Observations from Novel Oral Anticoagulant (NOAC) Trials for Stroke Prevention in Atrial Fibrillation (SPAF)

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Oral Anticoagulants

- Four oral anticoagulants approved for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation
  - Vitamin K antagonists: warfarin
    - Monitoring (INR), variable PK/PD, hemorrhagic stroke
  - Direct thrombin inhibitors: dabigatran
  - Direct factor Xa inhibitors: apixaban, rivaroxaban, edoxaban

- All drugs in this class have an on-target balance between efficacy/safety

ADME Properties of NOACs

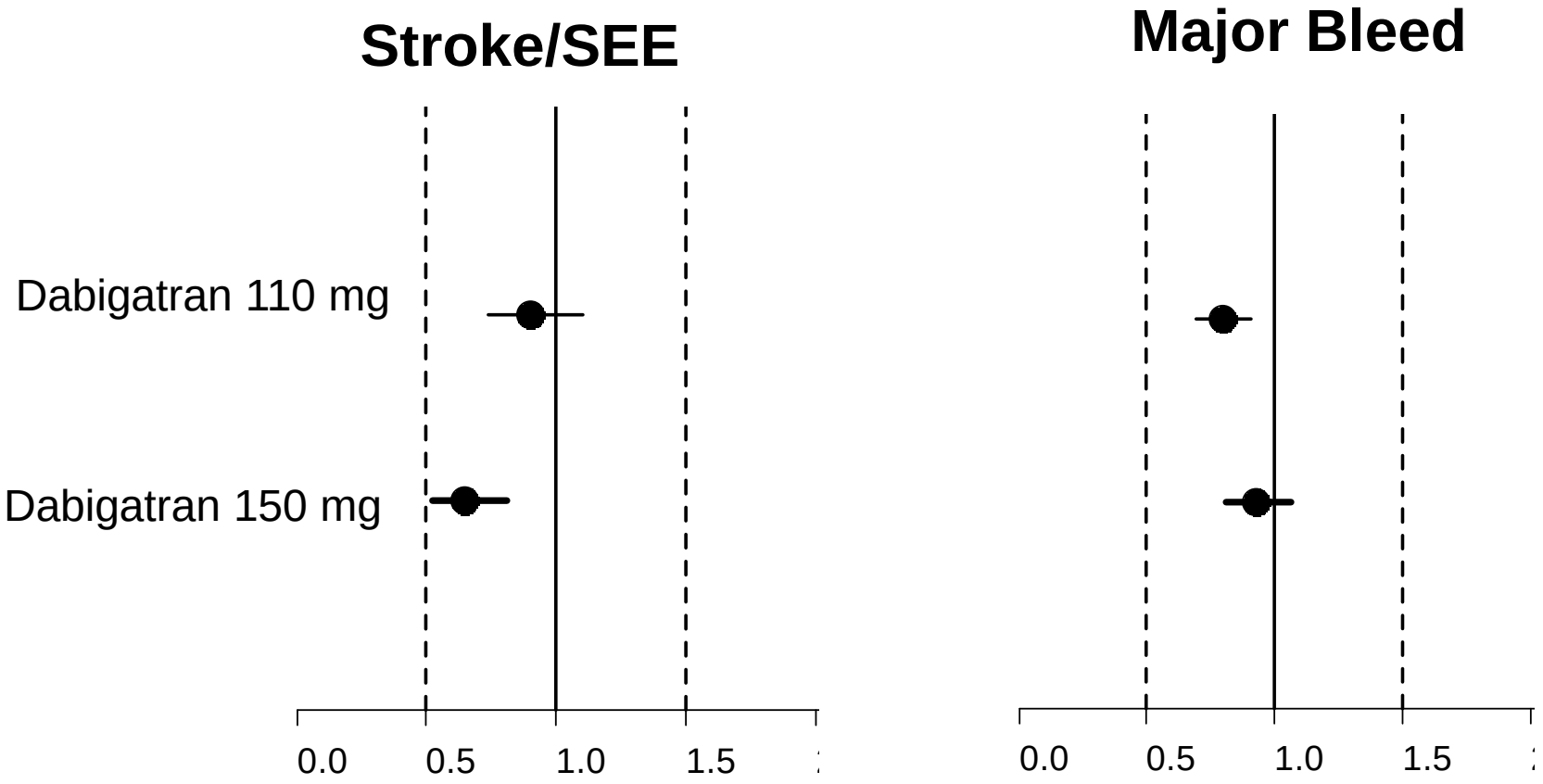
	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Mode of action	Direct inhibition of thrombin	Direct inhibition of FXa	Direct inhibition of FXa	Direct inhibition of FXa
Bioavailability	0.03-0.07	0.5	1.0 (fed)	0.62
Tmax	1 h (fasted)	3-4 h	2-4 h	1-2 h
Metabolism	< 10 % conjugation	25 % CYP3A	50 % CYP3A	< 10 % CES-1, CYP3A
Transporter	P-gp substrate	P-gp, BCRP substrate	P-gp, BCRP substrate	P-gp substrate
Elimination	Renal / 80 %	Renal / 27 %	Renal / 36 %	Renal / 50 %
Elimination half life	12-17 h	12 h	11-13 h	10-14 h
Dose proportionality	10-400 mg	2.5-10 mg	≤ 10 mg	10-150 mg
BSV (% CV) WSV (%CV)	40-60% 40%	30% 20%	30% 20%	20% 25 %
Accumulation	100% (BID)	100 % (BID)	< 10% (QD)	14 % (QD)

