Does Pharmacometric Modeling Reliably Predict Efficacy and Safety Outcomes in Registration Trials and Can It be Utilized to Optimize Benefit-Risk?

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CEDARS-SINAI

Duality of Interests

- Advisor/Consultant
  - United States FDA
- Consultant
  - Boehringer Ingelheim
- Stocks/Equity
  - Johnson & Johnson

Is the Glass Half-full or Half-empty or …..?

Half-empty
(pessimist)

Half-full
(optimist)

Is the Glass Half-full or Half-empty or …..?

Exact level of water
(impartial observer)

To the impartial observer, the glass is twice as big as it needs to be

Pharmacometric Modeling
Role in Regulatory Decision Making

- Pharmacometrics brings much-needed quantitative, mechanistic reasoning to the clinical review process
- Insights into concentration-response often enrich fixed dose-response data
- Exploration of exposure response relationships can:
  - *Complement planned analyses*
  - *Provide supportive evidence of effectiveness*
  - *Help with decisions relating to choice of dosing regimens to approve even when not evaluated in Phase III trials*
  - *Optimize benefit-risk*

Pharmacometric Modeling and Regulatory Decision Making

A Non-Pharmacologist's Perspective: Objective

- Pharmacometric modeling-derived exposure-response relationships have recently been utilized by regulatory agencies to support approval of doses of drugs not studied in the pivotal registration trials

- The presentation will use examples from novel oral anticoagulant drug development program for nonvalvular atrial fibrillation to illustrate the feasibility and reliability of such an approach

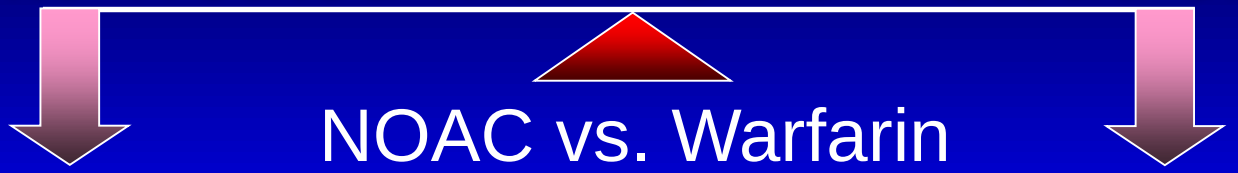
Novel Oral Anticoagulants (NOACs) for Non-Valvular Atrial Fibrillation (NVAF)

NOAC	Registration Trial	Year Approved	Doses Approved
Dabigatran (anti-IIa)	RE-LY (N=18,113)	2010	150 mg bid 75 mg bid
Rivaroxaban (anti-Xa)	ROCKET-AF (N=14,264)	2011	20 mg qd 15 mg qd
Apixaban (anti-Xa)	ARISTOTLE (N=18,201)	2012	5 mg bid 2.5 mg bid
Edoxaban (anti-Xa)	ENGAGE-AF (N=21,105)	2015	60 mg qd 30 mg qd

Rich quantum of evidence: 4 RCTS, N = 71,683
All trials passed noninferiority, but does it reflect optimal use?

Benefit-Risk Balance

1000 Patients Treated with NOAC Instead of Warfarin



Benefit

- 8 fewer deaths
- 8 fewer ICH
- 7 fewer strokes/TIA
  - 5 fewer hemorrhagic strokes
- No monitoring/fixed dose
- Limited potential for drug/food interaction

Harm

- 5 excess GI bleeding
- 9 excess ischemic strokes (low dose)
- 4 excess MI (low dose)
- Increased cost
- Antidotes (Praxabind)

Benefit exceeds harms, but differences are modest (NNT>130)
[NNT vs placebo for stroke/SEE = 21 (ARD = 4.7%)]

Ruff CT et al. Lancet 2014;383:955-962

Novel Oral Anticoagulants (NOACs) for Non-Valvular Atrial Fibrillation (NVAF)

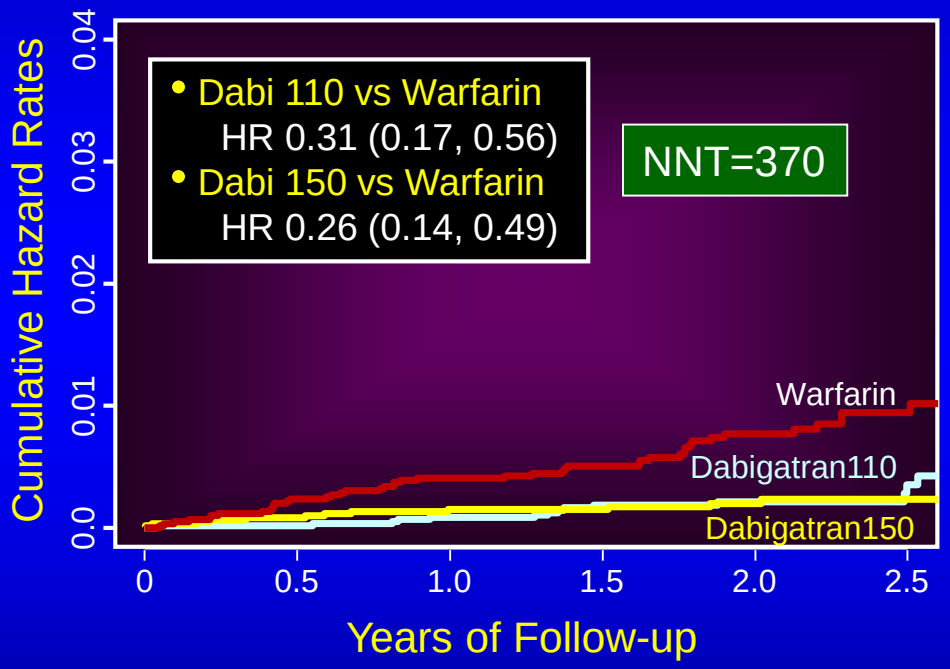
Regulatory Challenges

- Dabigatran
  - 110 mg dose not approved by the FDA
  - 75 mg dose approved for CrCL 15-30mL/min based on pharmacometric modeling
- Edoxaban
  - Not approved in patients with CrCl>95 mL/min
  - 90 mg dose not approved in patients with CrCl >95mL/min even though pharmacometric modeling was supportive

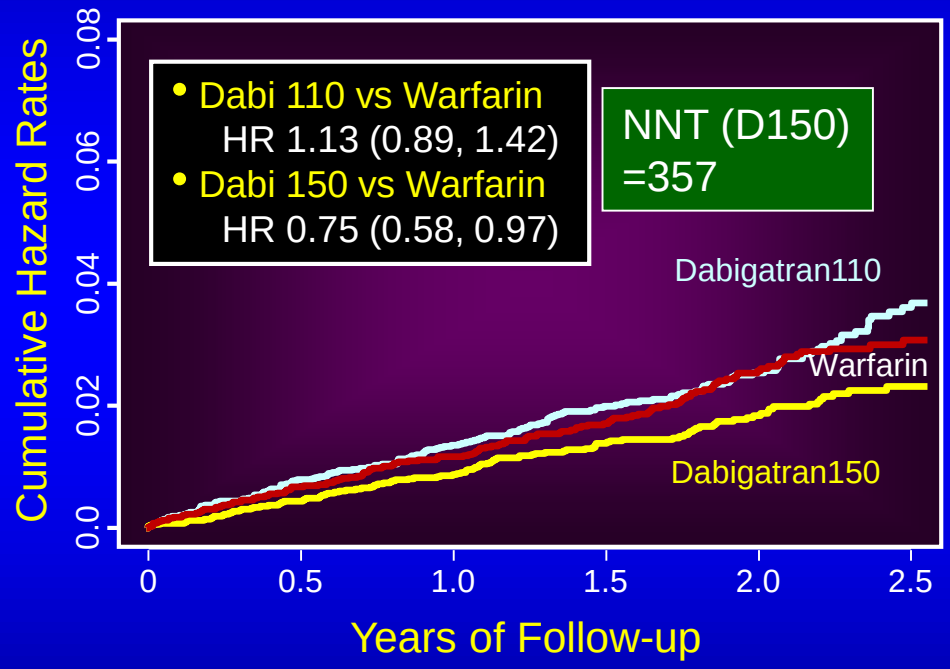
Dabigatran vs. Warfarin in RE-LY Trial

Impact on Stroke

Hemorrhagic Stroke



Ischemic/Unspecified Stroke



Reduced risk of hemorrhagic stroke and ischemic stroke (150mg)

Connolly et al. NEJM 2009;361:1139-1151

Assessment of Bleeding in RE-LY

	D 110 mg	D 150 mg	warfarin	D 110 mg vs. Warfarin		D 150 mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR 95% CI	p	RR 95% CI	p
Major Bleeding	2.7 %	3.1 %	3.4 %	0.80 0.69-0.93	0.003	0.93 0.81-1.07	0.31
Life-Threatening bleeding	1.2 %	1.5 %	1.8 %	0.68 0.55-0.83	<0.001	0.81 0.66-0.99	0.04
Minor Bleeding	13.2 %	14.8 %	16.4%	0.79 0.74-0.84	<0.001	0.91 0.85-0.97	0.005
Total Bleeding (Major+Minor)	14.6	16.6	18.4	0.78 0.74-0.83	<0.001	0.91 0.86-0.97	0.002
Major GI bleed	1.15%	1.56 %	1.07 %	1.10 0.86-1.41	0.43	1.48 1.18-1.85	<0.001

