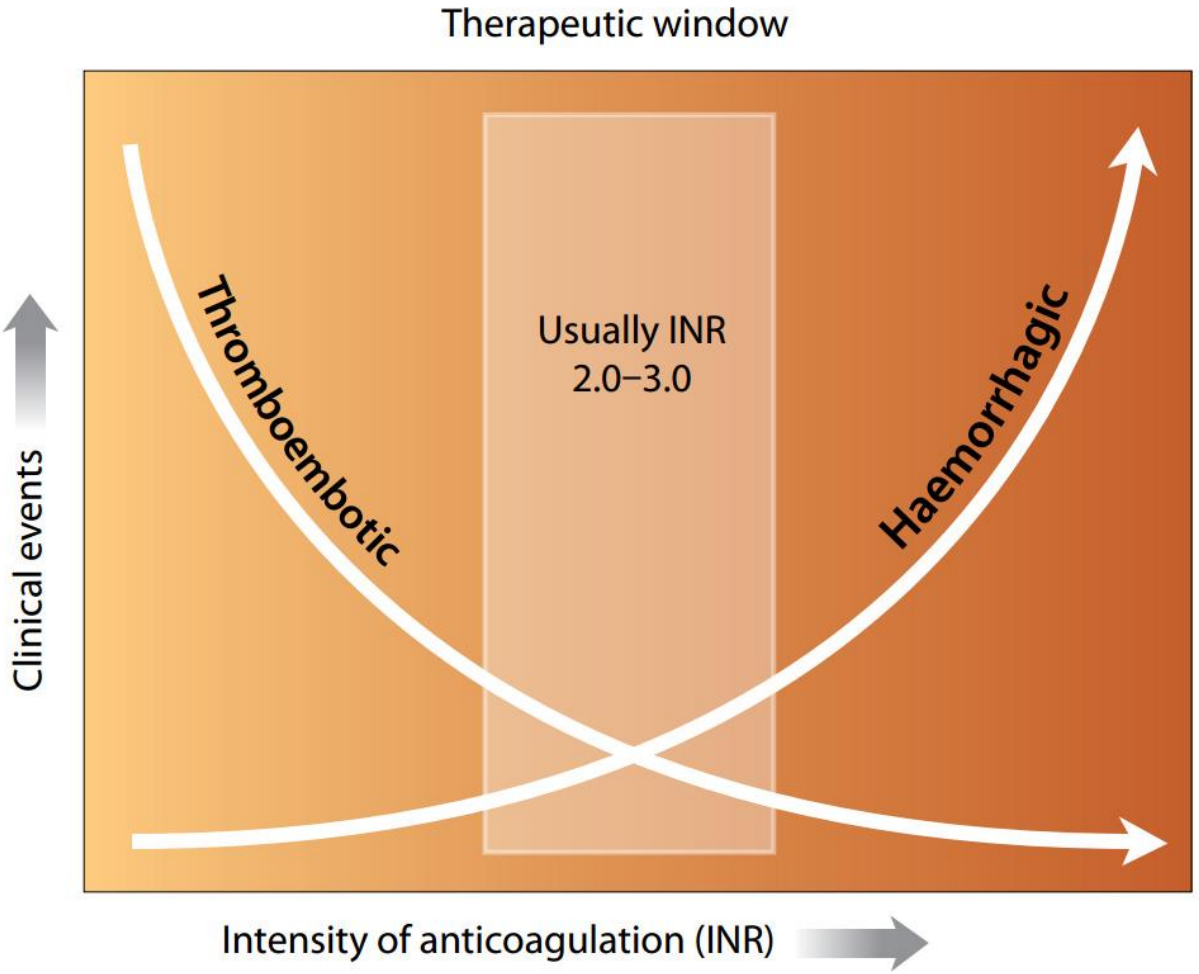
Joint Meeting of Coronary Revascularization
12-14th December 2019

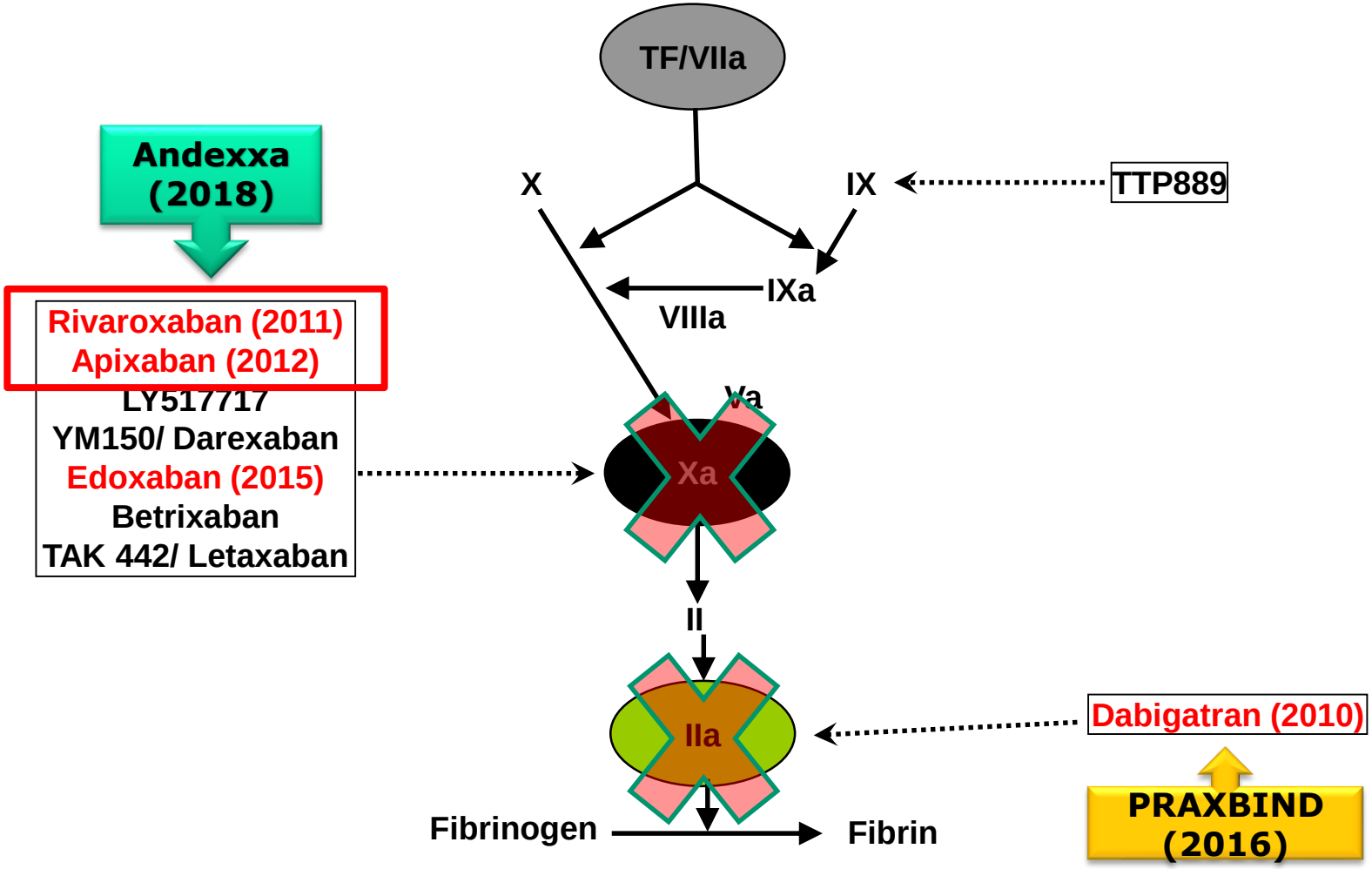
A 'NOAC Triad' - Review on the Dose, Plasma Concentration and Anticoagulation Effect of Novel Oral Anticoagulants