Dabigatran USPI, Apixaban USPI, Rivaroxaban USPI, Edoxaban USPI

Characteristics of Phase III Studies with NOACs for AF

- 10,000+ patient trials with on-treatment times of ~3 years
- Active control arm – warfarin
- Prospective dose adjustments based on intrinsic/extrinsic factors
- One or two active treatment arms
  - DCRP requested evaluation of multiple doses in all Phase III programs based on Phase II study results
- PK and PD sampling in 0-90% of the population
  - DCRP requested sampling in a majority of the population
- Data collection limits interpretation of the study results
  - exposure-response analyses/balance between risk-benefit

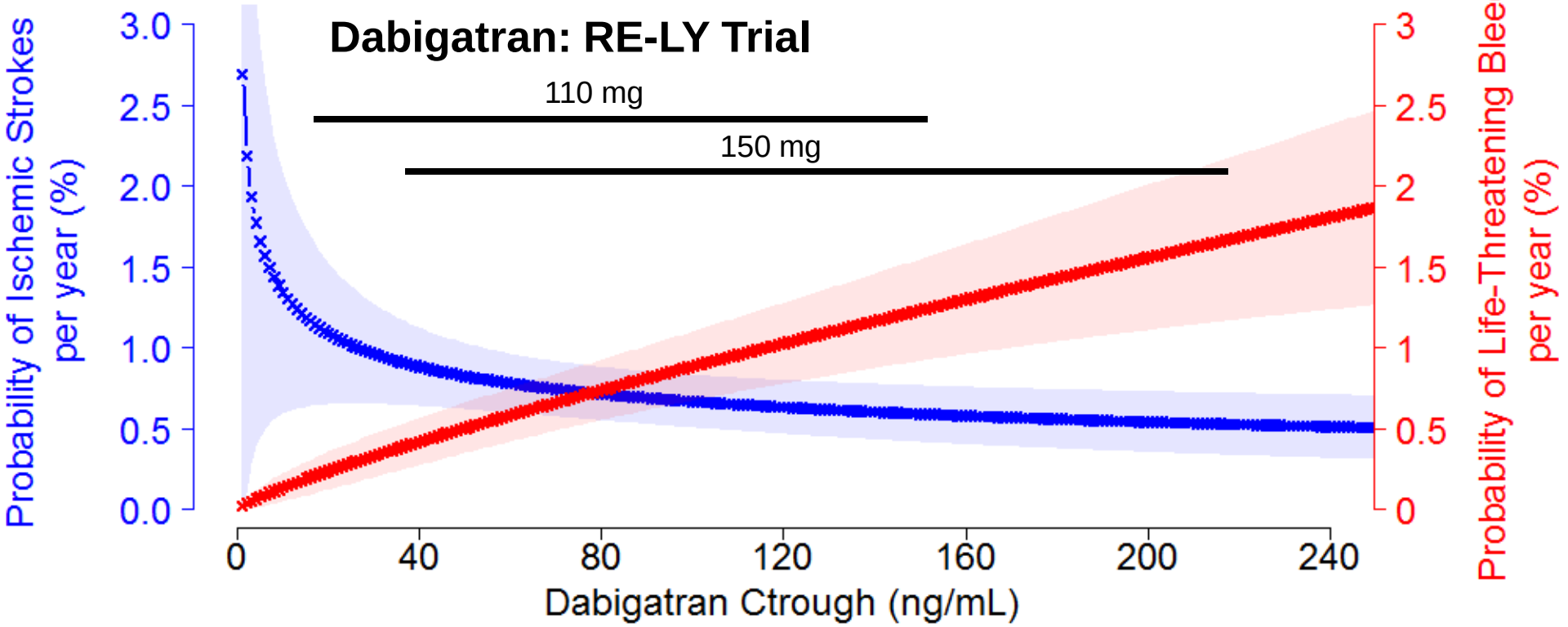
Dabigatran 110 mg: Non-inferior efficacy, fewer bleeds
Dabigatran 150: Superior efficacy, similar bleeds