Reduced risk of major bleeding observed with 110mg dose

Connolly et al. NEJM 2009;361:1139-1151

Assessment of Noninferiority in RE-LY

Impact of Target INR (NIM= HR1.38)

Endpoint	Optimal INR control (≥64%)				Suboptimal INR control			
	D110 (%)	W (%)	ARD (%)	HR	D110 (%)	W (%)	ARD (%)	HR
Stroke/SEE	1.60	1.40	0.20	1.12 (0.87-1.44)	1.5	2.0	-0.5	0.73 (0.58-0.92)
Major bleeding	2.88	2.90	-0.02	0.95 (0.80-1.13)				
	D150 (%)	W (%)	ARD (%)	HR	D150 (%)	W (%)	ARD (%)	HR
Stroke/SEE	1.10	1.40	-0.30	0.81 (0.62-1.05)	1.1	2.0	-0.9	0.53 (0.41-0.67)
Major bleeding	3.41	2.90	0.51	1.10 (0.93-1.31)				

- Noninferiority not met with dabigatran 110mg vs. optimal INR control
- Superiority in bleeding not met with dabigatran110 mg vs. optimal INR control

Who Might Benefit From Lower Dose of Dabigatran?
Event Rates by Three Critical Subgroups

Subgroup	Stroke/SEE		Major bleed	
	D110 (%)	D150 (%)	D110 (%)	D150 (%)
Cr Cl 30-<50 mL/min (n=3343)	2.4	1.3	5.7	5.3
Age - <65 (n=2981) -65-<75 (n=7894) -≥75 (n=7238)	 1.5 1.3 1.9	 0.7 1.0 1.5	 0.8 2.3 4.4	 0.9 2.6 5.1

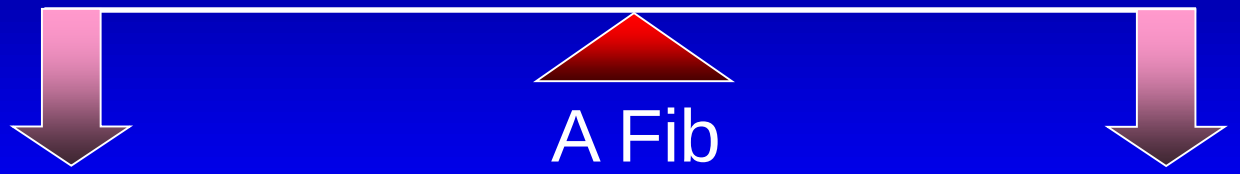
- 57% of subjects with a major bleed either resumed treatment or had no interruption
- Of these, the percentage with another major bleed were similar across all arms (D110 16%, D150 14%, W 12%)

"Unable to identify any subgroup in which use of the lower dose of dabigatran 110 mg would not represent a substantial disadvantage"

Beasley BN et al. NEJM 2011

How is Bleeding Different from a Stroke?

Variable Weights Based on "Perception"



Stroke risk

- Embolic strokes are part of the disease, incompletely prevented by therapy
- Can't count the strokes that are prevented
- Strokes usually associated with long-term effects

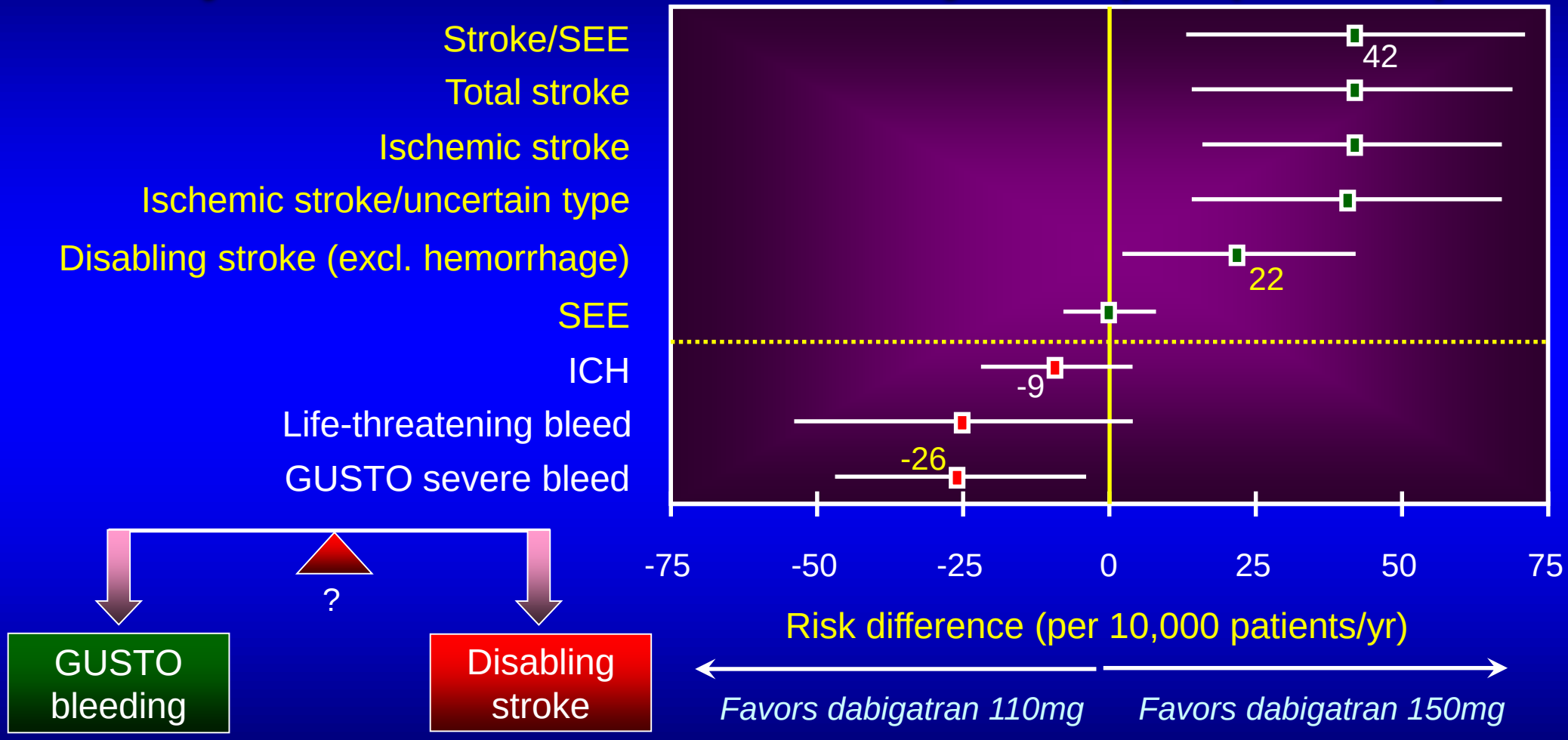
Bleeding risk

- Spontaneous major bleeding is unusual, bleeding unequivocally caused by Rx
- Events are easy to count
- Bleeding causes panic
- Consequences are typically finite

Asymmetry in assessment of benefit-harm (bleeding>>stroke)
Clinicians 'play it safe' (errors of commission trump errors of omission!)

Dabigatran 110 mg vs. 150 mg in RE-LY

Key Benefit-Risk Summary Graph (BRAT)



Is the benefit-risk balance for dabigatran 110 mg in the desirable range?

