Joint Meeting of Coronary Revascularization
12th to 14th December 2019

Point of Care Clotting Time and Drug Level Assessment in patients on Apixaban – A Case Series

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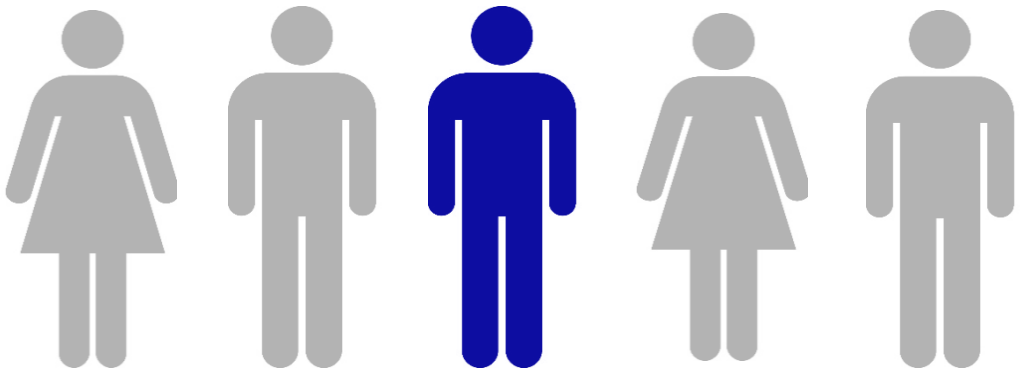
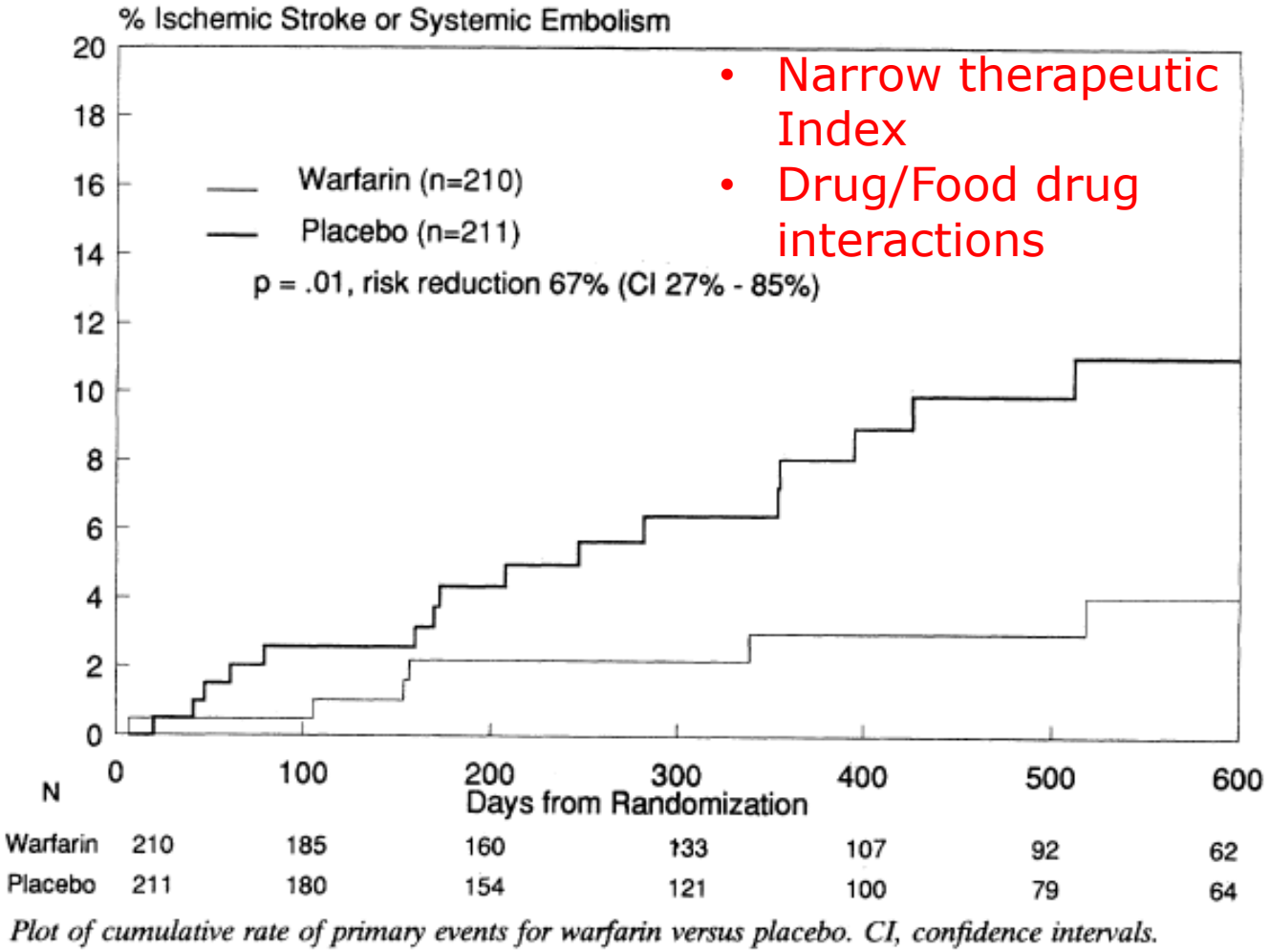
Burden of Stroke in Atrial Fibrillation

- Global prevalence[1]: 1-2%
- Malaysia prevalence (2016)[2] = 0.54%
- increases **5x** risk of stroke[3]



1 in 5 stroke occurs with patients with AF

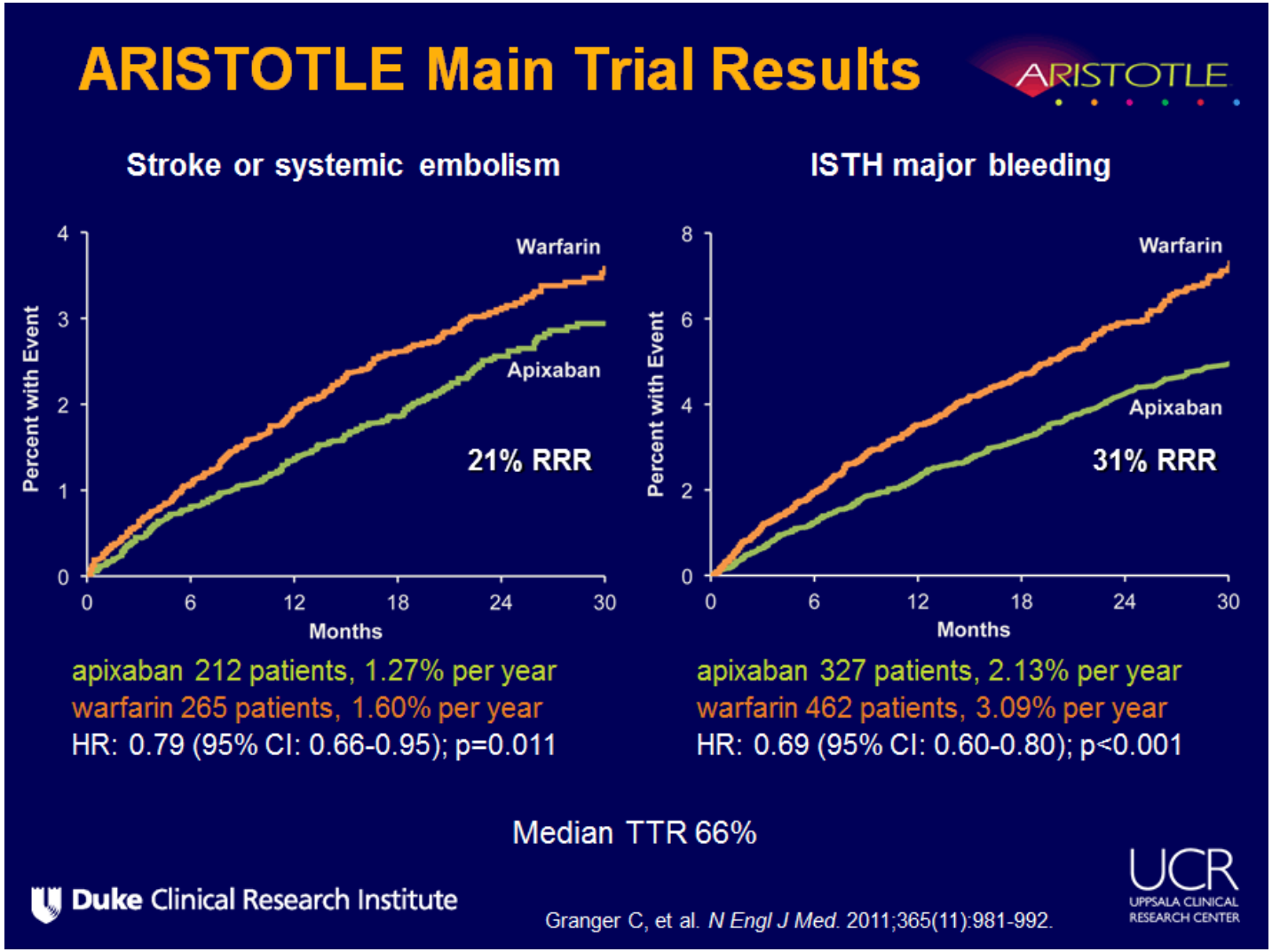
SPAF Study (1991)[4]



Plot of cumulative rate of primary events for warfarin versus placebo. CI, confidence intervals.