TIONG Lee Len
Senior Research Pharmacist
Clinical Research Centre, Sarawak General Hospital

Traditionally with Warfarin….

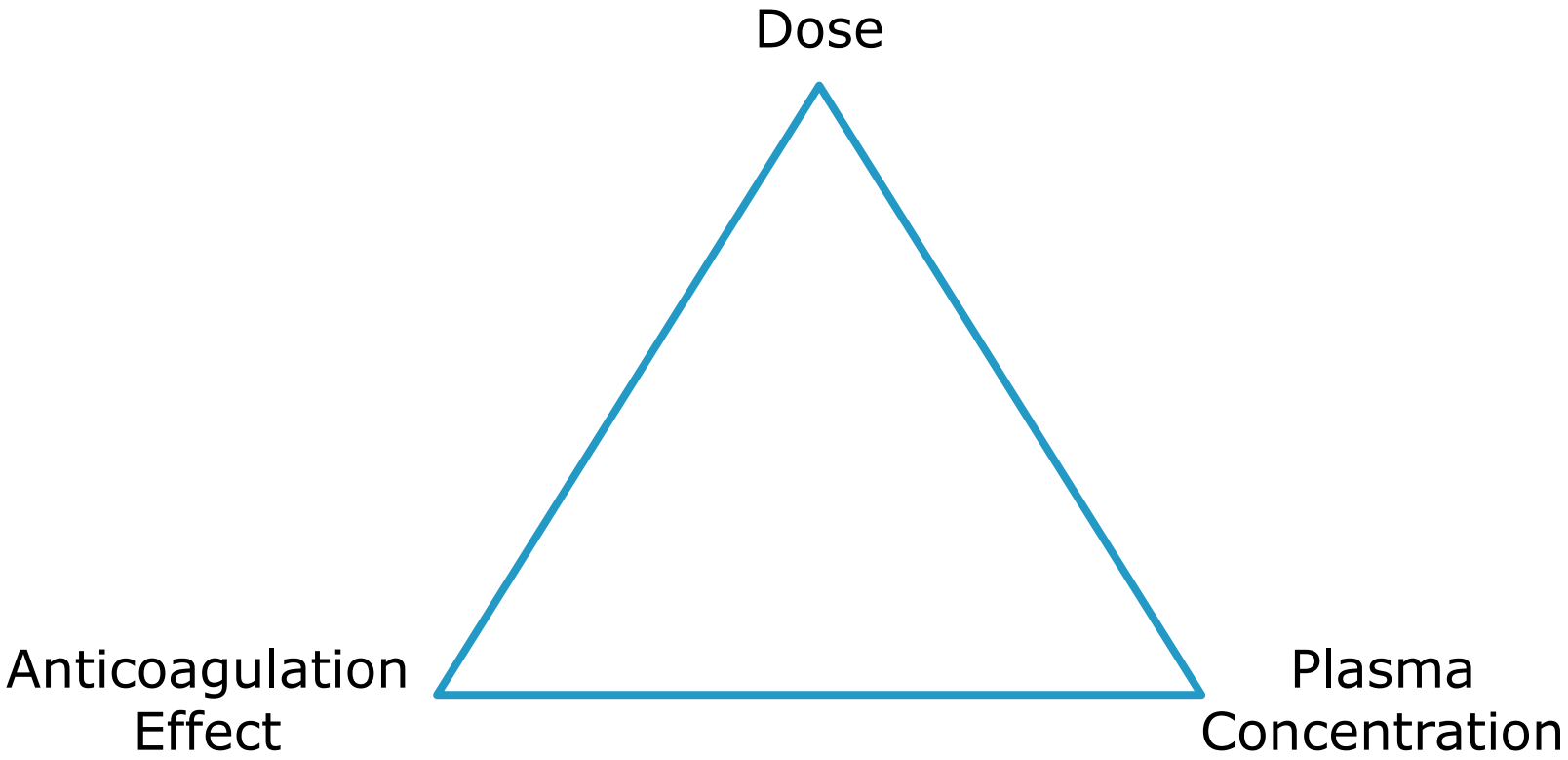


Novel Oral Anticoagulants

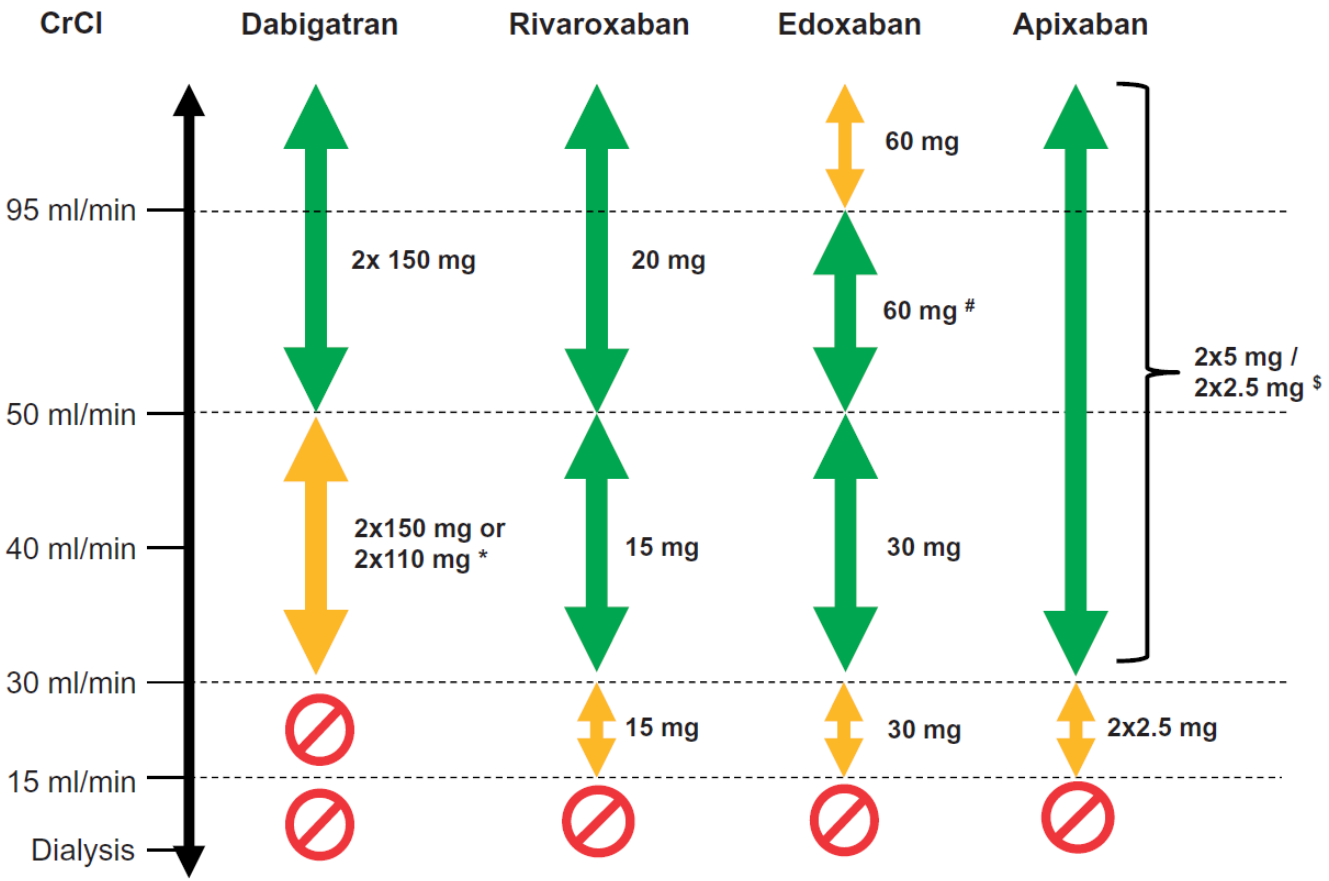


Adapted from Weitz & Bates, *J Thromb Haemost* 2007

NOAC TRIAD



NOAC Dose



* 2x110mg in patients at high risk of bleeding