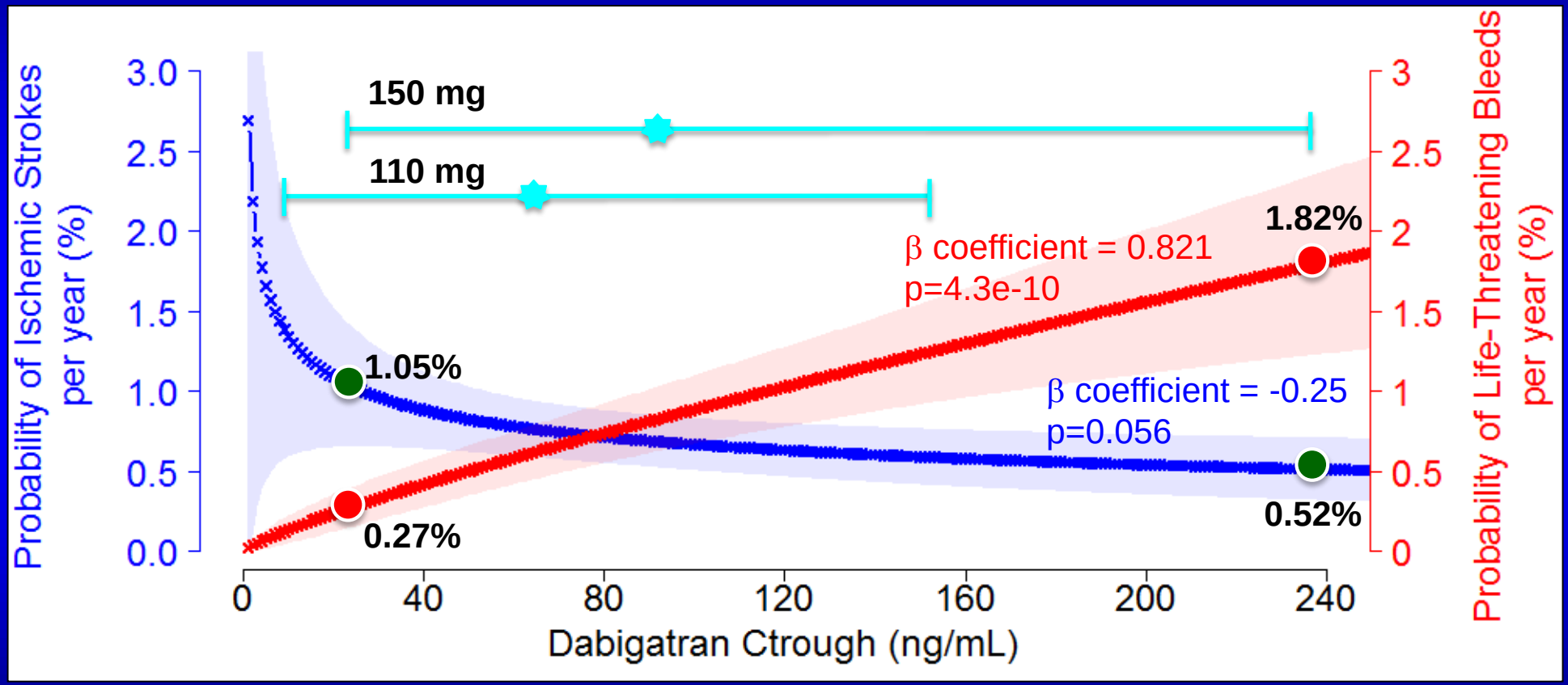
Pharmacometric Modeling and Regulatory Decision Making

Registration Trials of NOACs for NVAF

Trial	NOAC	Plasma concentration measured	Pharmacometric exploration	
			Ischemic events	Bleeding events
RE-LY	Dabigatran	Yes >70% of cohort	Yes	Yes
ROCKET-AF	Rivaroxaban	No	No	No
ARISTOTLE	Apixaban	Yes	No (too few events)	Yes
ENGAGE-AF	Edoxaban	Yes >90-95% of cohort	Yes	Yes

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

10th and 90th Percentile Dabigatran Concentrations

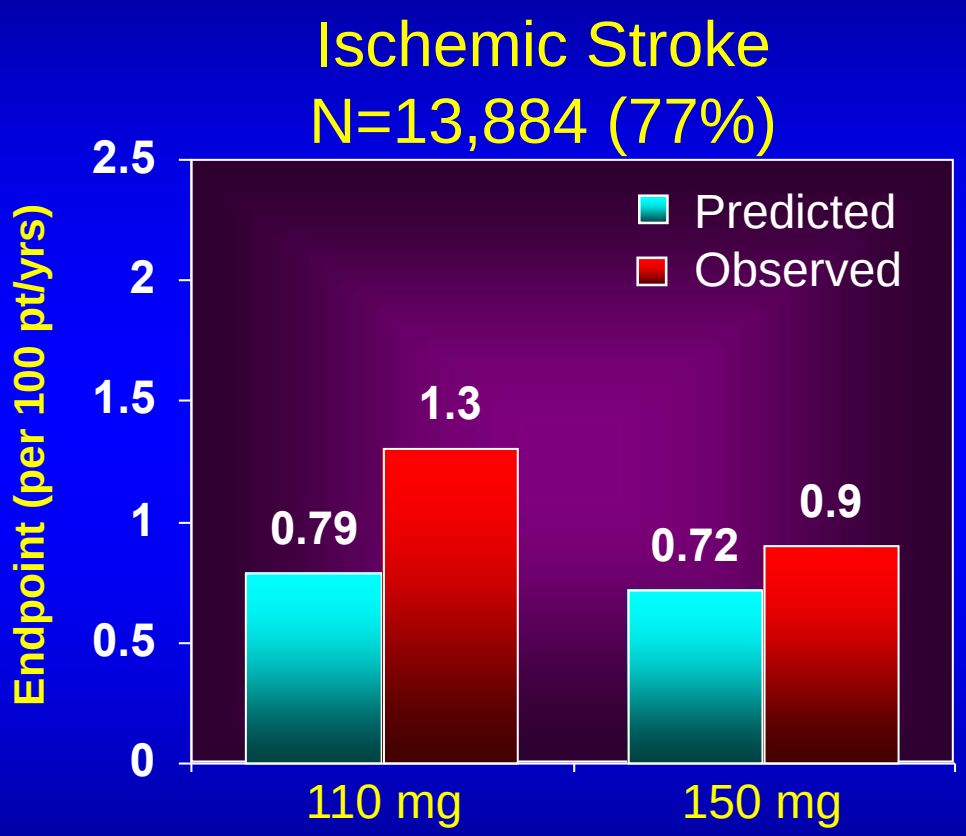


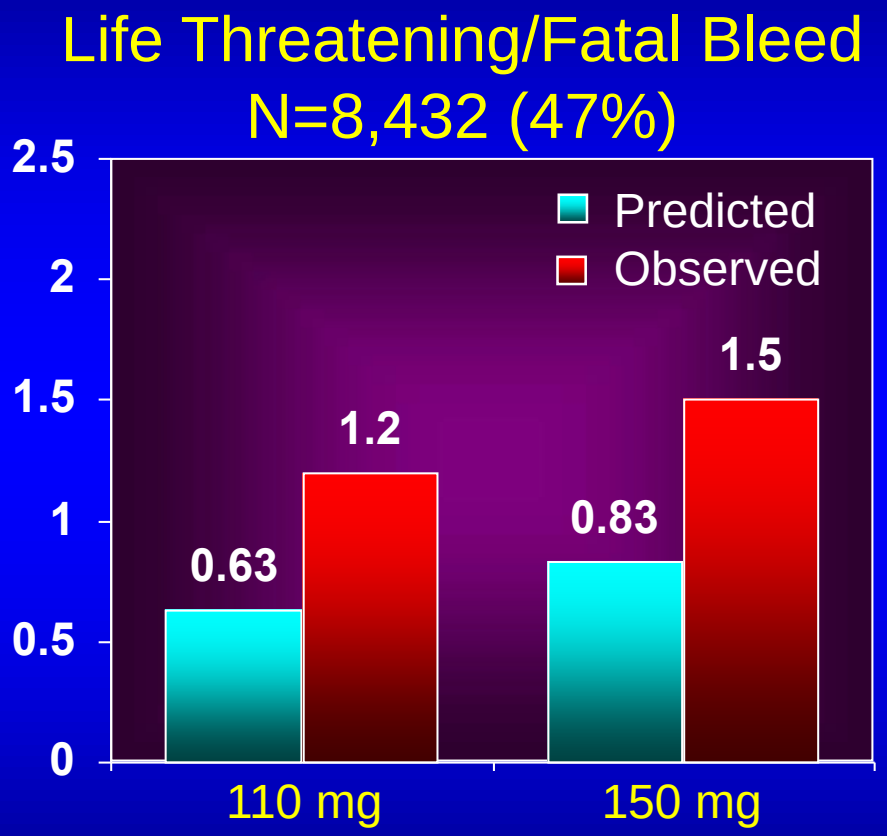
Relationship between dabigatran trough concentration & life threatening bleeding (direct, linear) >> ischemic stroke (inverse, nonlinear)

Predicted vs. Observed Event Rates

RE-LY Trial (Dabigatran 110 mg vs. 150 mg in NVAF)