- Narrow therapeutic Index
- Drug/Food drug interactions

ARISTOTLE (2011) [5]
Apixaban vs. warfarin in patients with AF



Wide interindividual variability [6]

	Dabigatran	Apixaban	Endoxaban	Rivaroxaban
Expected range of plasma levels or peak for standard dose (ng/ml)	64-443	69-321	91-321	184-343
Expected range of plasma levels at trough for standard dose (ng/ml)	31-225	34-230	31-230	12-137

- *Expected plasma levels of NOACs in AF patients (based on dtt/ECA for dabigatran and anti-Fxa activity for Xa inhibitors*

Objective (s)

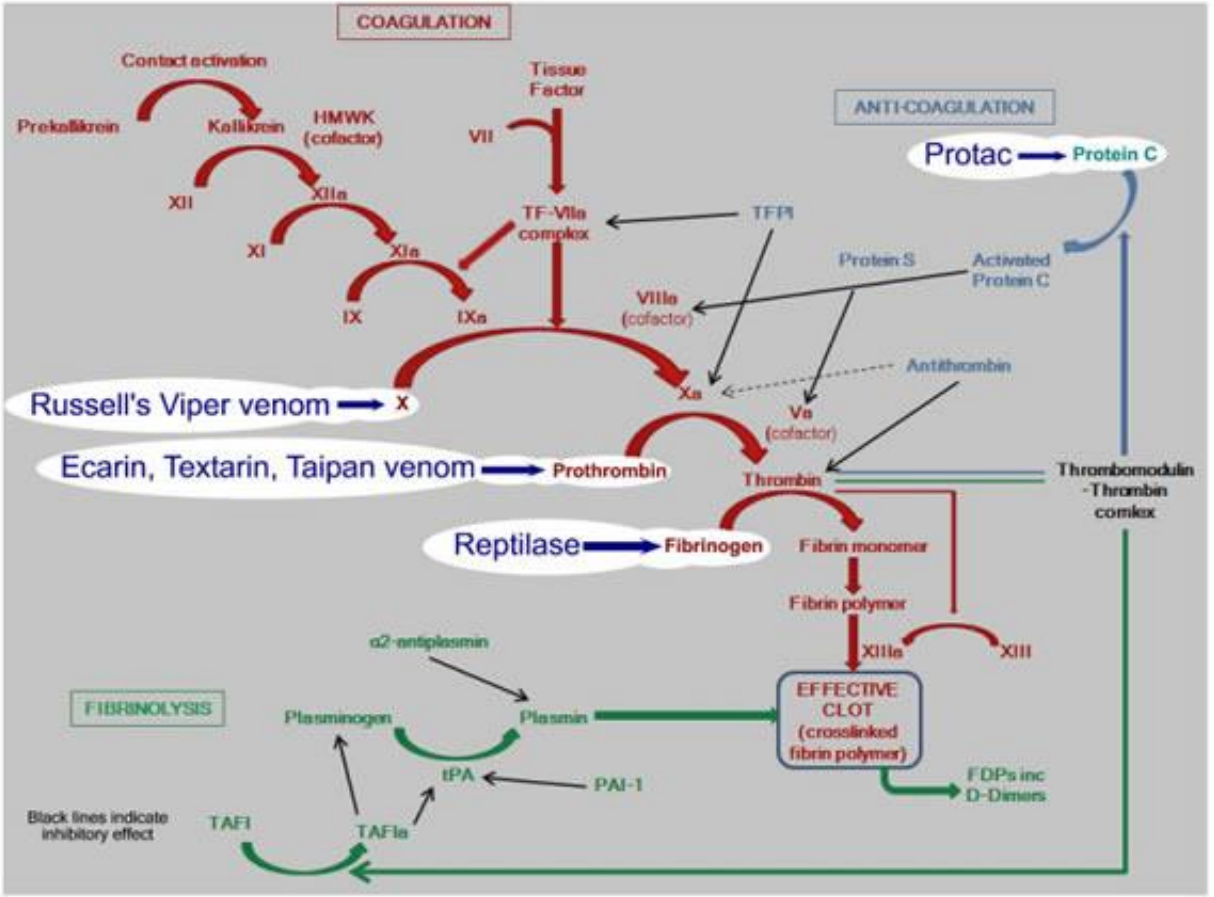
- We sought to determine the association between clotting time (CT) obtained from a novel POCI and drug level (DL) of two doses of apixaban prescribed in patients with non-valvular atrial fibrillation

Clotpro® Dynabyte, Germany

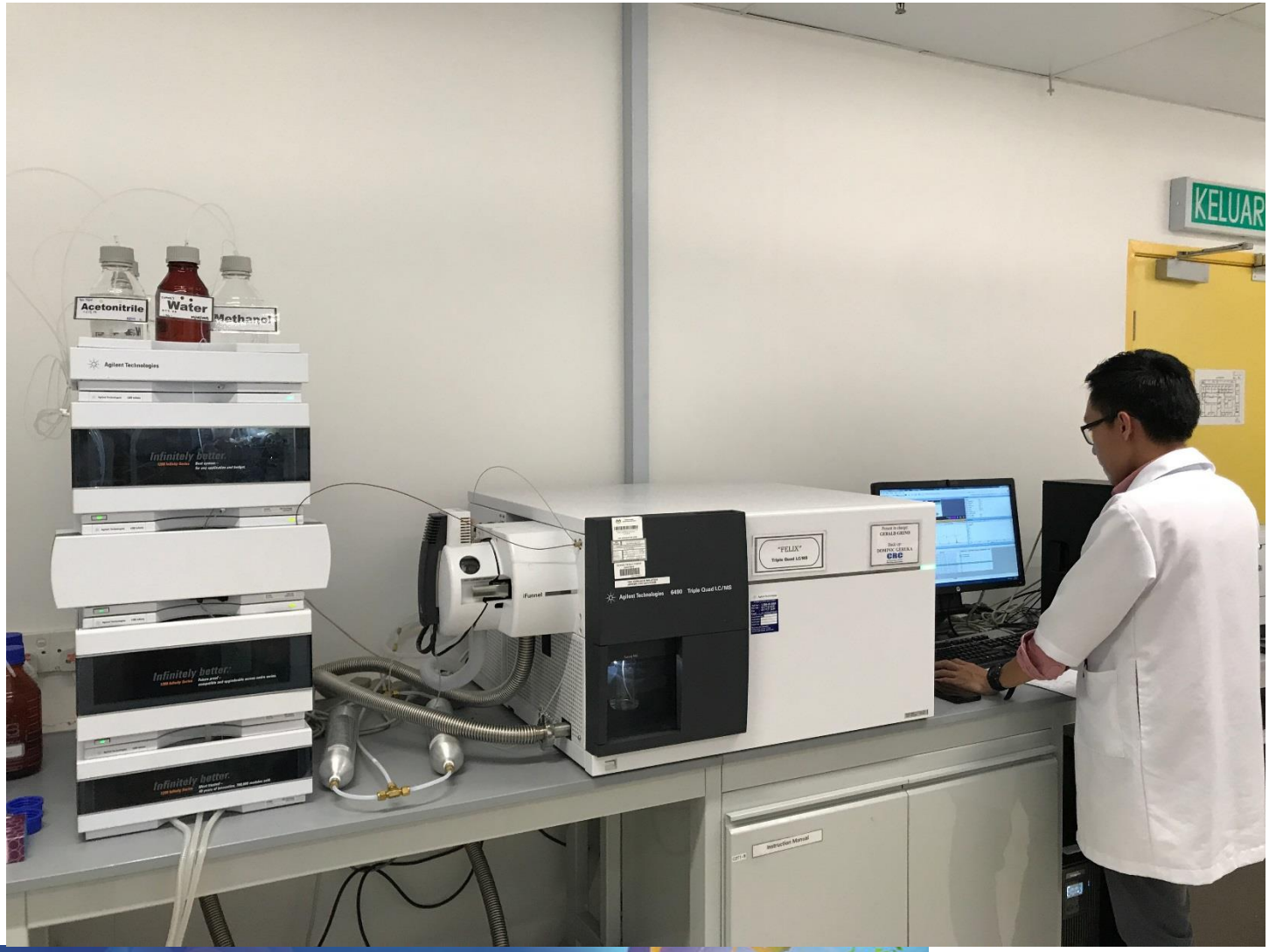
Clotpro® MOA

- 6- channel viscoelastometry analyzer
- Reagent in the pipette tips
- 1 hour for complete result (CT within 15 minutes)
- Measures drug effect (clotting time)

Russells Viper Venom test



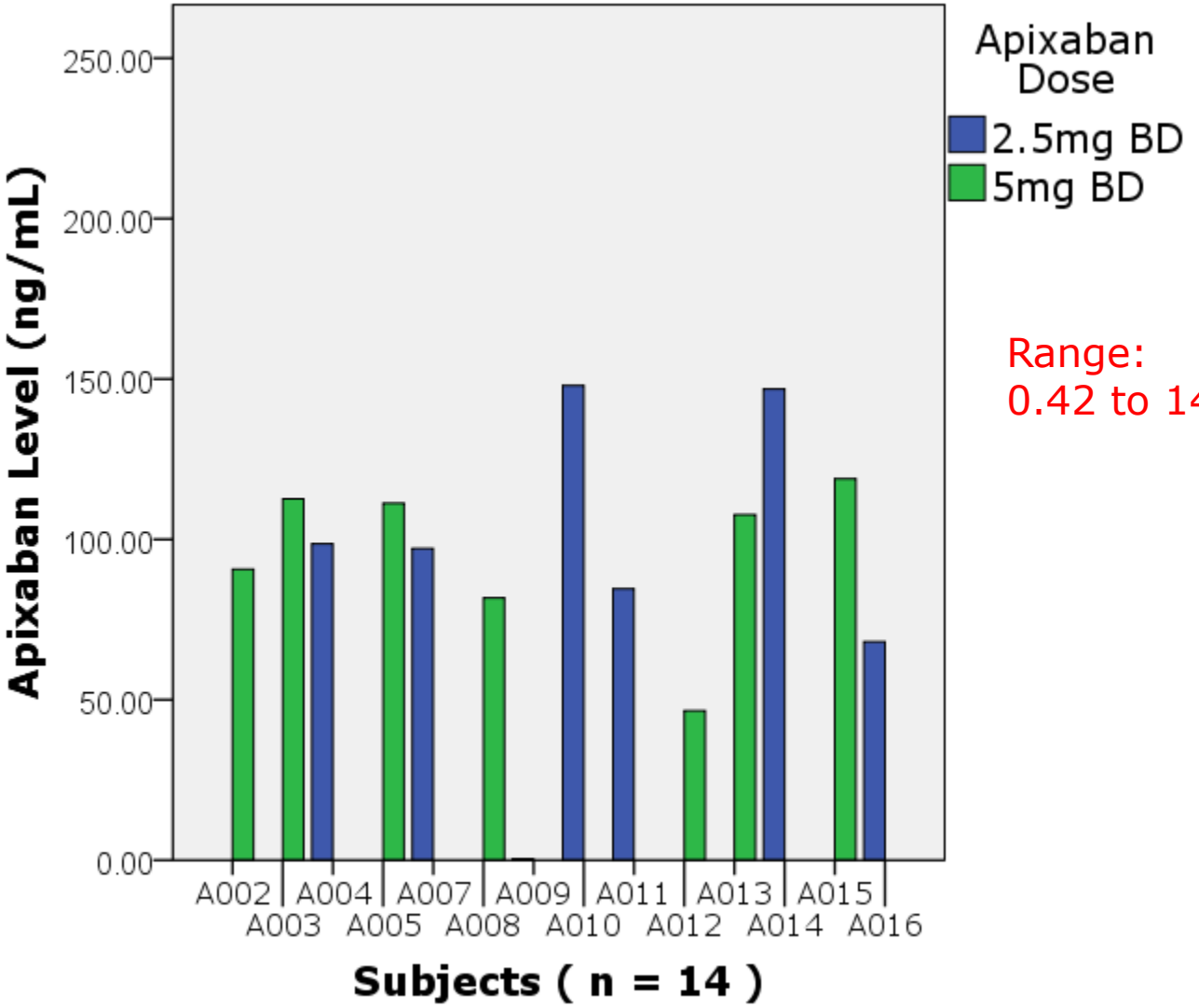
Triple Quadrupole LC-MS/MS



Demographics (n=14)