# other dose reductions may apply (i.e. weight, drug-drug interaction)
$ only if at least 2 out of 3 fulfilled: age ≥ 80 years old, weight ≤ 60kg, creatinine ≥ 1.5mg/dL (133umol/L)
Orange arrow indicates cautionary use

Adapted from EHRA 2018

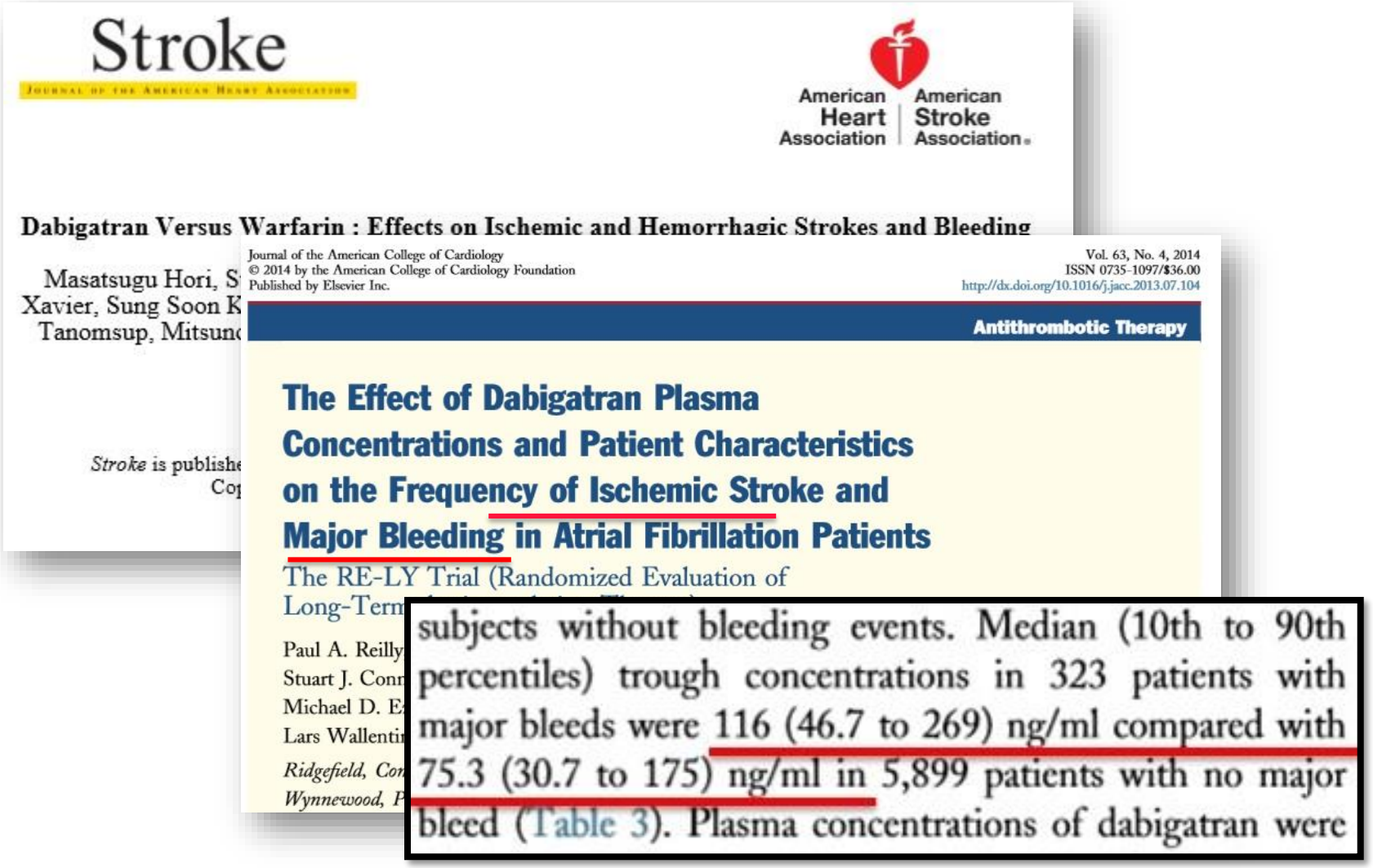
Ava sma
Conce neters

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	Too sensitive (lower LoD below	Yes	Yes	Not established
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