PK and Covariate Data available in 77%/47% of Trial Cohort



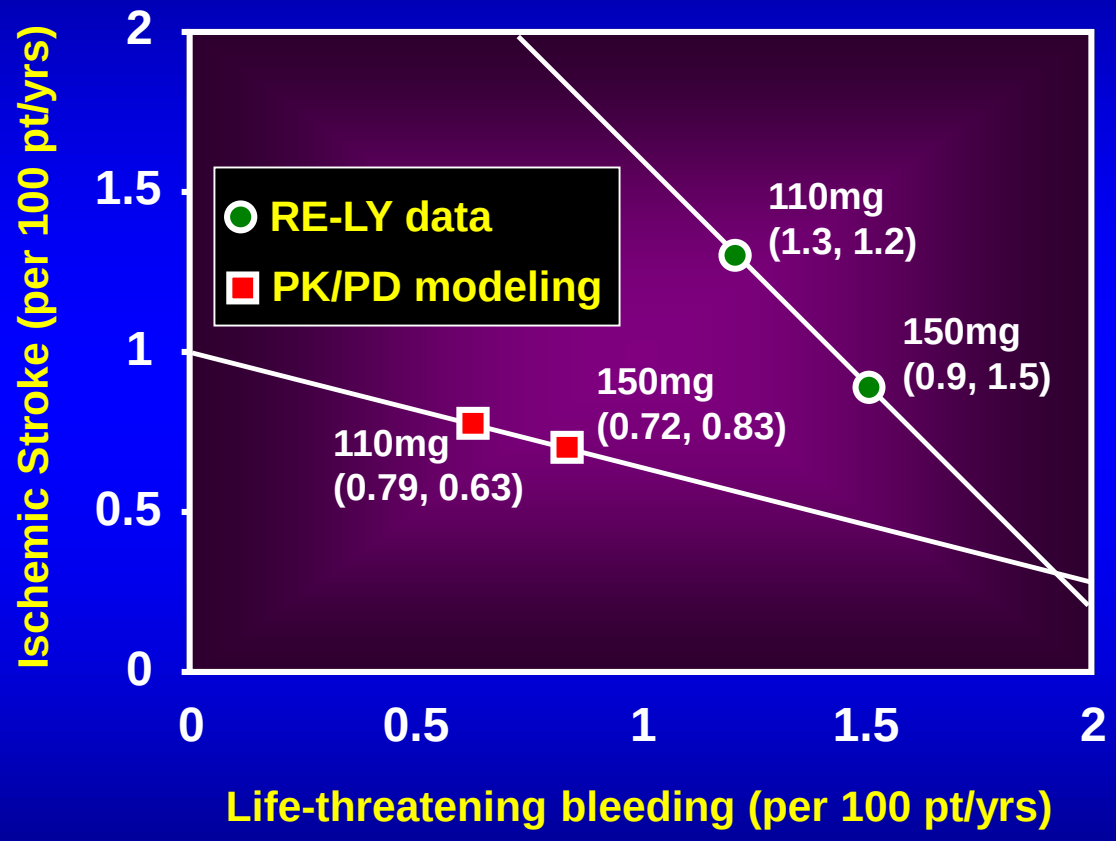


Model-predicted event rates don't agree with observed rates

http://www.fda.gov/downloads/UCM421612.pdf

Dabigatran 110 mg vs. 150 mg in RE-LY

Benefit-Risk: Trial Data vs. Pharmacometric Modeling



PK/PD modeling (150 vs 110)
1 stroke prevented per 1000 pts
2 bleeds incurred per 1000 pts
(? good trade off)

RE-LY data (150 vs 110)
4 strokes prevented per 1000 pts
3 bleeds incurred per 1000 pts
(good trade off)

Benefit-risk balance for dabigatran 150 mg not predicted by PM modeling

http://www.fda.gov/downloads/UCM421612.pdf

Exposure-Response Analysis of Dabigatran (RE-LY)

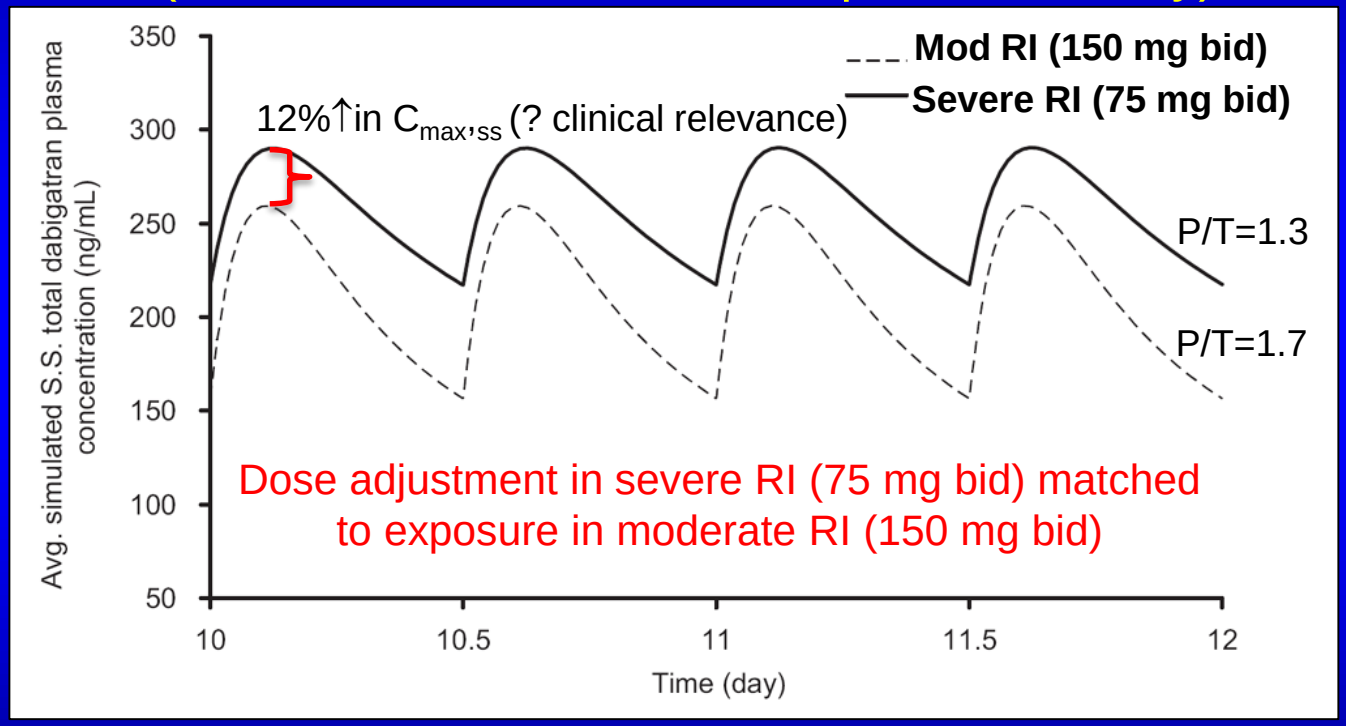
Why Suboptimal Prediction for Ischemic Stroke?

Parameter	Ischemic Stroke Cox PH Model (N=13,884)			Life Threatening Bleeding Cox PH Model (N=8,432)		
	Estimate	SE	P value	Estimate	SE	P value
Treatment	0.83	0.57	0.15			
Weight	-0.014	0.0041	0.00053			
Age	0.022	0.0090	0.015	0.0623	0.0166	8.6e-8
H/O TIA/Stroke	0.52	0.15	0.00038	0.454	0.170	0.0076
Diabetes, age >65	0.41	0.16	0.010			
Log dabigatran trough concentration	-0.25	0.13	0.056	0.821	0.132	4.3e-10

- Strength of E-R relationship not robust (small effect size, marginal p value)
- Other covariates likely to confound the E-R relationship

Dabigatran Dosing in Pts with Severe Renal Impairment
Clinical Pharmacology Basis of Deriving Dosing

PK Modeling and Simulation Approach (Phase I Dedicated Renal Impairment Study)



Benefit-Risk of Dabi 150 bid in RE-LY (Phase III) by Renal Fx

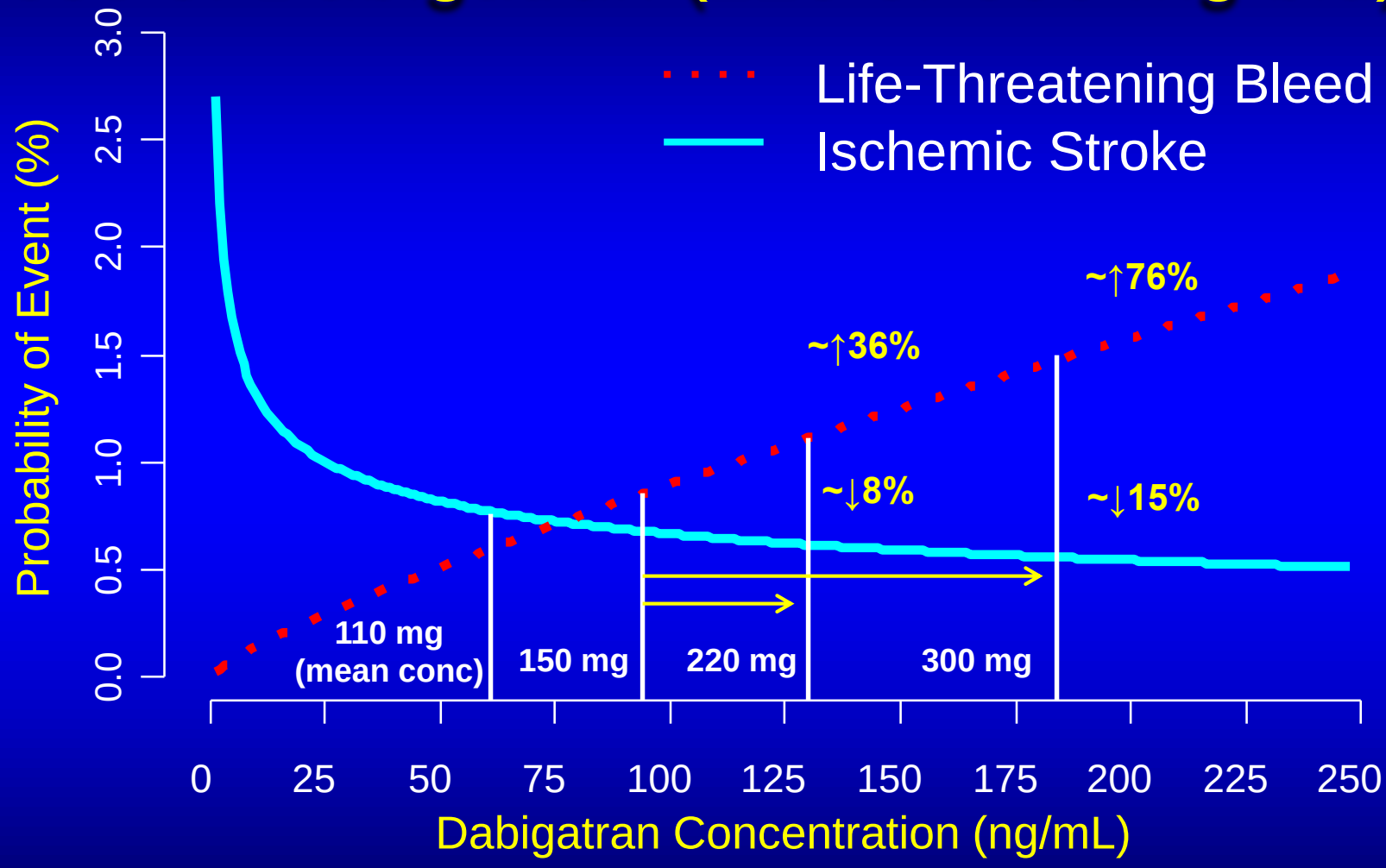
CrCl ml/min	Fold ↑ in Dabi trough conc.	Stroke/SEE HR, 95% CI	Major bleed HR, 95% CI
30-50 (mod RI)	2.3	0.46 (0.29-0.73)	0.97 (0.74-1.27)
50-80 (mild RI)	1.5	0.67 (0.49-0.91)	0.88 (0.71-1.07)
>80 (normal)	1.0	0.71 (0.44-1.15)	0.81 (0.59-1.11)