HR (95% CI) of Dabigatran vs. Warfarin

Adapted from FDA's Cardiovascular Renal Advisory Committee Meeting for Dabigatran, Slide 5 and 25

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

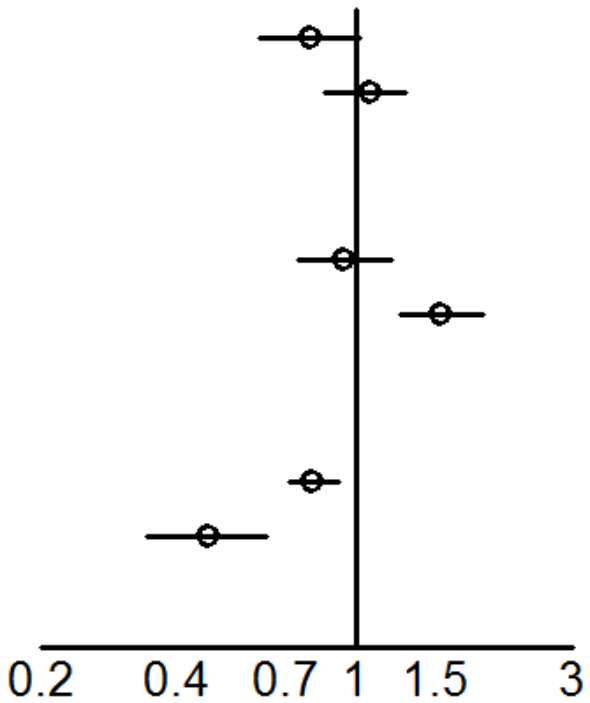


- Warfarin also has a similar relationship based on INR

Adapted from FDA's Cardiovascular Renal Advisory Committee Meeting for Dabigatran, Slide 56