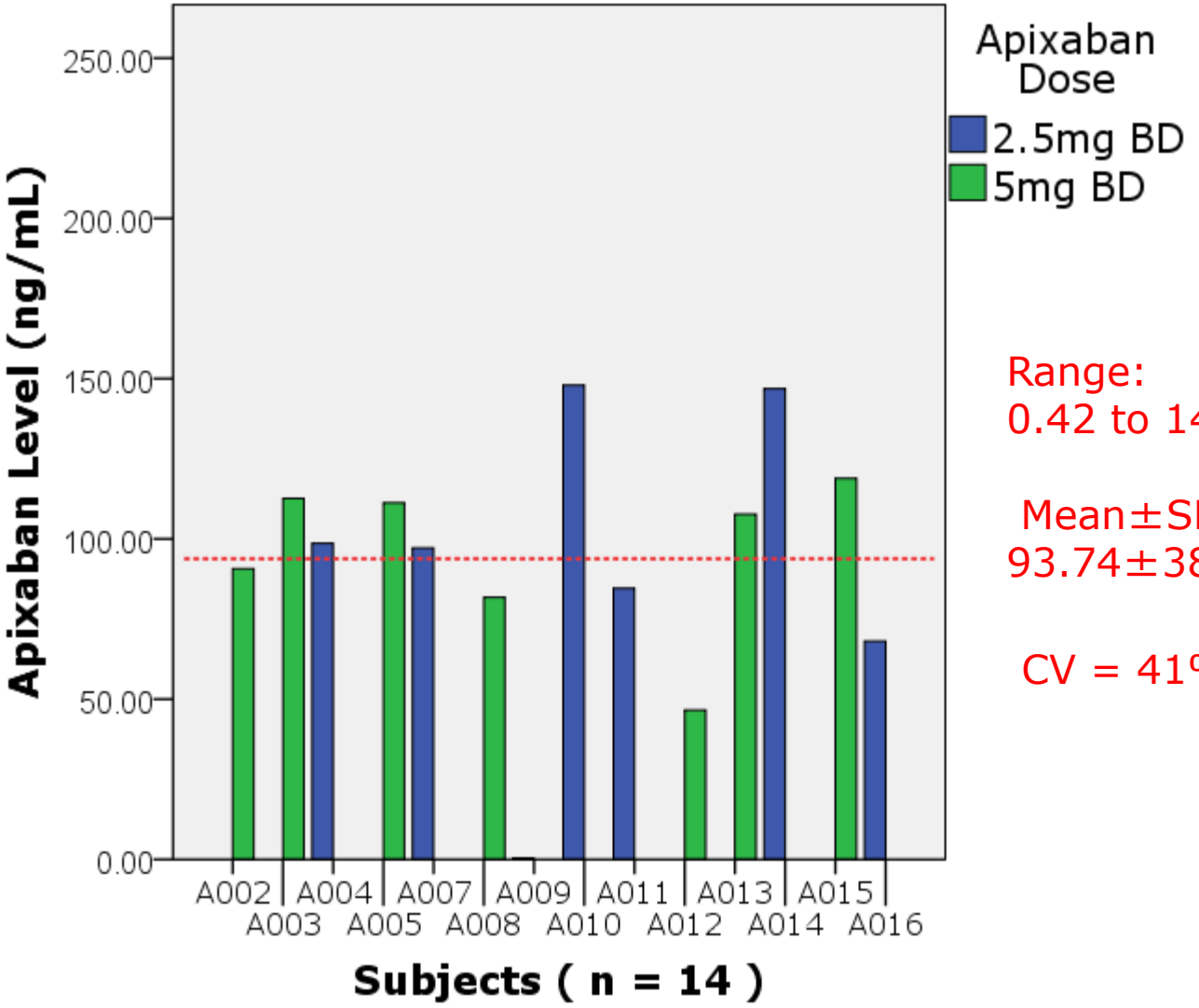
Age;years (Mean ± SD)	75.79 ±10.15
CHA_2DS_2-VASc Score	4.07 ± 1.39
HASBLED score	1.57 ± 0.85
Creatinine clearance (ml/min)	41.92 ± 18.62
Gender : male; n (%)	9 (64.3)
Race; n(%)	
Malay	2 (14.3)
Chinese	8 (57.1)
Non-Malay indegenious	4 (28.1)
Hypertension; n(%)	13 (92.9)
Chronic Heart Failure; n(%)	4 (28.6)
Diabetes Mellitus; n(%)	5 (35.7)
Smoking History; n(%)	5 (35.7)
Family History of CVD; n(%)	1 (7.1)
Family Hisory of AF; n(%)	0 (0)
Prior Haemorrhage; n(%)	0 (0)
Prior stroke; n(%)	3 (21.4)
ACS history; n(%)	3 (21.4)