In RE-LY, despite 2.3-fold in plasma trough conc., no dose adjustment necessary in pts with moderate RI given similar (or favorable) benefit risk balance. Pts with severe RI (CrCl<30) excluded from RE-LY.

‘Quantitative clinical pharmacology approaches provide a reasonable alternative to derive meaningful dosing recommendations for special populations’

Hariharan, S. and Madabushi, R. J Clin Pharmacol, 2012;52:119S–125S.

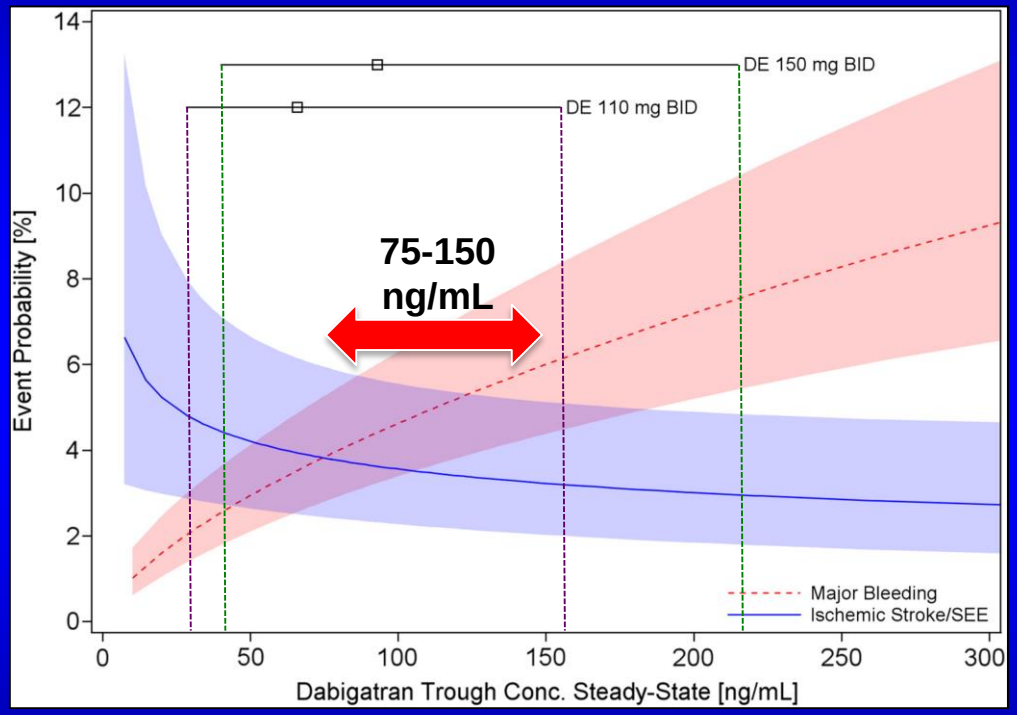
Does Benefit/Risk Support Exploration of Higher Doses of Dabigatran (220 or 300 mg bid)?



Value of higher doses depends on how one weights bleeding events vs. strokes

Dabigatran Exposure-Outcome Relationship

Probability of Major Bleeding Event and Ischemic Stroke/SEE Versus Trough Plasma Concentration

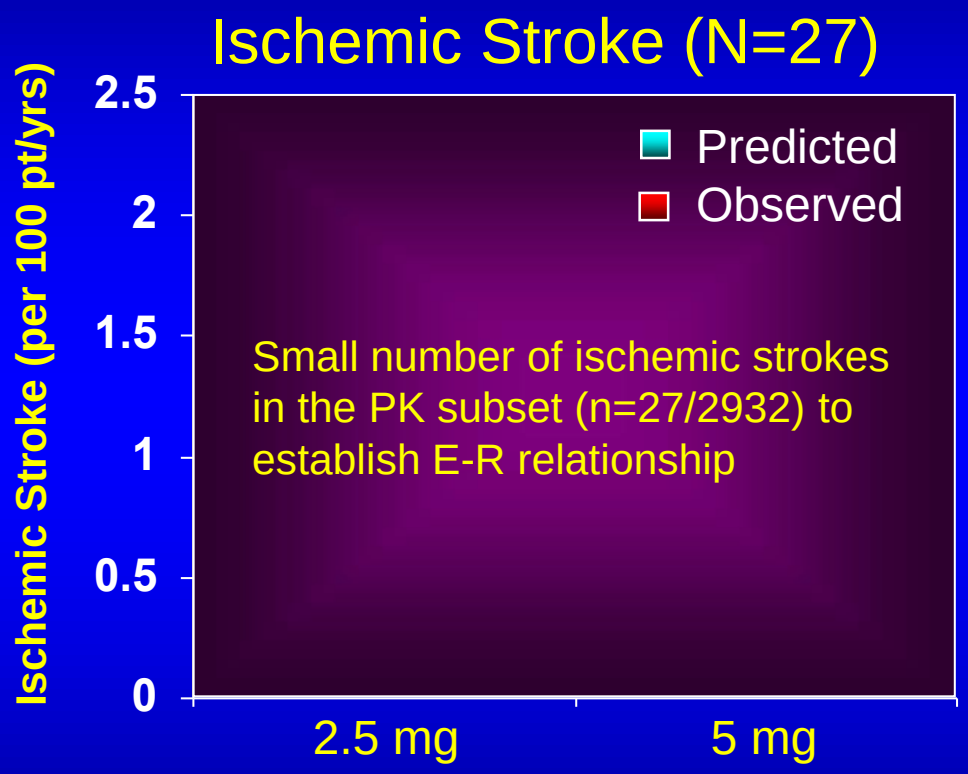


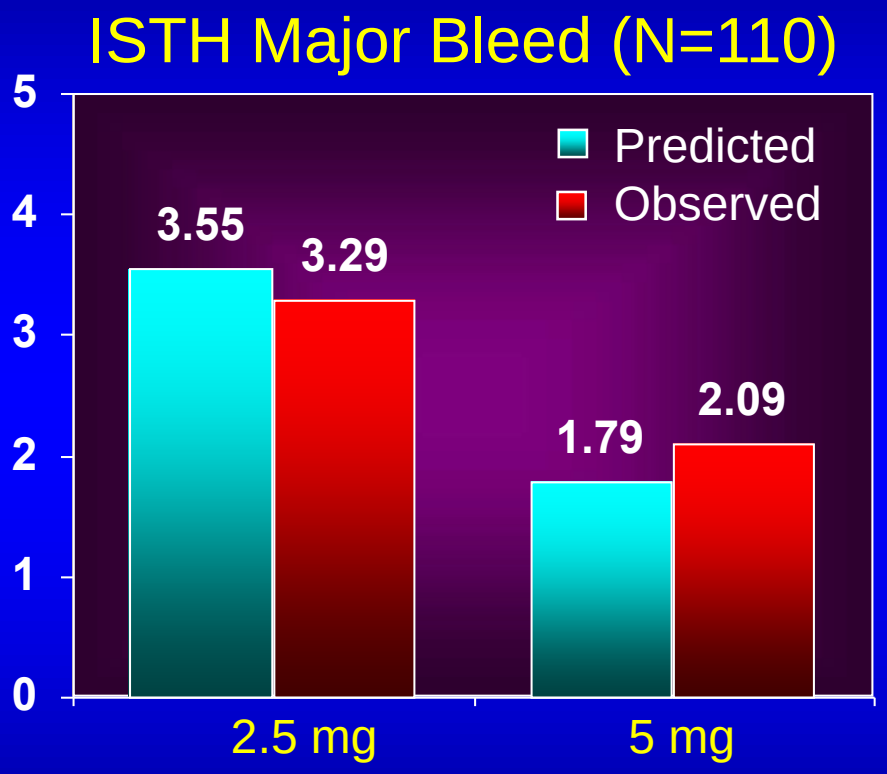
Calculated for 72-year-old male atrial fibrillation patient with prior stroke and diabetes