LC-MS/MS
the gold standard

[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.

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

Masatsugu Hori, S
Xavier, Sung Soon K
Tanomsup, Mitsun

Stroke is publishe
Co

Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 4, 2014
ISSN 0735-1097/$36.00
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

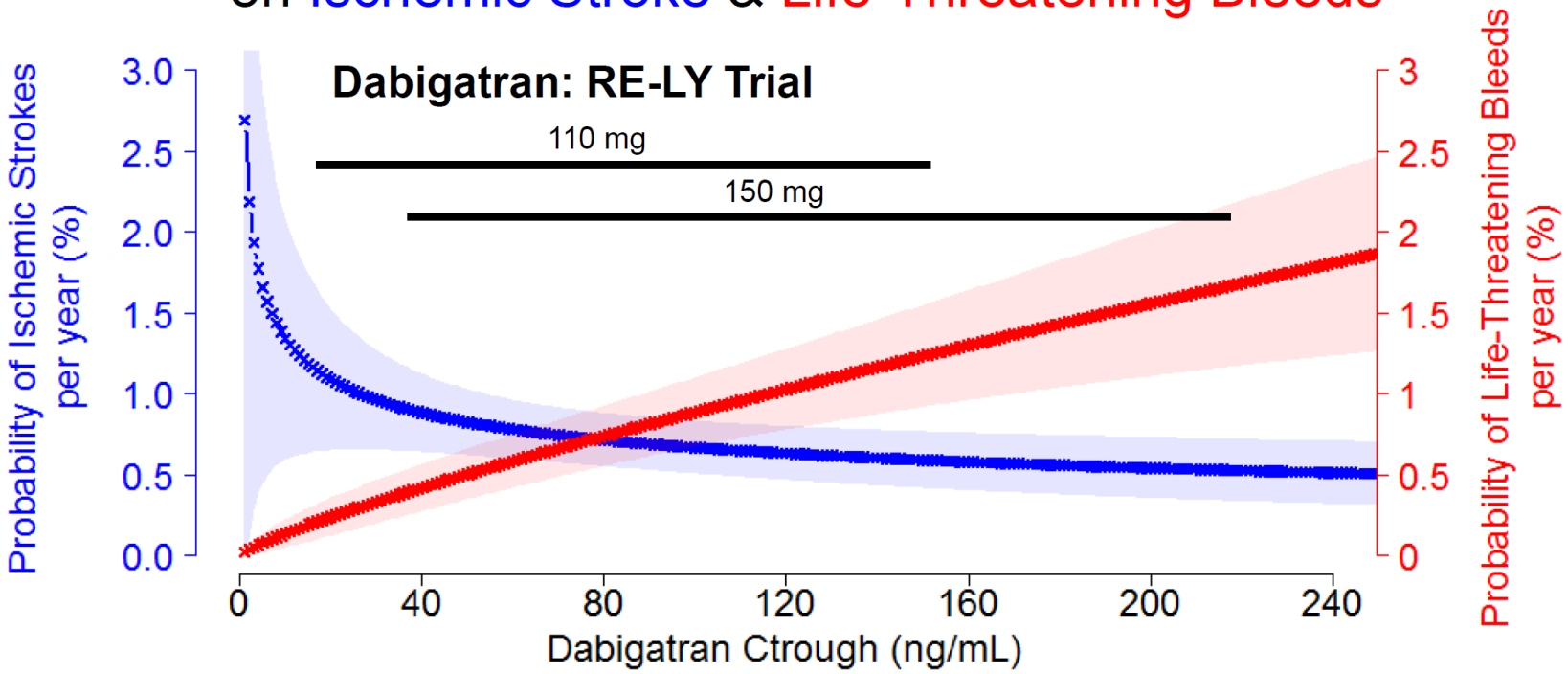
The RE-LY Trial (Randomized Evaluation of Long-Term