Apixaban Trough Drug Level



Range:
0.42 to 147.91 ng/ml

Apixaban Trough Drug Level

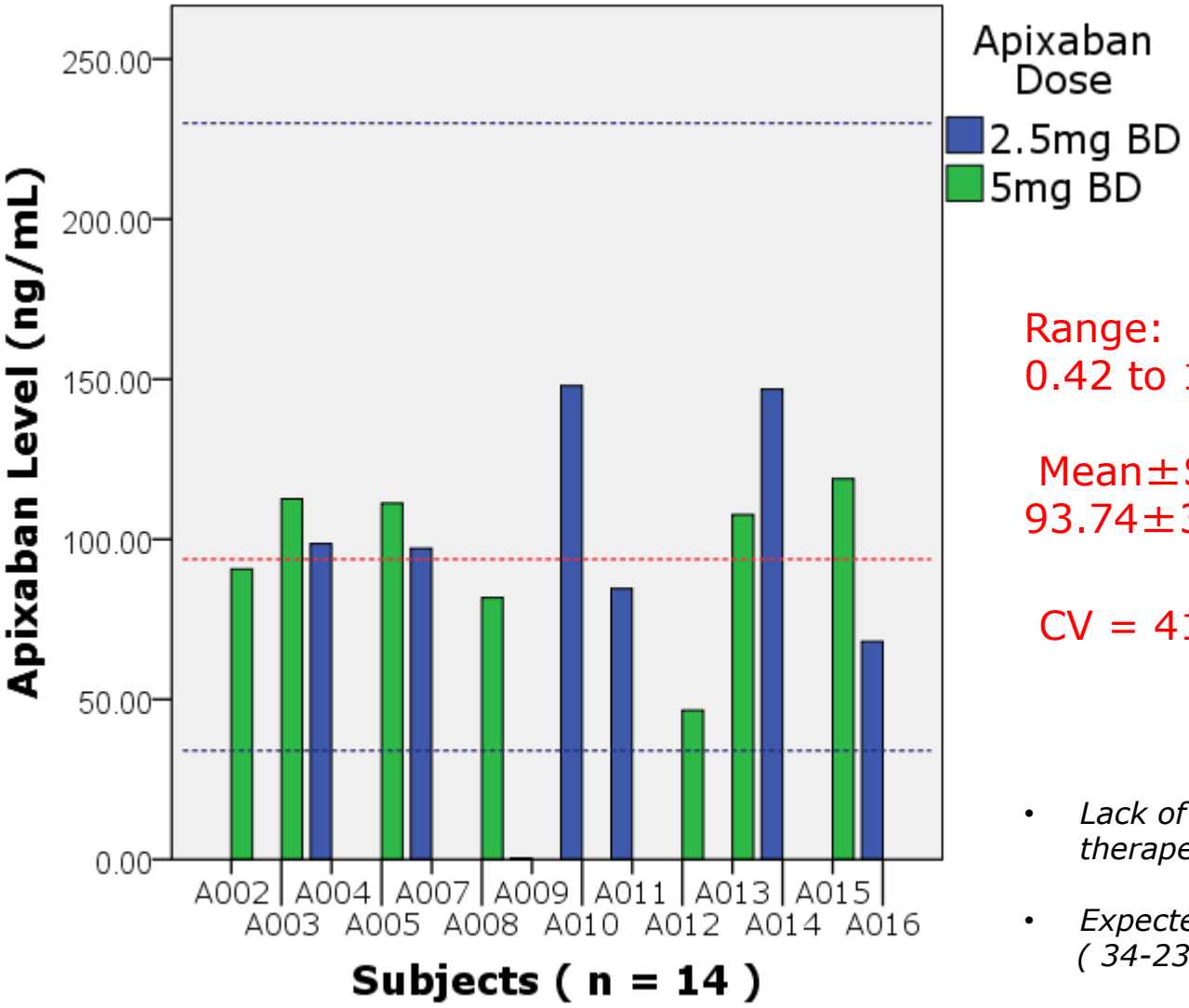


Range:
0.42 to 147.91 ng/ml

Mean±SD:
93.74±38.34 ng/ml

CV = 41%

Apixaban Trough Drug Level



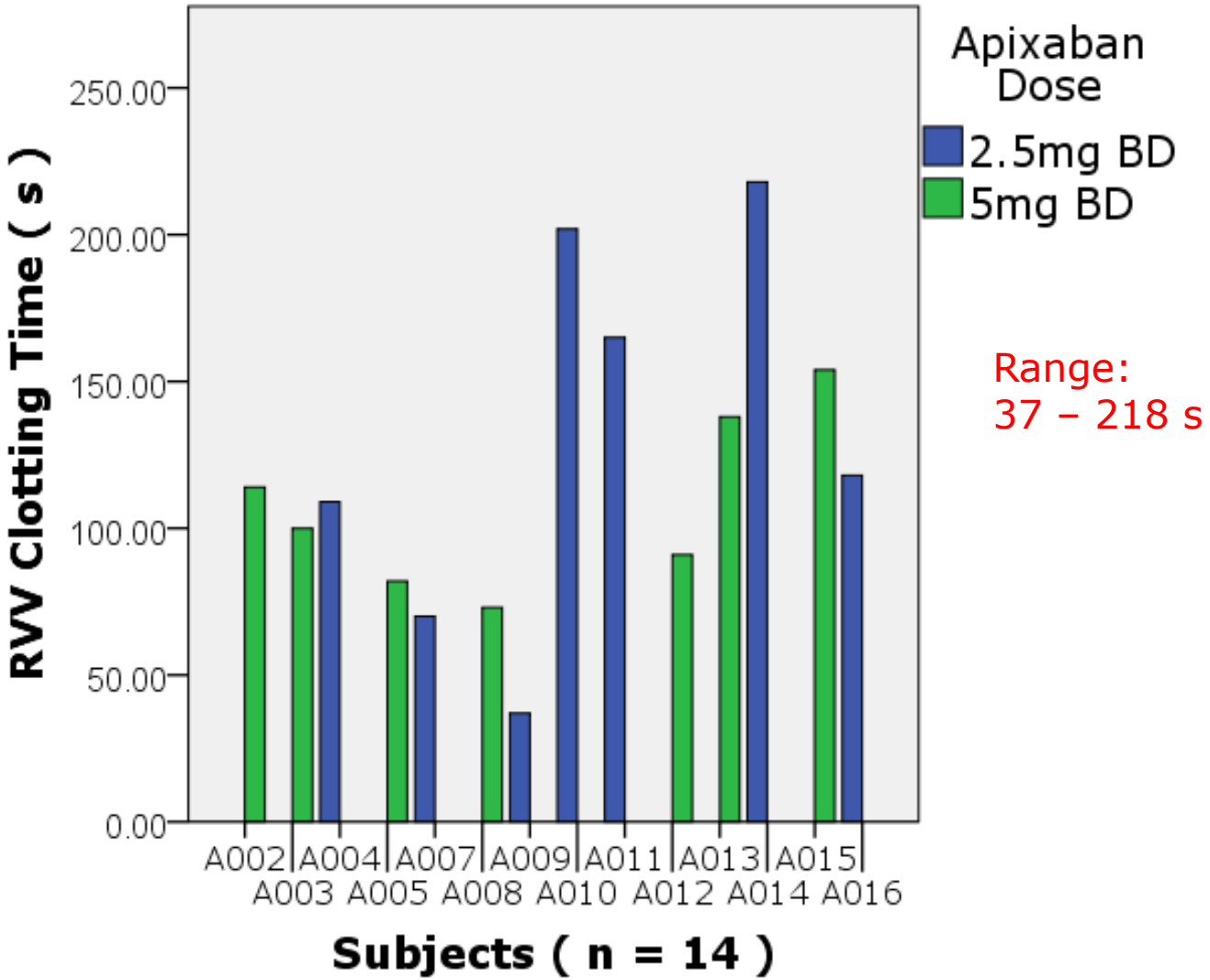
Range:
0.42 to 147.91 ng/ml

Mean±SD:
93.74±38.34 ng/ml

CV = 41%

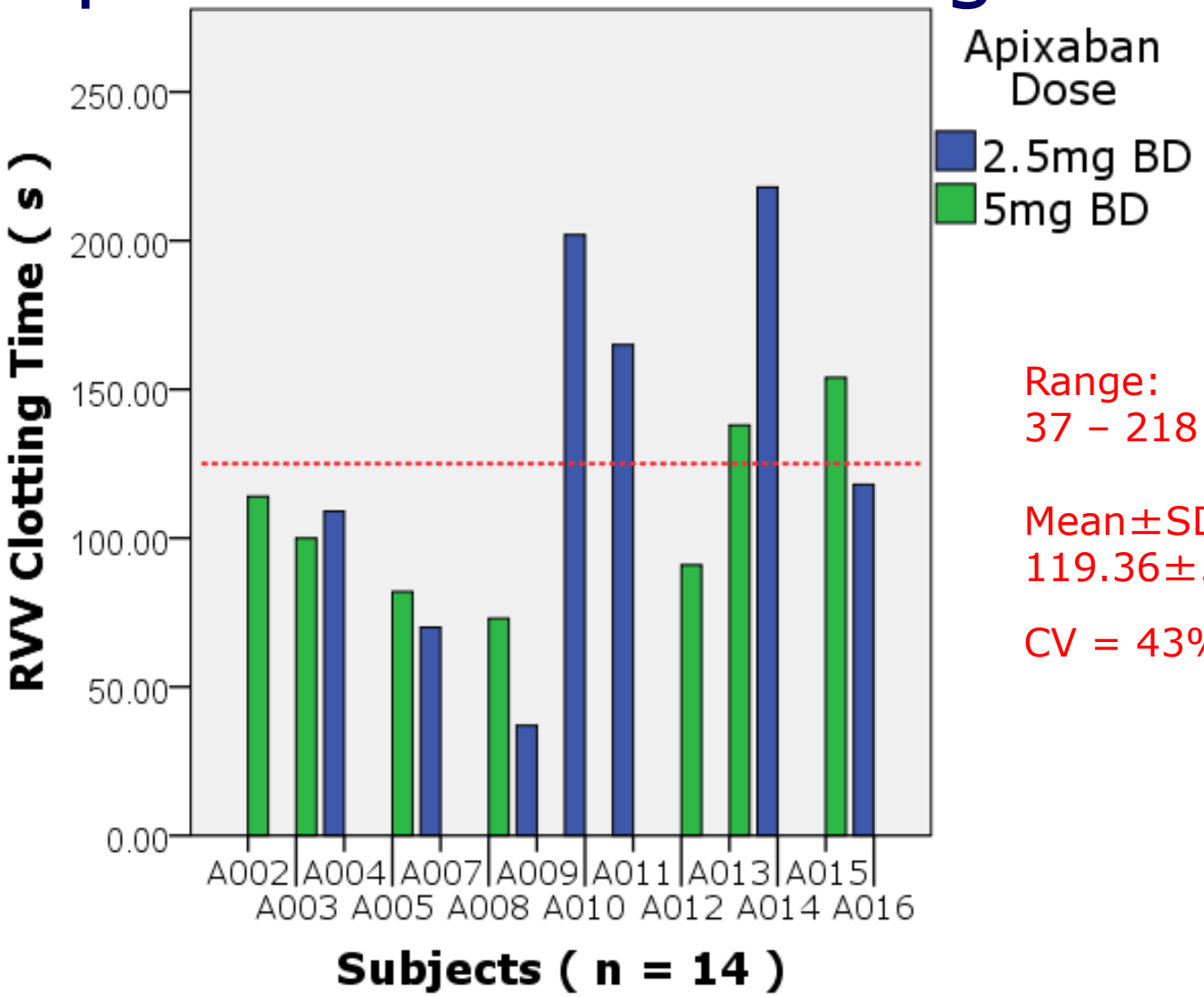
- *Lack of DOACS therapeutic range*
- *Expected trough level (34-230ng/ml)*