Dose Response Is Evident For Stroke & Major Bleeding Events

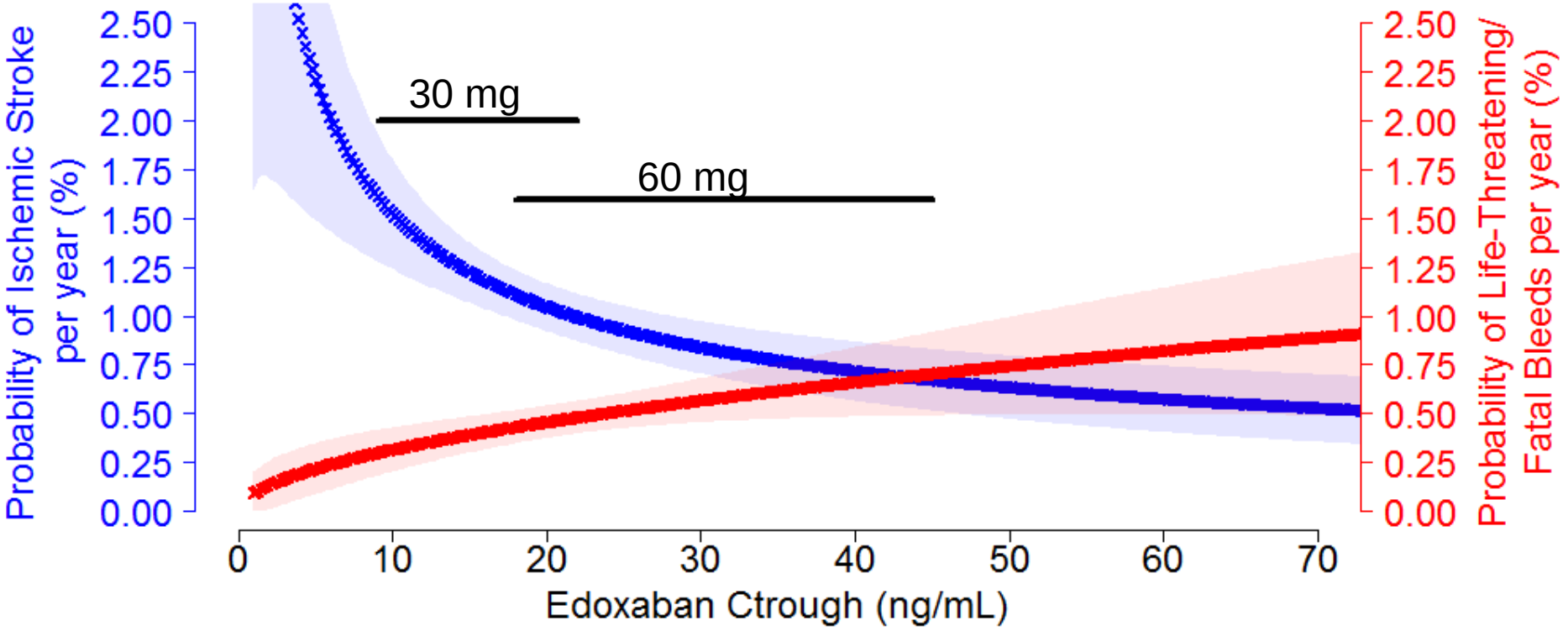
Edoxaban Dose	Hazard Ratio (95% CI)
Stroke/SEE	
High Dose (60/30 mg)	0.79 (0.61 to 1.02)
Low Dose (30/15 mg)	1.08 (0.85 to 1.28)
Ischemic Stroke	
High Dose (60/30 mg)	0.94 (0.75 to 1.19)
Low Dose (30/15 mg)	1.54 (1.25 to 1.90)
Major Bleeds	
High Dose (60/30 mg)	0.80 (0.71 to 0.91)
Low Dose (30/15 mg)	0.47 (0.34 to 0.63)



mITT population, on-treatment events

Adapted from FDA Cardiovascular Renal Advisory Committee Meeting for Edoxaban, Slide 48

Edoxaban Exhibits Concentration Dependent Relationships for Ischemic Stroke & Life-Threatening/Fatal Bleeds



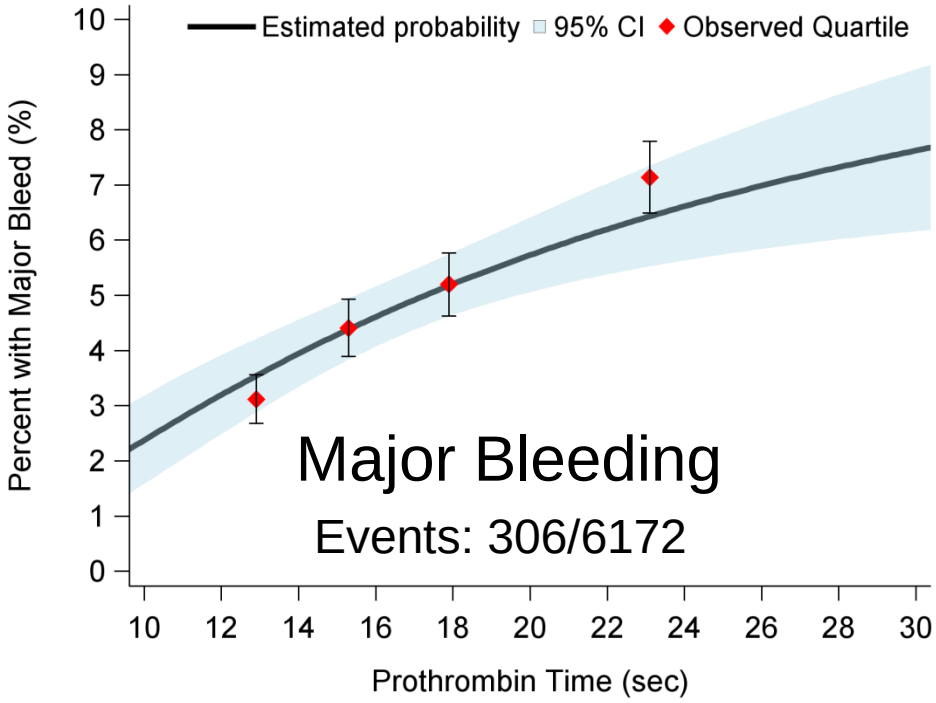
Analysis shown for "typical" patient population: Age: 72 years old, Renal Function: (70.4 mL/min), 28.3% with prior stroke, 29.2% with baseline aspirin use.