Paul A. Reilly
Stuart J. Conn
Michael D. E
Lars Wallenti

Ridgefield, Con
Wynnewood, P

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

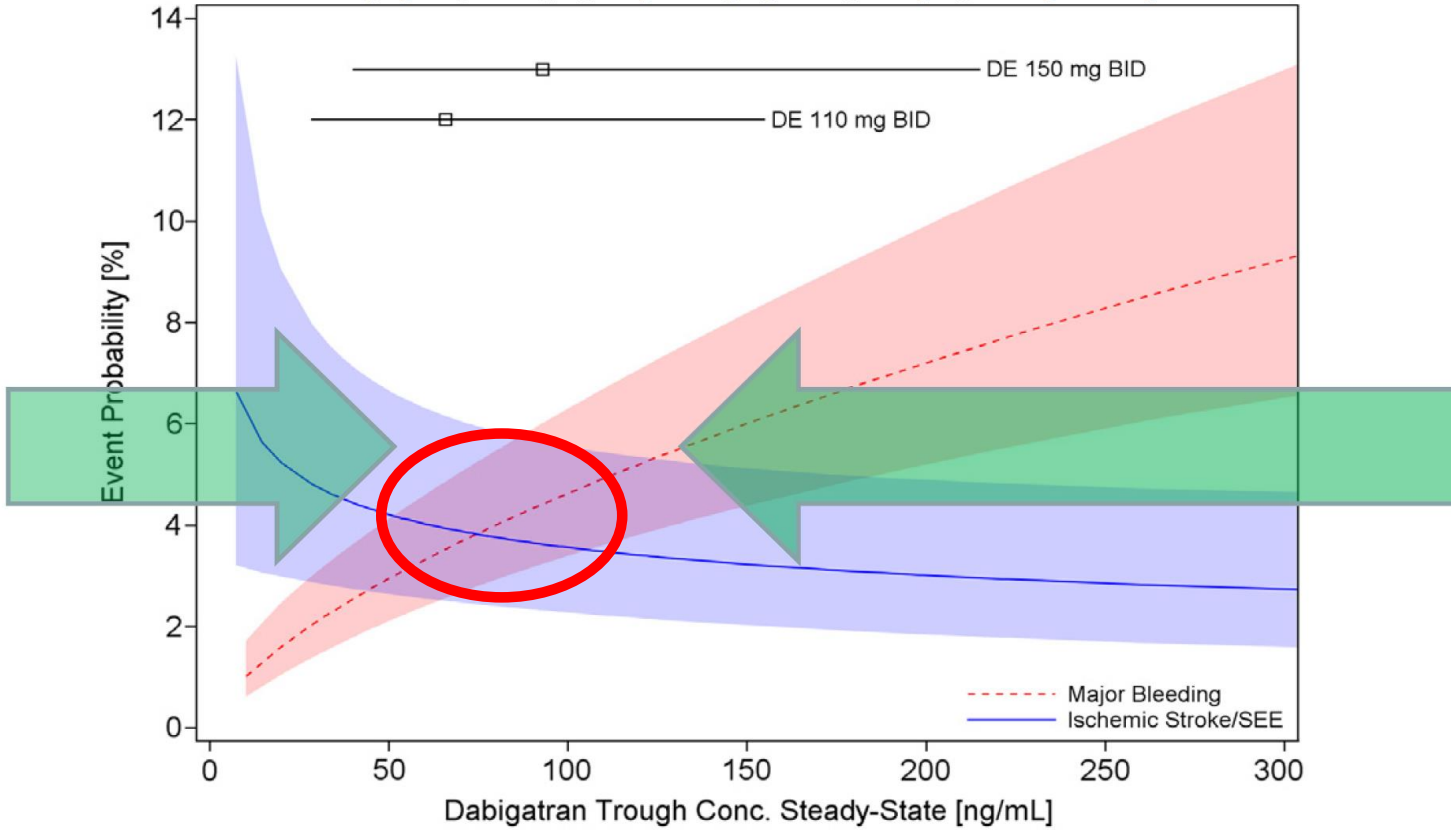
Dabigatran Exhibits Concentration Dependent Relationship on Ischemic Stroke & Life-Threatening Bleeds



- Warfarin also has a similar relationship based on INR

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

Rivaroxaban

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 P. Giug
Sabina A. Mui
Albert L. Walc
Jindři
Yukihirc
Laura
James J. Hany

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

1 Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. Electronic address: cruff@partners.org.
2 Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.
3 Quintiles Inc, Research Triangle Park, NC, USA.
4 Daiichi-Sankyo Pharma Development, Edison, N.

Abstract

BACKGROUND: New oral anticoagulants for stroke p
for the routine monitoring that has hindered usage ar
measurement of drug concentration or anticoagulant
increase bleeding risk. In the ENGAGE AF-TIMI 48 t
atrial fibrillation. Each regimen incorporated a 50% d
exposure. We aim to assess whether adjustment of e
events.

METHODS: We analysed data from the randomised,
concentration, and anti-Factor Xa (FXa) activity and
Patients with atrial fibrillation and at moderate to high
to an international normalised ratio of 2·0-3·0, higher
Randomisation was done with use of a central, 24 h,
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.

BACKGROUND

Edoxaban is a
The long-term
with atrial fib

- 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.

EHRA 2018 – Plasma concentrations and coagulation levels

	Dabigatran[229,230]	Apixaban[231], SmPc	Edoxaban[184,232]	Rivaroxaban[131,186]
Expected plasma levels of NOACs in patients treated for AF (based on dTT/ECA for dabigatran and anti-FXa activity for Xa inhibitors)				
Expected range of plasma levels *at peak* for standard dose (ng/mL)[a]	64–443	69–321	91–321	184–343
Expected range of plasma levels *at trough* for standard dose (ng/mL)[a]	31–225	34–230	31–230	12–137
Expected impact of NOACs on routine coagulation tests				
PT	↑	(↑)	↑(↑)	↑↑ (↑)
aPTT	↑↑(↑)	(↑)	↑	↑
ACT	↑(↑)	↑	↑	↑
TT	↑↑↑↑	—	—	—

Ranges indicate the P5/95 percentiles for dabigatran, rivaroxaban, and apixaban, and the interquartile ranges for edoxaban.
The reagents influence the sensitivity of the PT for FXa inhibitors and of the aPTT for dabigatran. When a sensitive assay is used, normal aPTT excludes above on-therapy levels in dabigatran-treated patients, and normal PT excludes above on-therapy levels in rivaroxaban and edoxaban, but not apixaban treated patients. Point-of-care INR devices developed to monitor vitamin K antagonists do not accurately reflect the anticoagulant status of NOAC treated patients.
ACT, activated clotting time; aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECA, ecarin clotting assay; INR, international normalized ratio; PT, prothrombin time.

ICSH Recommendations – Plasma Concentrations

	Dabigatran		Rivaroxaban		Apixaban		Edoxaban	
Indication	Stroke prevention in NVAF	Treatment PE/VTE	Stroke prevention in NVAF	Treatment PE/VTE	Stroke prevention in NVAF	Treatment PE/VTE	Stroke prevention in NVAF	Treatment PE/VTE
Dose	150 mg bid	150 mg bid	20 mg qd	20 mg qd	5 mg bid	5 mg bid	60 mg qd	60 mg qd
Peak concentration, ng/mL	175[a] (117–275)	175[a] (117–275)	249[b] (184–343)	270[b] (189–419)	171[c] (91–321)	132[c] (59–302)	170[d] (125–245)	234[e] (149–317)
Trough concentration, ng/mL	91[a] (61–143)	60[a] (39–95)	44[b] (12–137)	26[b] (6–87)	103[c] (41–230)	63[c] (22–177)	36[e] (19–62)	19[e] (10–39)

Abbreviations: bid, twice daily; IQR, interquartile range; NVAF, non-valvular atrial fibrillation; PE, pulmonary embolism; qd, once daily; VTE, venous thromboembolism.

Notes: Other approved indications for DOACs include secondary prevention of PE/VTE, and post hip and knee replacement, which may have alternative dosing strategies. Additionally, changes in doses may occur after initiation phase of DOAC treatment. Consultation of regional DOAC labeling information is required before interpreting or using these peak and trough DOAC concentration data.