Apixaban RVV Clotting Time



Range:
37 – 218 s

Apixaban RVV Clotting Time

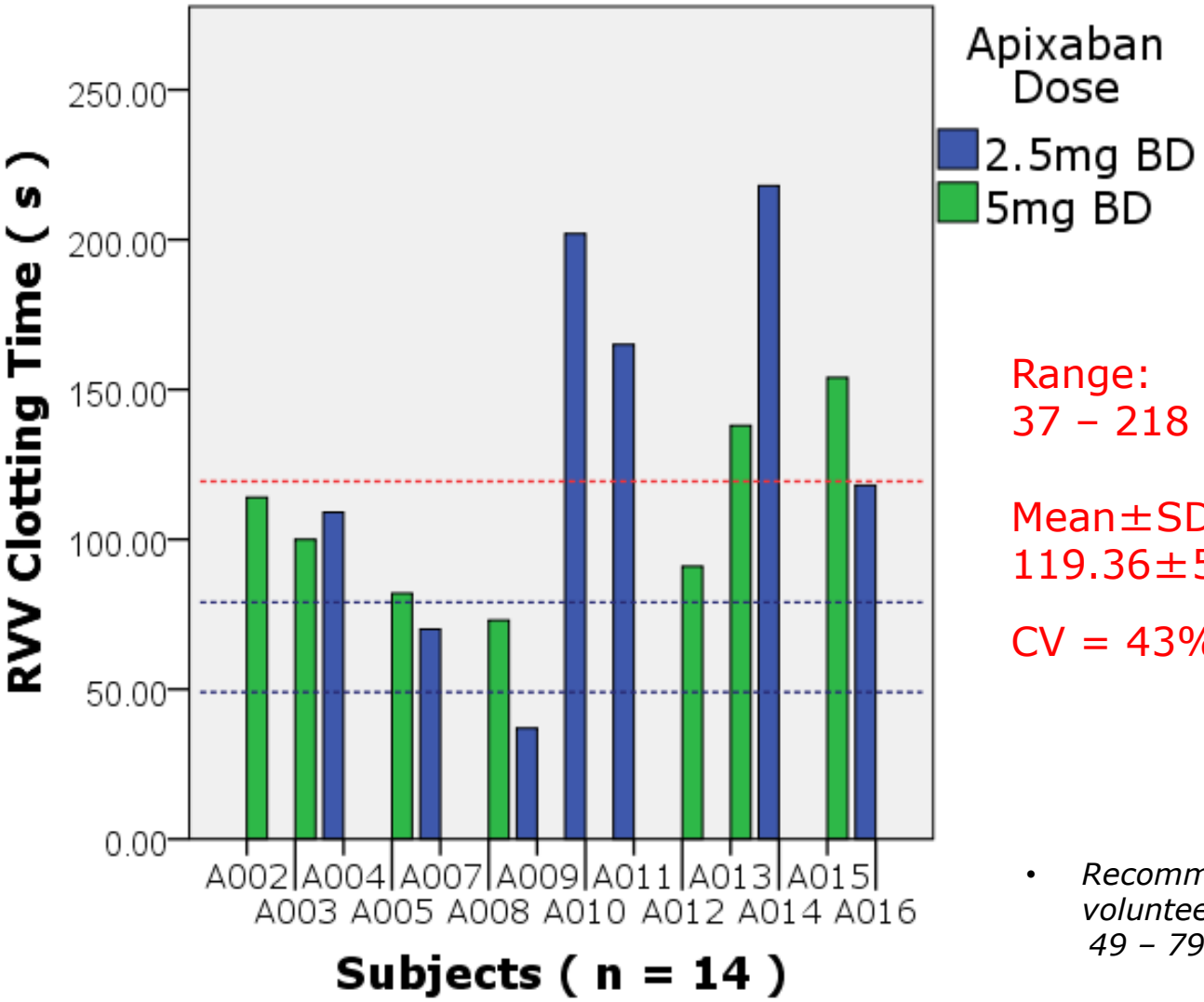


Range:
37 – 218 s

Mean±SD:
119.36±51.34 s

CV = 43%

Apixaban RVV Clotting Time



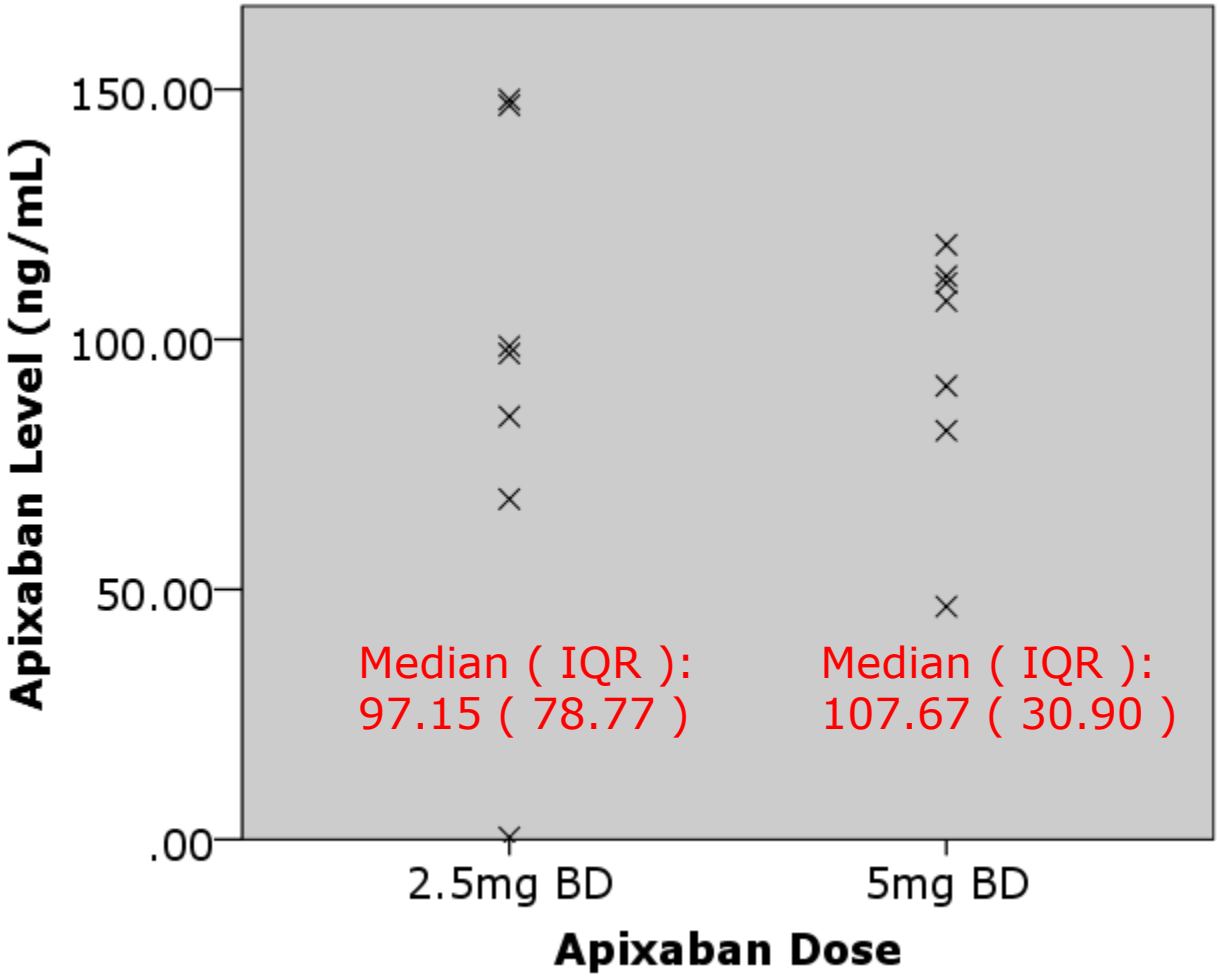
Range:
37 – 218 s

Mean±SD:
119.36±51.34 s

CV = 43%

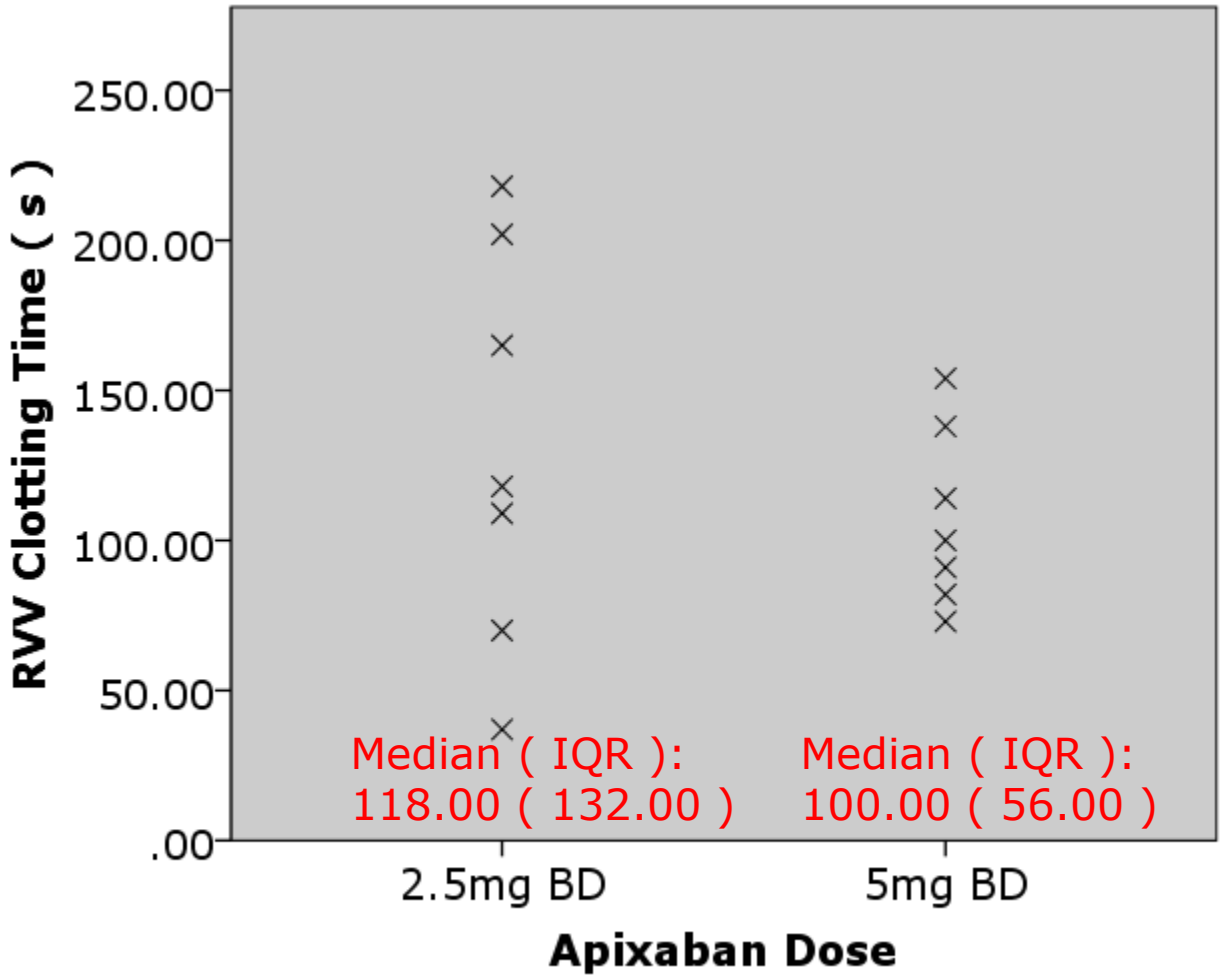
- *Recommended healthy volunteer range:*
  49 – 79 s

Dose vs. Trough Level



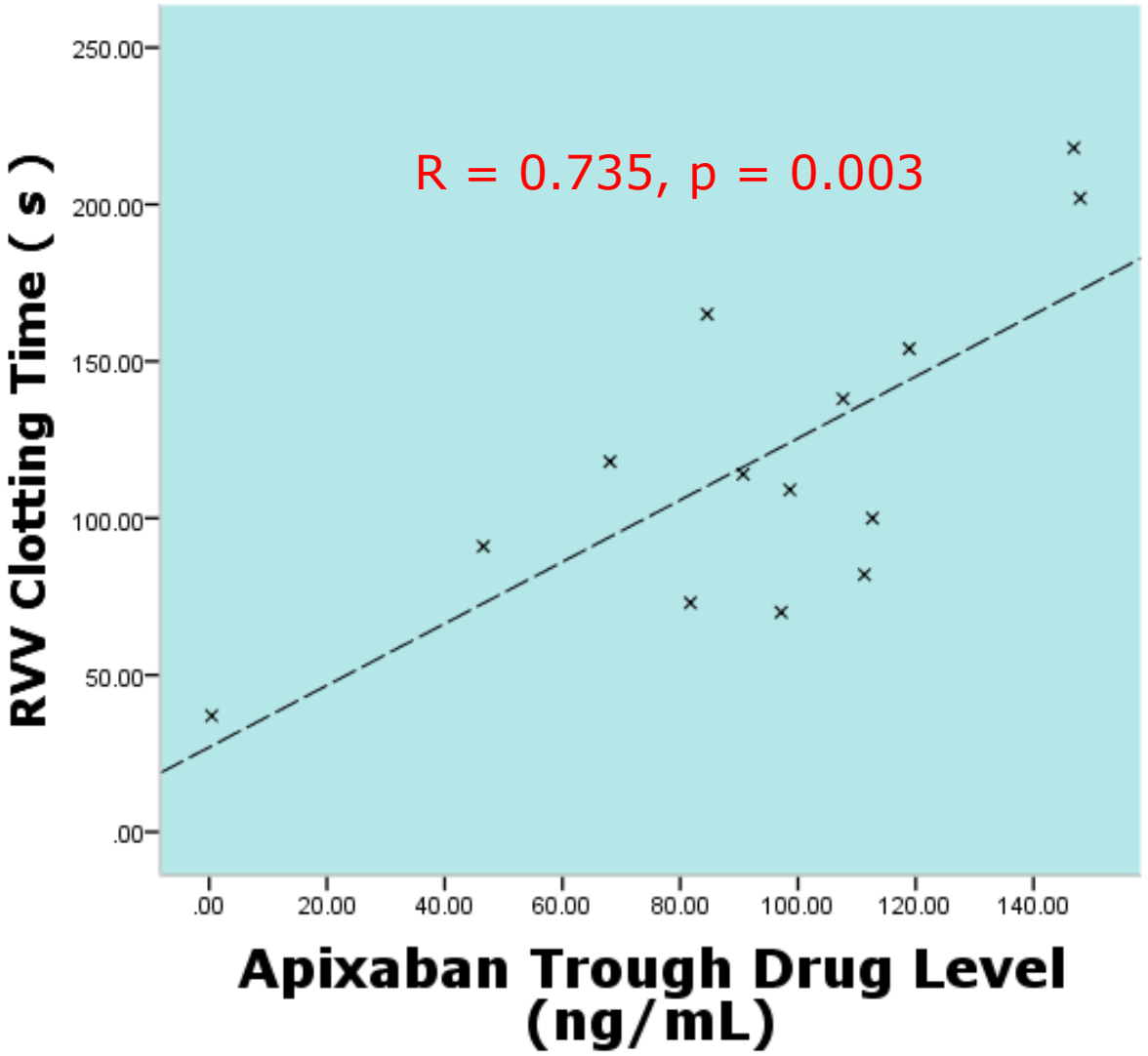
p=0.848

Dose vs. Clotting Time



p=0.482

RVV CT vs. Trough DL



Case 1: Mdm. TLS

- 90 yo female,
- non-smoker,
- weight 51.0kg,
- CrCl: 24 min/min
- Paroxymal AF diagnosed since 05.04.2019
- Apixaban 2.5mg BD started.