Target window ('sweet spot') to optimize benefit-risk of dabigatran in clinical practice

Reilly PA et al, J Am Coll Cardiol. 2014;63:321-328

Predicted vs. Observed Event Rates
ARISTOTLE Trial (Apixaban vs. Warfarin in NVAF)

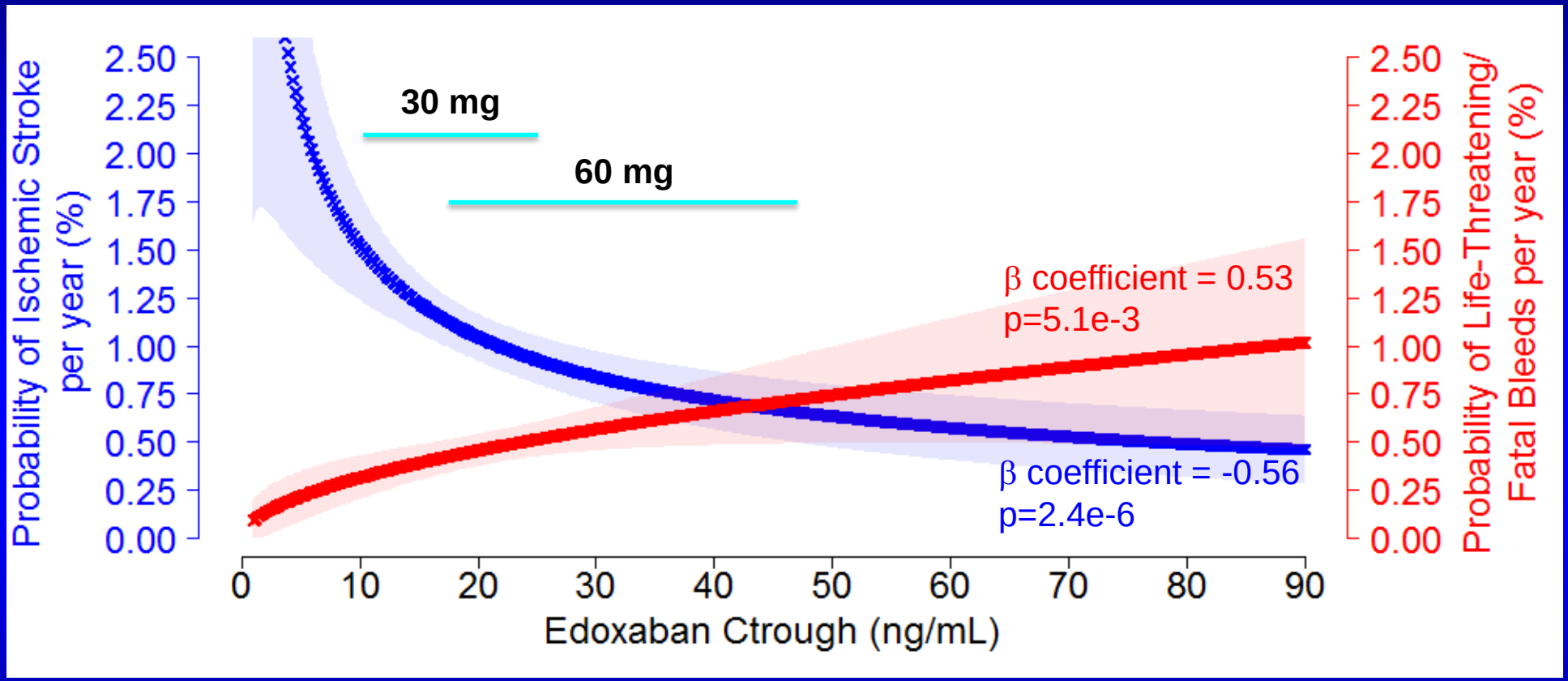




Model-predicted bleeding generally agrees with observed rates

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

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

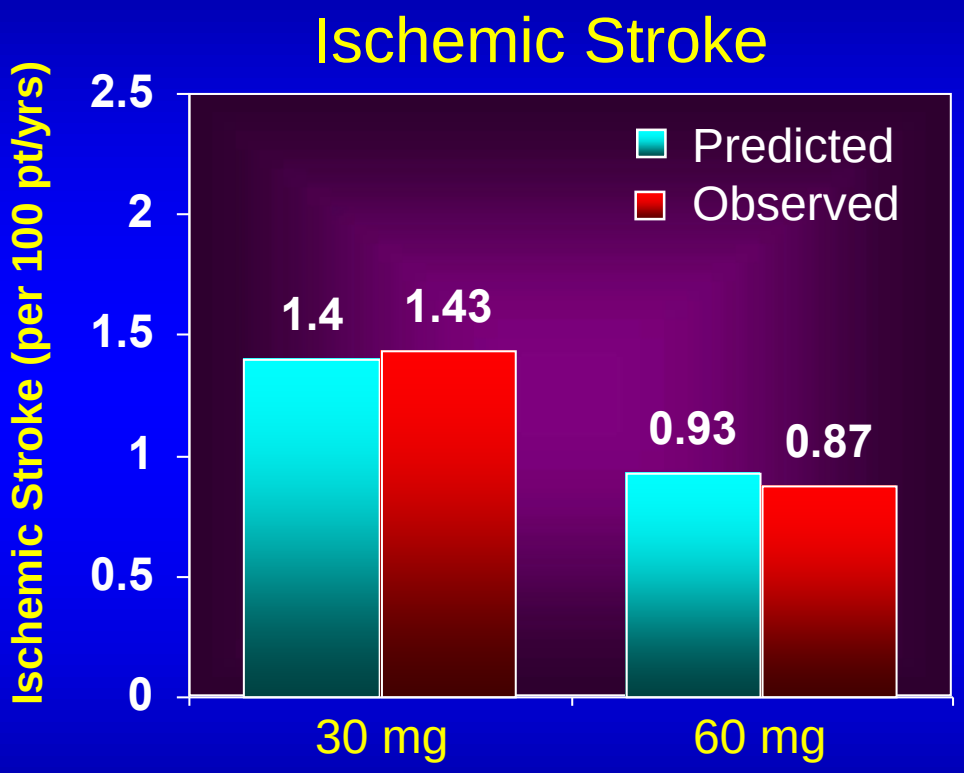


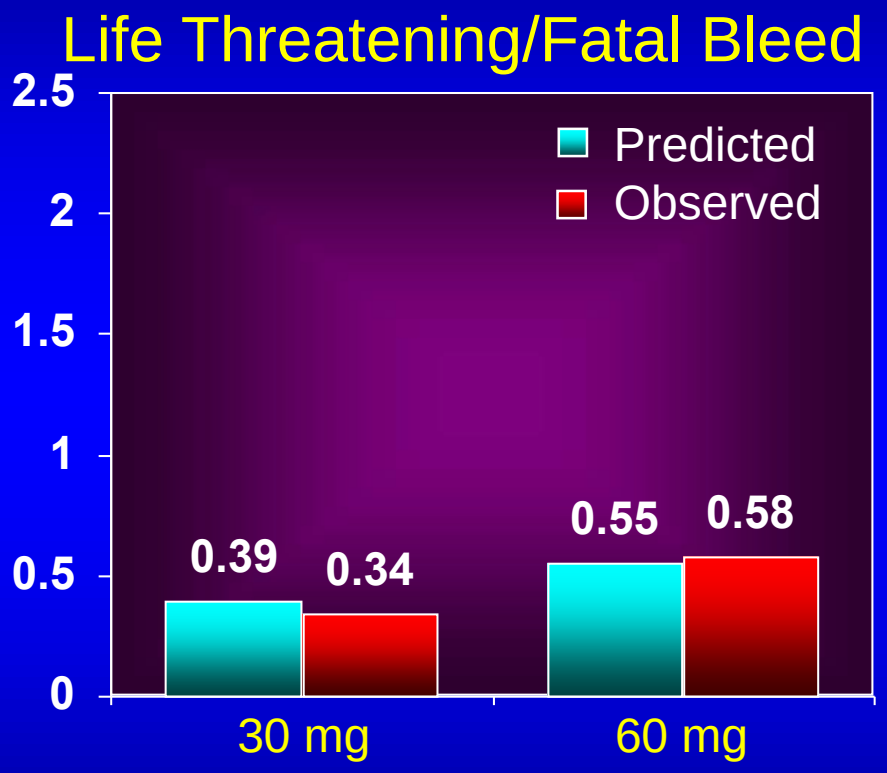
Relationship between edoxaban trough concentration & life threatening bleeding (direct, linear) >> ischemic stroke (inverse, nonlinear)

Predicted vs. Observed Event Rates

ENGAGE-AF Trial (Edoxaban vs. Warfarin in NVAF)

PK and Covariate Data available in >90-95% of Trial Cohort





Model-predicted event rates agree with observed rates

http://www.fda.gov/downloads/UCM421612.pdf

Exposure-Response Analysis of Edoxaban (ENGAGE-AF)
Why Optimal Prediction for Stroke and Bleeding?