[a]Mean (25th–75th percentile).

[b]Mean (5th–95th percentile).

[c]Median (5th–95th percentile).

[d]Median (1.5 x IQR).

[e]Median (IQR).

ICSH Recommendations – Coagulation assays

	Dabigatran		Anti-Xa DOACs		
	Clot-based assays	Chromogenic-based assays	Clot-based assays	Chromogenic-based assays	Clinical impact of reported test result
Relationship between prolonged clotting time and increased drug concentration	PT/INR[a,b] APTT[a,b] Thrombin time Ecarin-based assays		PT/INR[a,b,c] APTT[a,b,c]		Diagnosis and/or Management
Relationship between DOAC presence and factitiously decreased reported result	Fibrinogen[b,d] Factor activity[a] (II, V, VII, VIII, IX, X, XI, XII)		Factor activity[a,b,c] (II, V, VII, VIII, IX, X, XI, XII)	Factor VIII[b] Factor IX	(Mis)Diagnosis and/or (Mis)Management
Relationship between DOAC presence and factitiously increased reported result	Inhibitor screen[a,b] Inhibitor assay[a,b] Lupus anticoagulant[a] Protein C activity[a,b] Protein S activity[a,b] APCR[a,b]	Antithrombin[b] (thrombin substrate)	Inhibitor screen[a,b,c] Inhibitor assay[a,b,c] Lupus anticoagulant[a,b] Protein C activity[a,b] Protein S activity[a,b] APCR[a,b,c]	Antithrombin[b] (factor Xa substrate) UFH, LMWH or heparinoids/ pentasaccharide	(Mis)Diagnosis and/or (Mis)Management

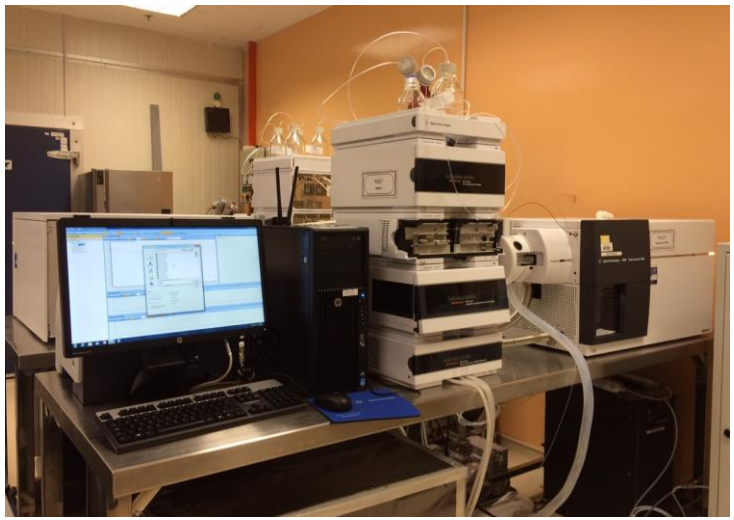
[a]Reagent dependent.
[b]Concentration dependent.
[c]Apixaban usually not affecting result.
[d]For fibrinogen—if measured using the Clauss method, most reagents will not be affected. For PT-derived measurements, results are more likely to be factitiously increased.

Inter-individual variability

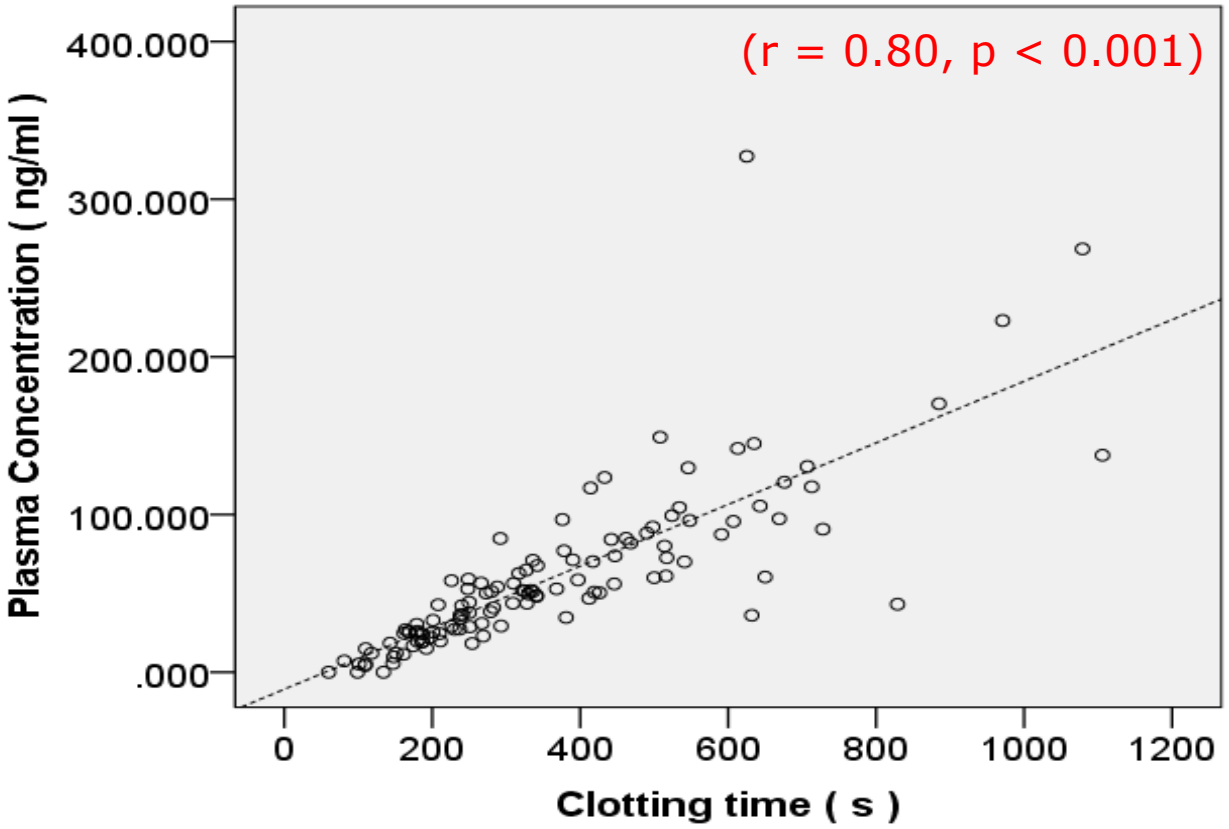
- Wide IIV in plasma concentration was observed across standard doses of NOAC
- Multicenter Italian study by Testa *et. al.* observed higher IIV at lower doses of NOAC; and at trough plasma concentrations
- Expressed as %CV of 55-66 for dabigatran, 33-52 for rivaroxaban and 19-46 for apixaban

CRC SGH Local Data

- 118 patients with non-valvular atrial fibrillation established on dabigatran
- Trough plasma concentrations in ng/mL measured on LC-MS/MS (Agilent, USA)
- Coagulation assay determined by ClotPro® (Dynabyte, Germany) expressed as clotting time in seconds.