Concomitant Drugs:
Clopidogrel 75mg OD , Vildagliptin 50mg OD, Gliclazide MR 30mg OD, Pantoprazole 40mg OD, Atorvastatin 40mg ON, Bisoprolol 1.25mg OD, Isosorbide Dinitrate 10mg TDS, Digoxin 0.0625mg OD, Slow K 1.2g OD, Frusemide 20mg OD

Concomitant diseases:

- H/O NSTEMI TIMI 6 for medical therapy (13/5-17/5/19)
- Currently admitted for NSTEMI 19-24/5/19)
- In ward, NCNC Anemia (Hb: 9.8 -> 9.6-> 8.6-> 9.9 (after 1 pint PC))
- Diabetes Mellitus
- Hypertension
- Multiple Myeloma in remission (not on active therapy)
- Diastolic Heart Failure

Case 1: CHA_2DS_2-VASc vs. HAS-BLED

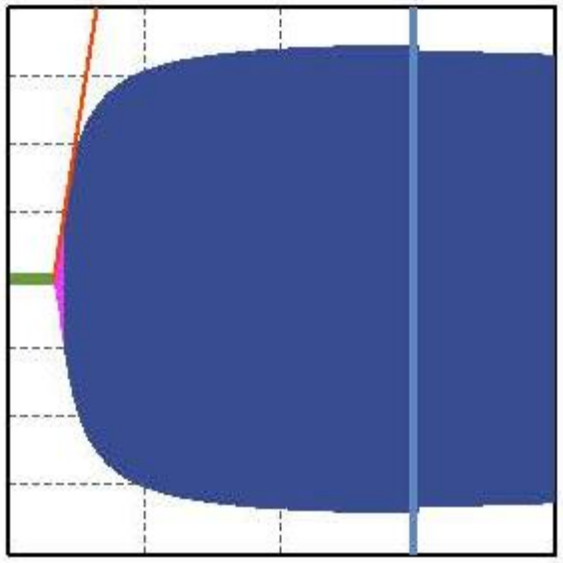
CHA_2DS_2-VASc	Score	HAS-BLED	Score
Congestive heart failure/LV dysfunction	1	Hypertension i.e. uncontrolled BP	1
Hypertension	1	Abnormal renal/liver function	1 or 2
Aged ≥75 years	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency or predisposition	1
Stroke/TIA/TE	2	Labile INR	1
Vascular disease [prior MI, PAD, or aortic plaque]	1	Age (e.g. >65)	1
Aged 65-74 years	1	Drugs (e.g. concomitant aspirin or NSAIDSs) or alcohol	1
Sex category [i.e. female gender]	1		
Maximum score	**9**		**9**

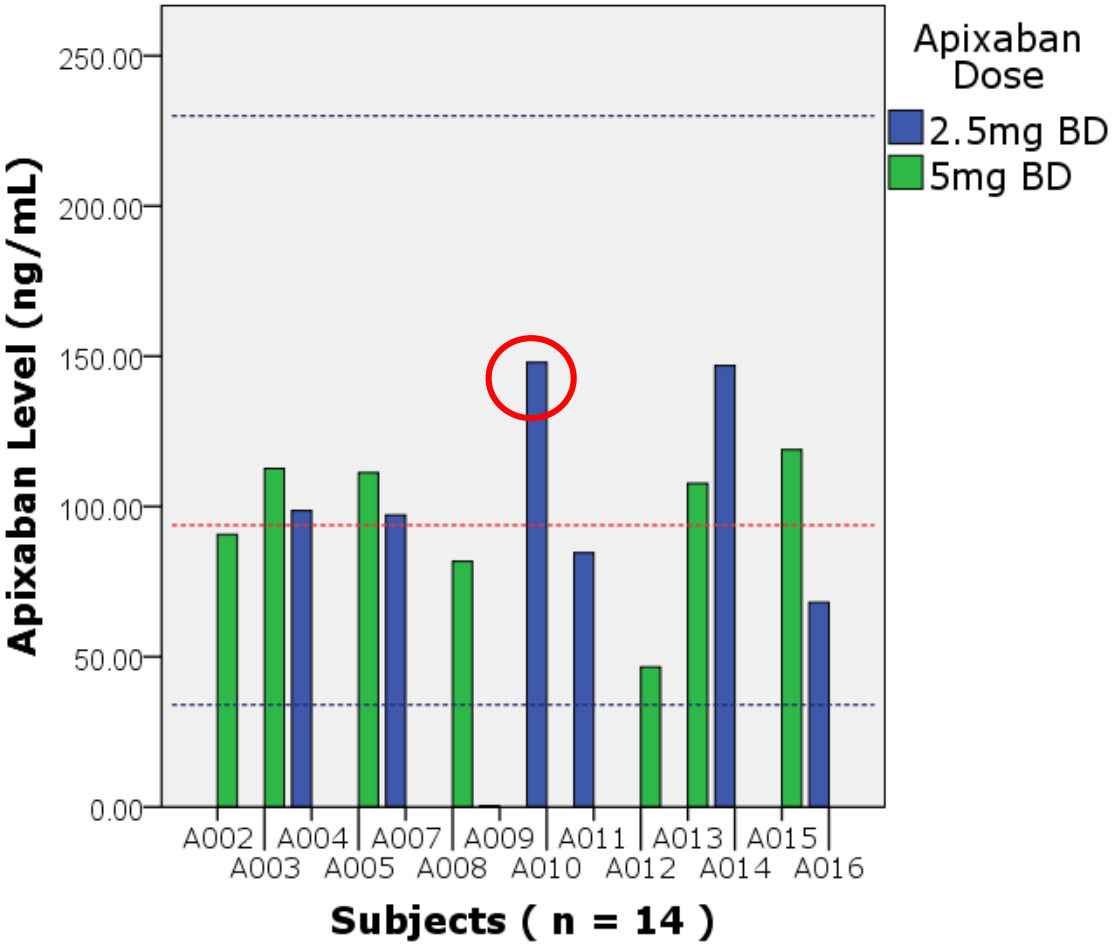
6

3

Case 1:Clotting Time vs. Drug Level

RVV-test		
CT	202s	▲ 49-79
A5	58mm	▲ 40-55
A10	65mm	▲ 49-63
A20	68mm	▲ 53-67
MCF	68mm	▶ 53-69
CFT	42s	
LT		





Trough Drug Level:
147.91 ng/ml

Case 2: Mr. KTT

- 90 yo male,
- Former-smoker,
- weight 44.0kg,
- CrCl: 23/min
- Paroxymal AF diagnosed since December 2014
- Apixaban 2.5mg BD started.

Concomitant diseases:

- Hypertension
- Mild aortic stenosis
- Osteopenia
- B12 deficiency

<u>Concomitant Drugs:</u>
Amlodipine 5mg OD ,
Fosamax Plus 1/1 a week,
Ca Carbonate 500mg BD,
Bisoprolol 5mg OD,
Pantoprazole 20mg OD,
Vitamin B12 1/1 OD

Case 2: CHA_2DS_2-VASc vs. HAS-BLED

CHA_2DS_2-VASc	Score	HAS-BLED	Score
Congestive heart failure/LV dysfunction	1	Hypertension i.e. uncontrolled BP	1
Hypertension	1	Abnormal renal/liver function	1 or 2
Aged ≥75 years	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency or predisposition	1
Stroke/TIA/TE	2	Labile INR	1
Vascular disease [prior MI, PAD, or aortic plaque]	1	Age (e.g. >65)	1
Aged 65-74 years	1	Drugs (e.g. concomitant aspirin or NSAIDSs) or alcohol	1
Sex category [i.e. female gender]	1		
Maximum score	**9**		**9**