Parameter	Ischemic Stroke Cox PH Model			Life Threatening Bleeding Cox PH Model		
	Estimate	SE	P value	Estimate	SE	P value
Weight	-0.0078	2.93e-3	7.9e-3			
Age	0.0153	6.36e-3	7.9e-3	0.0363	9.91e-3	2.5e-4
H/O TIA/Stroke	0.6002	1.39e-1	1.5e-5			
CHAD score	0.2932	1.45e-1	4.4e-2			
Log edoxaban trough concentration	-0.5597	1.19e-1	2.4e-6	0.5339	1.91e-1	5.1e-3

- Strength of E-R relationship robust (large effect size, persuasive p value)
- Other covariates less likely to confound the E-R relationship

FDA 2014

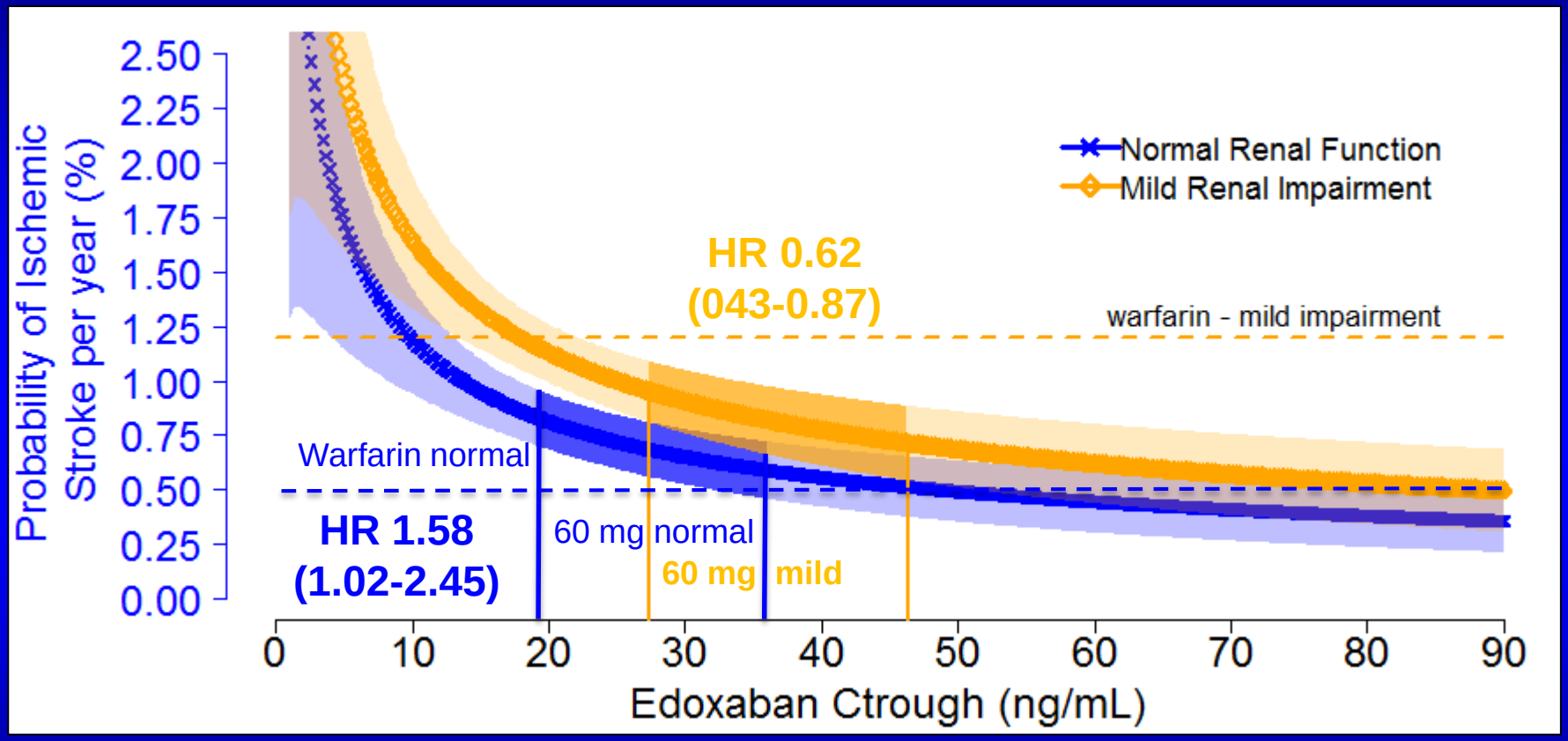
Edoxaban vs. Warfarin in NVAF (ENGAGE-AF)
Outcomes as a Function of CrCl

Endpoint	Renal function subgroup (CrCl)	Edoxaban 60	Warfarin	HR (95% CI)
		Event Rate (%/yr)	Event Rate (%/yr)	
Stroke/SE (PEP)	≤95	1.2	1.8	0.68 (0.55, 0.84)
	>95	1.0	0.6	1.87 (1.10, 3.17)
Ischemic stroke	≤95	0.9	1.1	0.80 (0.62, 1.04)
	>95	0.9	0.4	2.16 (1.17, 3.97)
Major bleeding	≤95	3.1	3.7	0.84 (0.73, 0.97)
	>95	1.3	2.3	0.59 (0.41, 0.84)

Benefit-risk balance not desirable in patients with CrCl>95!

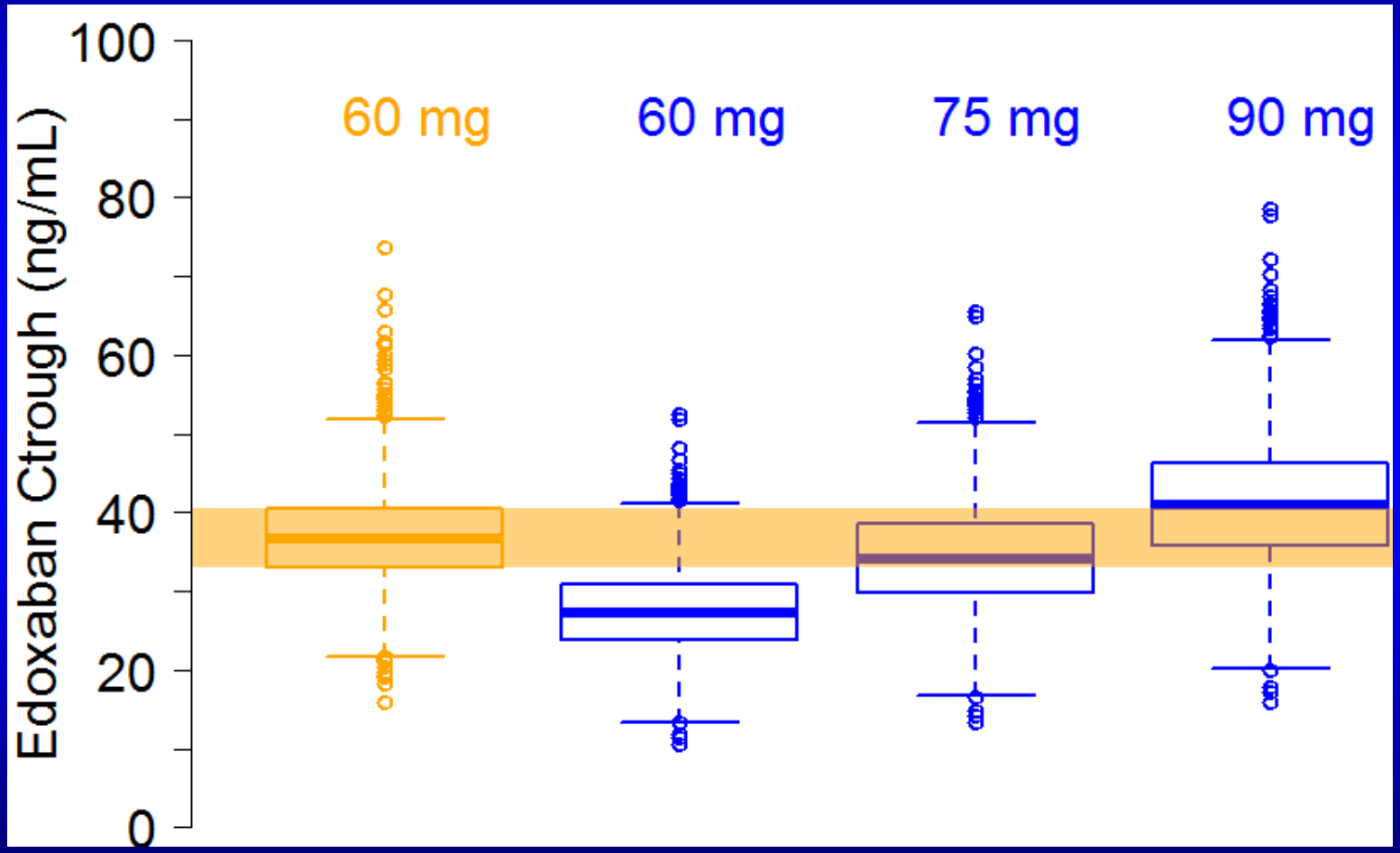
FDA, 2015

Exposure Response Relationship of Edoxaban 60 mg in Normal & Mildly Impaired Renal Function