Adapted from FDA Cardiovascular Renal Advisory Committee Meeting for Edoxaban, Slide 51

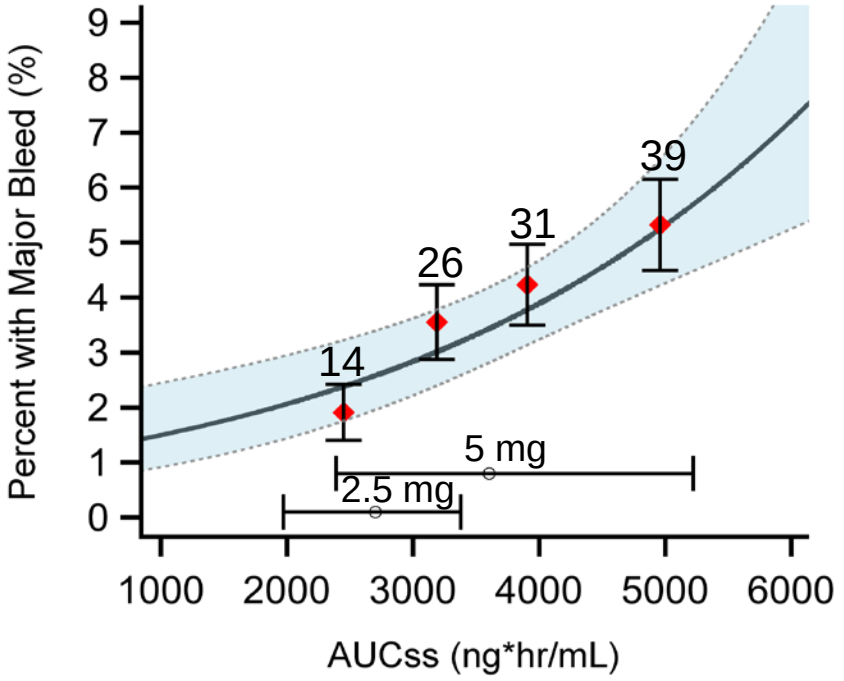
Rivaroxaban and Apixaban

- Large trials evaluating <u>one</u> dose level versus warfarin

Rivaroxaban



Apixaban



http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202439Orig1s000ClinPharmR.pdf
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202155Orig1s000ClinPharmR.pdf

Observations from NOAC trials for SPAF

- Four NOACs have been evaluated and approved over the past 5 years
  - Demonstrated non-inferiority compared to warfarin on stroke/SEE
  - Higher exposure groups demonstrated better HR relative to warfarin
- All NOACs have underlying balance between efficacy and safety events
  - Higher exposures associated with a decreased risk of strokes and an increased risk of bleeding
  - Ability to identify these relationships may be limited by data collected and dose-ranging during Phase II/III
- Trials represent an extensive amount of patient and outcome data for informing use of these products
  - How can that information best be used to improve upon patient outcomes?

Dosing Strategies for Drugs Based on Sources of Variability

		Between Subject Variability (subject to subject)	
		Low	
Within Subject Variability (dose to dose in same subject)		• Fixed dosing	• If factors are known, adjust based on factors • If factors are unknown, single point measurement and dose adjustments

Adjustment Based on Patient Factors

Considerations	Limitations
• Factors the influence NOAC exposures have been well characterized (CrCL) and can be used to adjust exposures • Trials included prospective dose adjustments based on patient factors • Information on patient factors is readily obtainable	• Identified factors do not explain all variability • Patient factors (renal function, drug-drug interactions) may change over the course of treatment

Therapeutic Drug Monitoring

Considerations	Limitations
• Better ensure that patients are maintained within a target exposure window • Utilized for other drugs where there is a narrow balance between efficacy and safety • Knowledge of a patient's true exposure in special situations	• Identification of a target exposure window may not be feasible with available information or appropriate for all patients • Complex logistics for implementation (adherence, timing of sampling, intrasubject variability • No approved tests

Summary

- Getting the dose of anticoagulants right is very important but often not easy
- Results from completed trials and ongoing studies could serve as the basis for dose adjustment schemes based on patient factors
- Unclear if therapeutic drug monitoring is necessary for all NOACs
  - Quick turn-around diagnostic tests may be helpful in special situations for managing treatment

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