3

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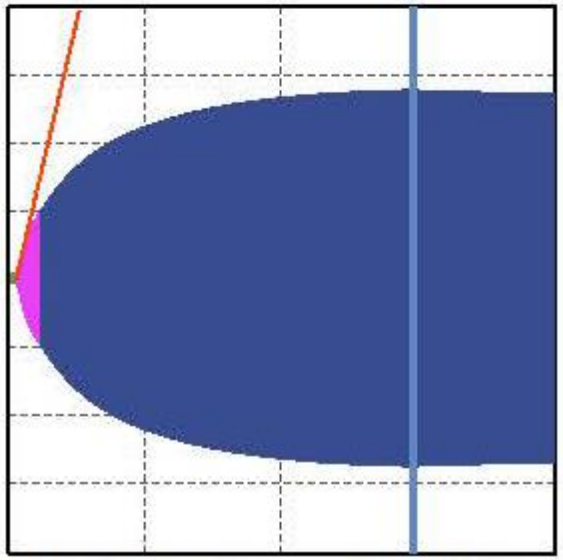
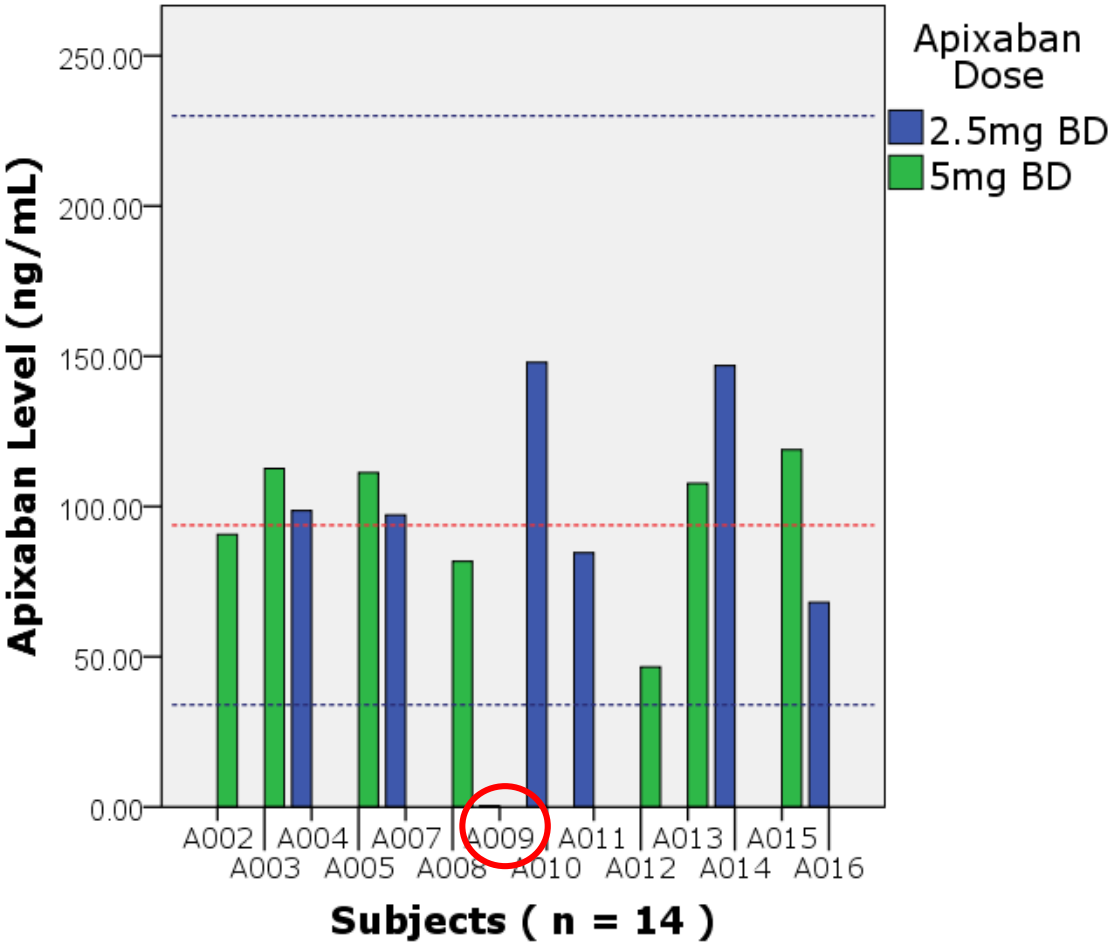
Case 2:Clotting Time vs. Drug Level

RVV-test		
CT	37s	▼ 49-79
A5	35mm	▼ 40-55
A10	46mm	▼ 49-63
A20	53mm	▶ 53-67
MCF	56mm	▶ 53-69
CFT	105s	
LT		

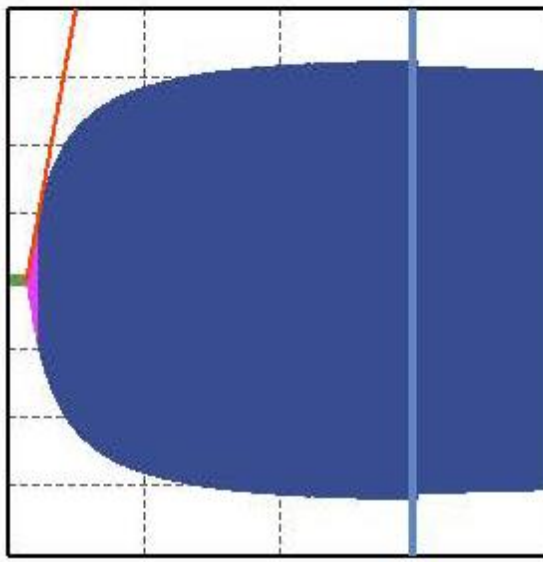


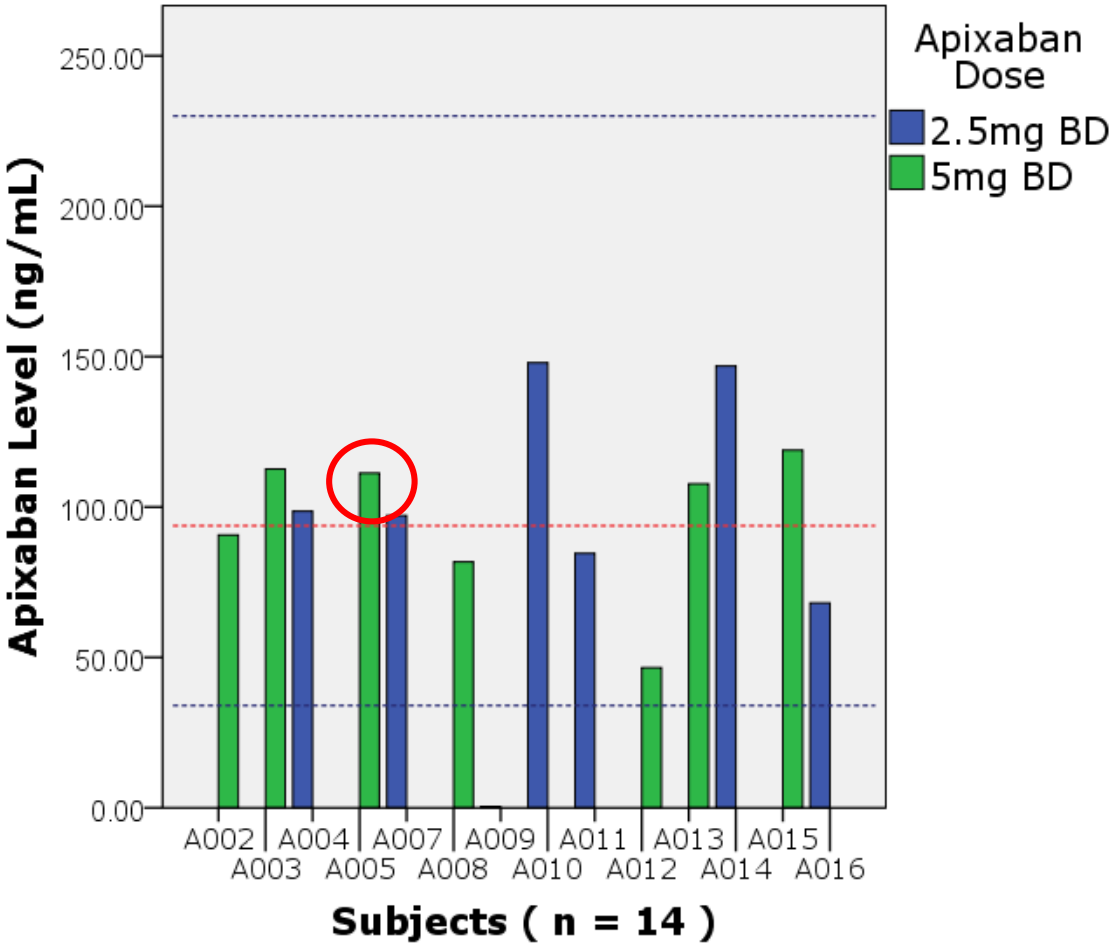


Trough Drug Level: < 1.0 ng/ml

Case 3:Clotting Time vs. Drug Level

RVV-test		
CT	82s	▲ 49-79
A5	50mm	▶ 40-55
A10	58mm	▶ 49-63
A20	63mm	▶ 53-67
MCF	64mm	▶ 53-69
CFT	50s	
LT		





Trough Drug Level:
111.28 ng/ml

Case 3: Mr. YHJ

- 66 yo male,
- Former-smoker,
- weight 76.0kg,
- CrCl: 84 mls/min
- Paroxymal AF diagnosed during admission in July 2018.
- Apixaban 5mg BD started.
- After elective admission for stage-PCI, discharged with triple therapy for 6/12.

Concomitant diseases:

- Hypertension
- Dyslipidemia
- Hx of NSTEMI and PCI to LCX in 2004, 2011: SVD – PCI to prox LCX, 2018: DVD – PCI toLCX with DEB,
- Stage PCI to LAD with DES. Date of PCI: 26.11.2018

Concomitant Drugs:
Cardiprin 100mg OD,
Clopidogrel 75mg OD,
Atorvastatin 40mg OD,
Amlodipine 50mg OD,
Bisoprolol 1.25mg OD
Telmisartan/Hydrochlorothiazide 80/12.5 1/1 OD

Case 3: CHA_2DS_2-VASc vs. HAS-BLED

CHA_2DS_2-VASc	Score	HAS-BLED	Score
Congestive heart failure/LV dysfunction	1	Hypertension i.e. uncontrolled BP	1
Hypertension	1	Abnormal renal/liver function	1 or 2
Aged ≥75 years	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency or predisposition	1
Stroke/TIA/TE	2	Labile INR	1
Vascular disease [prior MI, PAD, or aortic plaque]	1	Age (e.g. >65)	1
Aged 65-74 years	1	Drugs (e.g. concomitant aspirin or NSAIDSs) or alcohol	1
Sex category [i.e. female gender]	1		
Maximum score	**9**		**9**