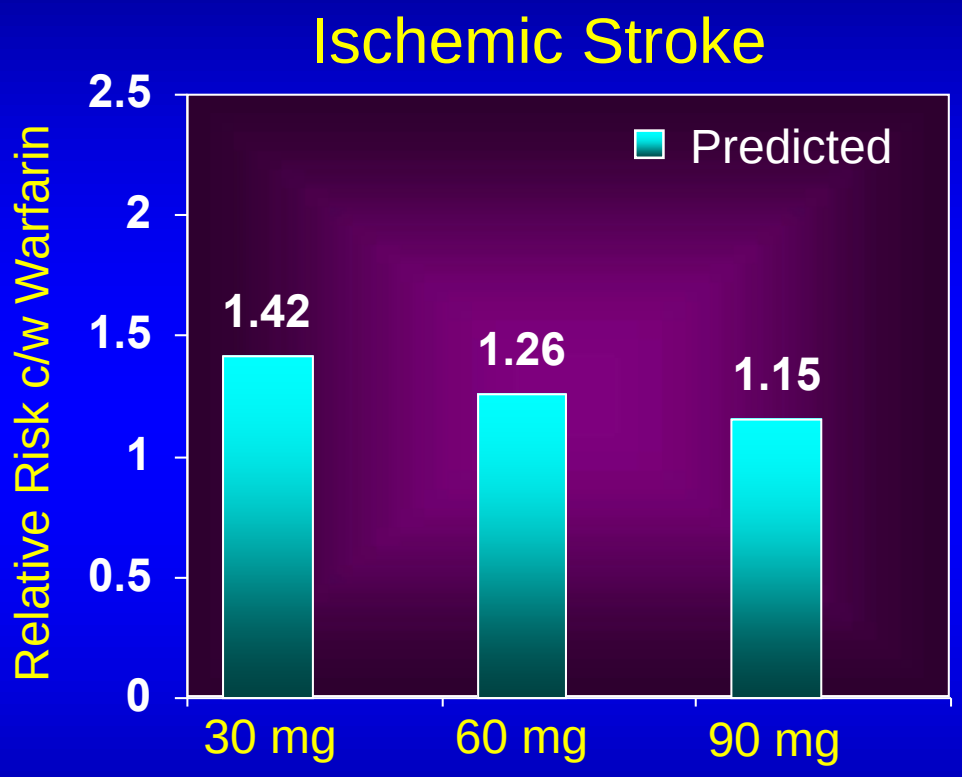
60 mg edoxaban dose in pts with normal renal fx is associated with lower exposure and higher ischemic stroke c/w warfarin

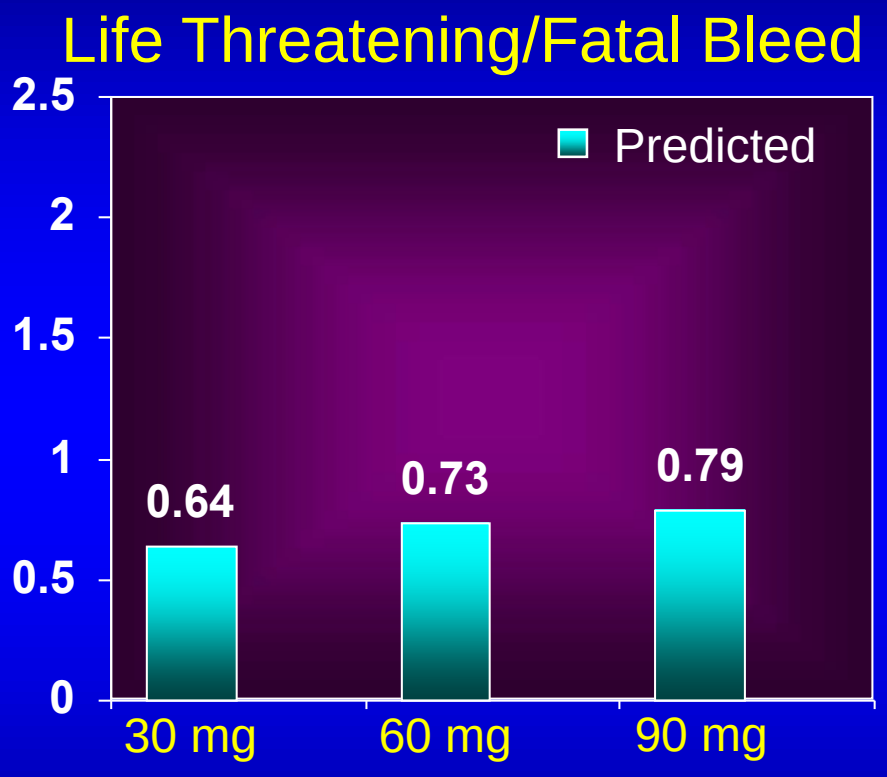
Exposure Matching Requires Edoxaban Dose Higher than 75 mg



Predicted Event Rates with Higher Doses

ENGAGE-AF Trial (Edoxaban vs. Warfarin in NVAF)





Fewer ischemic strokes with less increase in bleeding at higher doses

http://www.fda.gov/downloads/UCM421612.pdf

Predicted Events in Normal Renal Fx (CrCl>80mL/min)

Excess Events (Edoxaban minus Warfarin) per 10,000 PY

Endpoint	Edoxaban 60 mg	Edoxaban 90 mg
Stroke/SEE	18 (RR 1.24, 1.00-1.46)	4 (RR 1.05, 0.91-1.28)
Ischemic Stroke	22 (RR 1.42, 1.21-1.62)	8 (RR 1.15, 0.92-1.40)
Life threatening/ Fatal bleeding	-23 (RR 0.64, 0.53-0.80)	-14 (RR 0.78, 0.56-1.05)
Major bleeding	-59 (RR 0.77, 0.71-0.83)	48 (RR 1.19, 1.03-1.41)
Major GI bleeding	-5 (RR 0.99, 0.89-1.18)	81 (RR 1.85, 1.48-2.21)

- Further ↑ in efficacy without prohibitive ↑ in bleeding is attainable
- However, noninferiority (M2 1.38) may not be achieved at 90 mg
- Potential concern for major GI bleeding discouraged a positive AdCom vote

http://www.fda.gov/downloads/UCM421612.pdf

Benefit–Risk Balance of Edoxaban (CrCl>80mL/min)

10,000 Patients Treated with Edoxaban vs Warfarin

Edoxaban 90 (P) vs Warfarin (O)

Efficacy

- 4 excess Stroke/SEE
  - 8 excess ischemic stroke
  - 1 excess hemorrhagic stroke
- 38 fewer MACE

Safety

- 48 excess major bleeds
  - 81 excess major GI bleeds
- 40 fewer CRNM + major bleeds
- 14 fewer LT/ fatal bleeds

Is this an acceptable benefit-risk tradeoff?

Dosing Recommendations for Edoxaban

Different Opinions, Arbitrary CrCl Cutoffs!

- Sponsor proposal
  - Seeking only high dose (60/30) as it was studied
- FDA recommendations
  - Statistical team
    - Both high (60/30) and low (30/15) doses should be approved
    - 60 mg effective in eCrCL>80 mL/min subgroup (prespecified normal)
  - Medical and clinical pharmacology teams
    - Only high dose (60/30 mg) should be approved
    - 60 mg in eCrCL>80 mL/min subgroup should NOT be approved (37%)
- FDA final decision
  - 30 mg once daily for CrCl 15-≤50 mL/min
  - 60 mg once daily for CrCl >50-≤95 mL/min
  - Should not be used in patients with CrCl>95 mL/min (Boxed Warning)

Pharmacometric Modeling and Regulatory Decision Making

A Non-Pharmacologist's Perspective: Conclusion

- Monitoring drug levels to optimize benefit-risk has intuitive appeal
- Exposure-response (ER) relationship is complex
- Getting the dose right is critical and often challenging

  - Steep ER with NOACs

  - Serious consequences of being either too low or too high

  - Demographic variables (age, renal function, weight, etc.) can potentially confound ER, especially when ER relationships are steep

Pharmacometric Modeling and Regulatory Decision Making

A Non-Pharmacologist's Perspective: Conclusion

- Exploration of ER relationship of NOACs led to 2 different decisions for doses not evaluated in phase III trials despite supportive PM data
  - *Dabigatran 75 mg bid approved for patients with CrCl 15-30mL/min*
  - *Edoxaban 90 mg qd not approved for patients with CrCl >95mL/min*
- ER relationship should remain an area of active investigation
- Optimally performing ER models needed to inform dose selection and regulatory decisions and to guide clinical practice

Modeling and ‘Rosy’ Projections
Caveat Emptor, Caveat Lector

- *Essentially, all models are wrong, but some are useful*
- *Since all models are wrong the scientist cannot obtain a "correct" one by excessive elaboration*
- *Remember that all models are wrong; the practical question is how wrong do they have to be to not be useful*

George EP Box

Alternative Methodology for Benefit-Risk Assessment

“Paul the Psychic Octopus”

Accurate Prediction of Outcomes for German Soccer Team in all 8 Games in 2010 World Cup