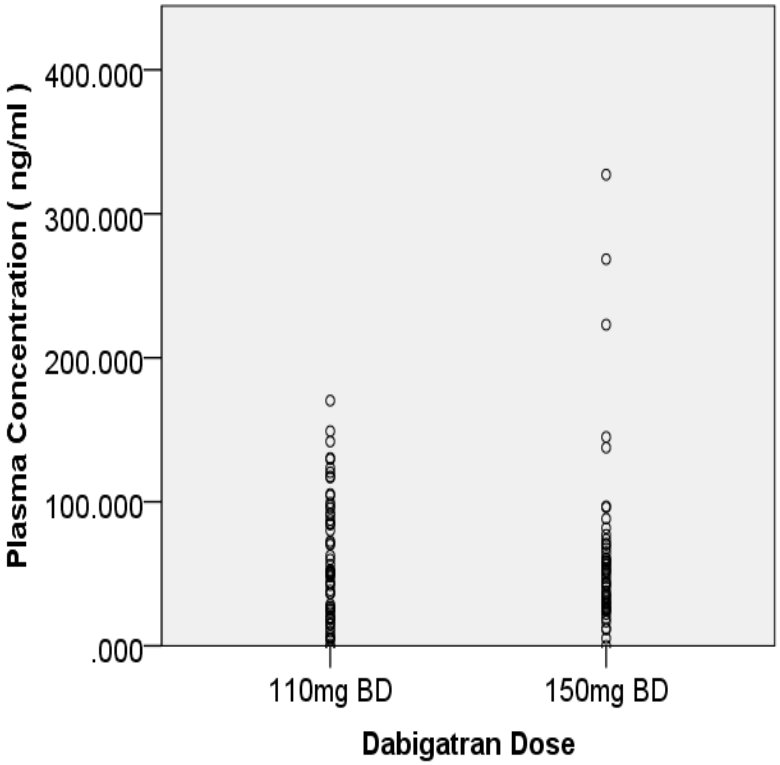
Result – trough plasma concentration vs coagulation effect

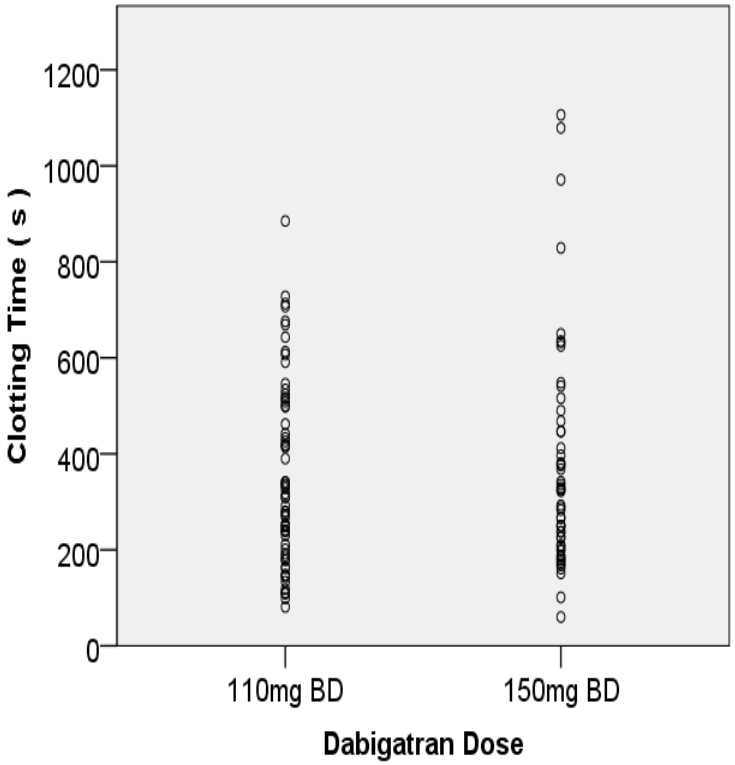


Mean trough plasma concentrations = 59.81ng/mL

Mean clotting time = 361.38s

Result – trough plasma concentration vs dose & coagulation effect vs dose





($p > 0.50$)

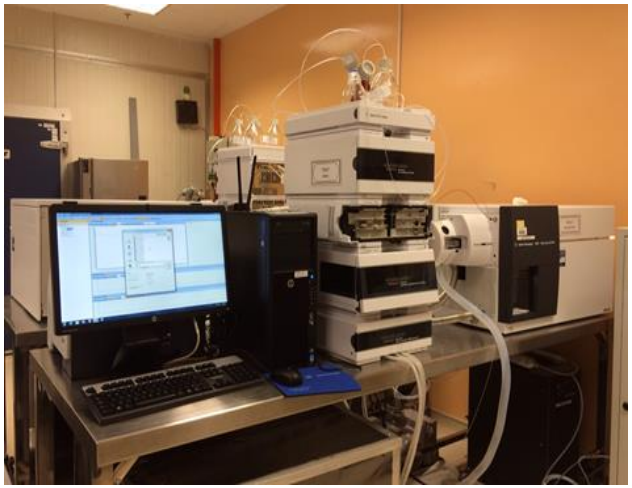
Clinical Utility

- 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 NOAC)

Real World Practice

- 52 y/o Malay, Male
- AF with dilated cardiomyopathy
- On Apixaban 5mg BD
- Developed ischemic stroke
- Decision for thrombolysis