3

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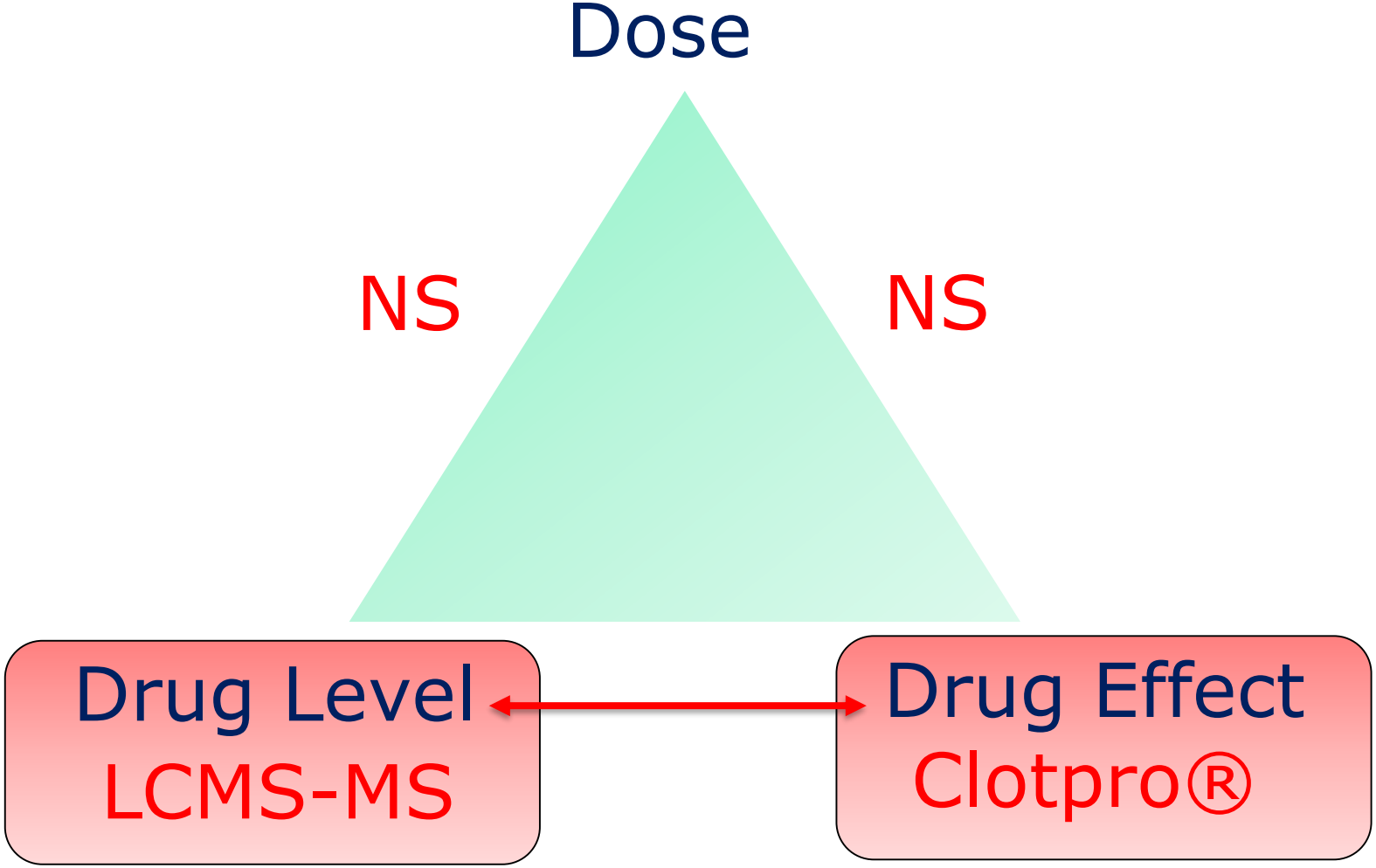
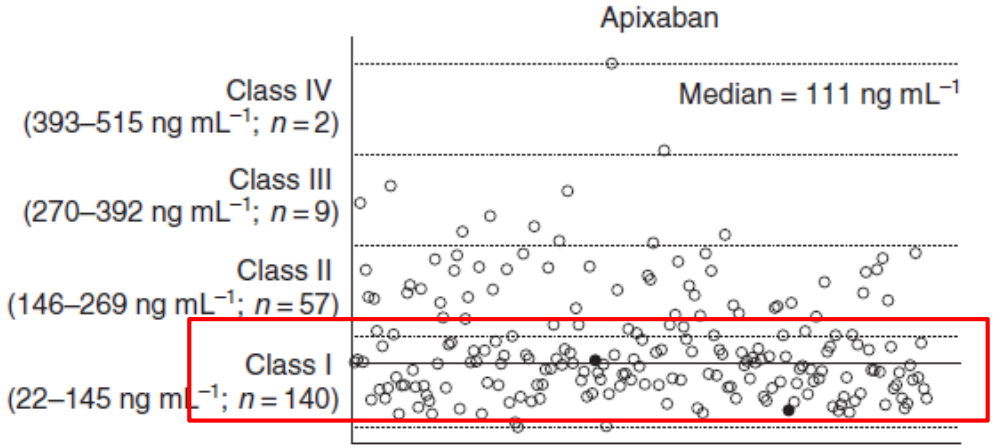
Conclusions

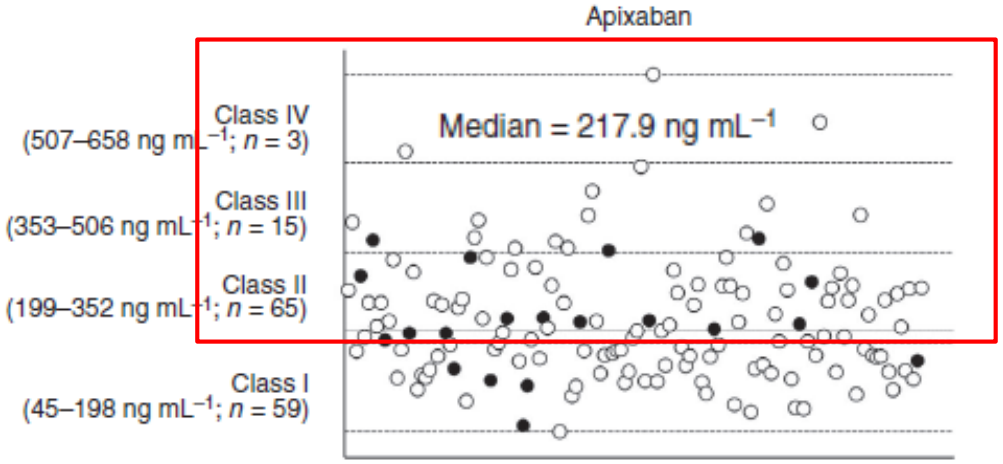


START2-Registry (2019) [7,8]



Trough level

Thromboembolic events



Peak level

Bleeding

Other real world studies… [9,10,11]

Association between prothrombin time
in hospitalized patients receiving rivarc

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Anti-Xa Activity and Event Risk in Patients With Direct Factor Xa Inhibitors Initiated Early After Stroke

Direct-acting oral anticoagulant drug level monitoring in clinical patient management

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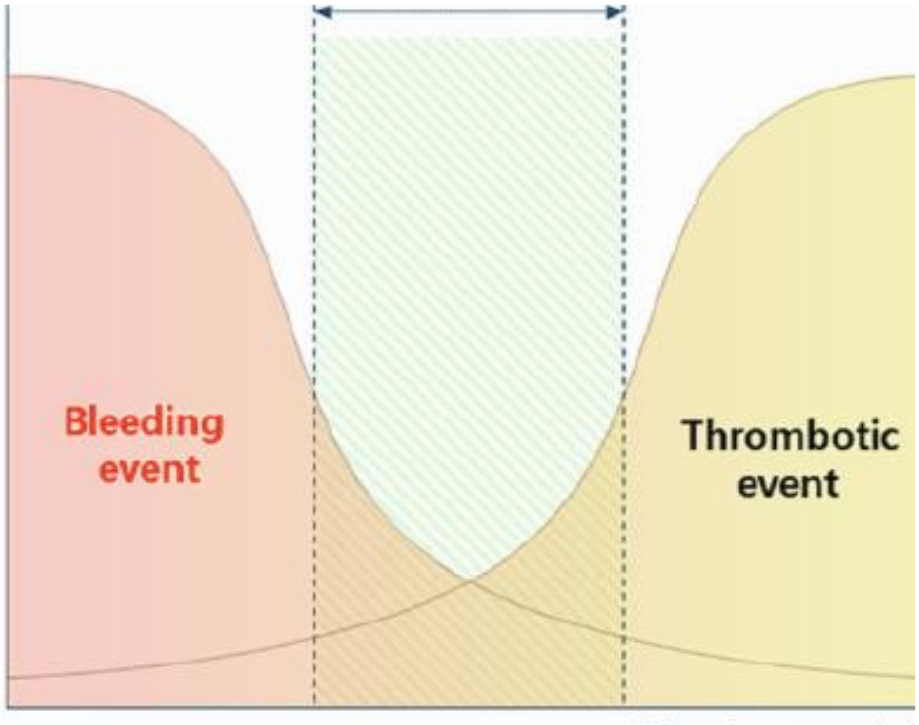
Abstract

The role of drug-level monitoring among patients using direct-acting oral anticoagulant (DOAC) is unclear. We aimed to investigate its 'real-life' utilization and effect on clinical management. A review of records of patients who underwent DOAC level testing during 2013–2017. Overall, 212 patients (median age 77 years) underwent 292 DOAC measurements [apixaban (n = 147), rivaroxaban (n = 102), dabigatran (n = 43)]. Monitoring volume increased by 460% during study period. DOAC level testing was performed during routine follow-up in 51 (17.5%) cases, whereas the remaining 241 (82.5%) measurements were performed due to selected clinical circumstances, most commonly: bleeding (n = 60), perioperative status (n = 45), breakthrough thrombosis (n = 37) and renal failure (n = 35). Drug levels were within the expected range in 210 (71.9%), above the expected range in 62 (21.2%) and lower than expected range in 20 (6.8%). In multivariate analysis, older age (P = 0.005), lower glomerular filtration rate (P = 0.001) and lower body mass index (P = 0.006) were associated with DOAC levels above the expected range. Clinical decisions were affected by DOAC monitoring following most (140/241, 58.1%) measurements for which we identified an indication for testing; yet only rarely when monitoring was performed during routine follow-up (7.8%, 4/51) (P < 0.0001). While no benefit of routine DOAC monitoring was observed, drug level measurement has an important role in the management of patients in selected circumstances. Age, body weight and creatinine clearance were found to be significant predictors of drug levels. Future studies are warranted to establish associations between drug levels and outcomes, and better delineate the role of DOAC monitoring.

Take home message



Drug Level ⟷ Drug Effect

To determine therapeutic window

To establish correlation

To determine means of measure and cut offs

Limitations

- Only ONE time point blood.
- To take both peak and trough.
- Moderate correlation - future studies warranted in terms of interchangability of POCI and LCMS

References

- 1 . Camm, A. J., P. Kirchhof, et al. (2010). "Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)." Eur Heart J **31**(19): 2369-2429.
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- 4. (1991). "Stroke Prevention in Atrial Fibrillation Study. Final results." Circulation **84**(2): 527-539.
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- 7. Testa S, Paoletti O, Legnani C, Dellanoce C, Antonucci E, Cosmi B, et al. Low drug levels and thrombotic complications in high-risk atrial fibrillation patients treated with direct oral anticoagulants. Journal of Thrombosis and Haemostasis. 2018;16(5):842-8.
- 8. Testa S, Legnani C, Antonucci E, Paoletti O, Dellanoce C, Cosmi B, et al. Drug levels and bleeding complications in atrial fibrillation patients treated with direct oral anticoagulants. Journal of Thrombosis and Haemostasis. 2019;17(7):1064-72
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THANK YOU.