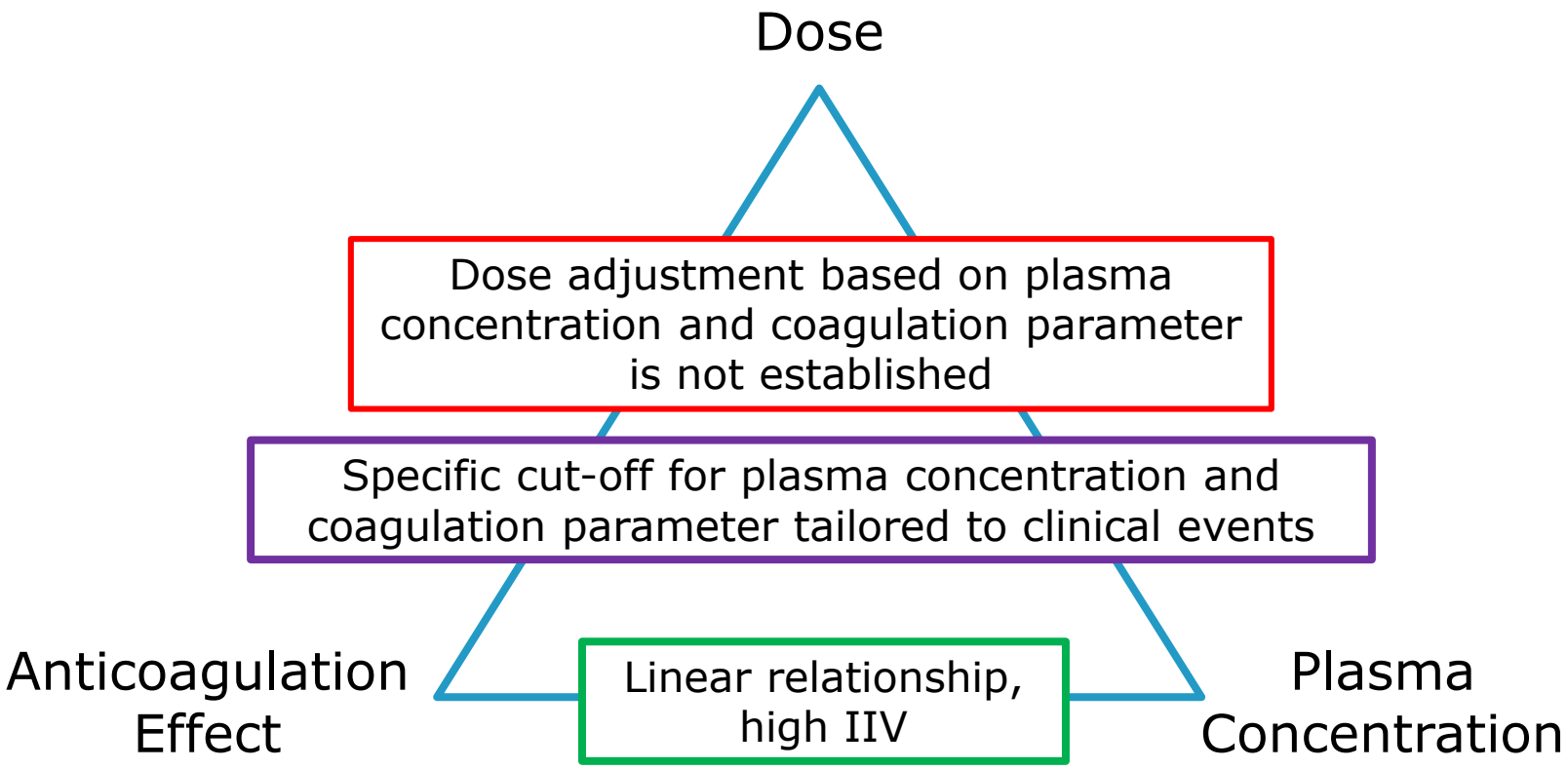
Laboratory Parameters Aided Therapy



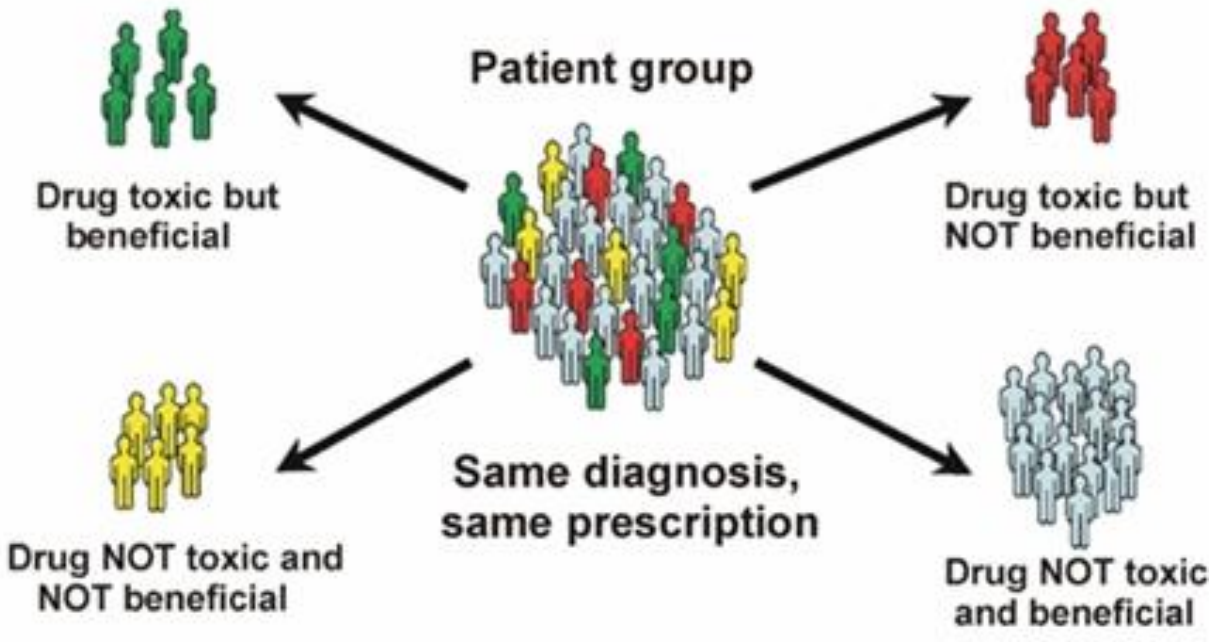
114 s

102.3 ng/mL

NOAC TRIAD


Dose
Dose adjustment based on plasma concentration and coagulation parameter is not established
Specific cut-off for plasma concentration and coagulation parameter tailored to clinical events
Anticoagulation Effect
Linear relationship, high IIV
Plasma Concentration

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