

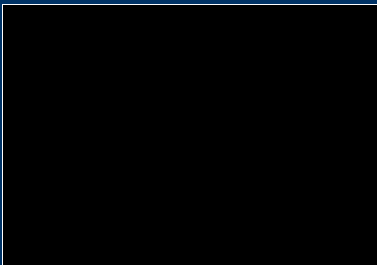
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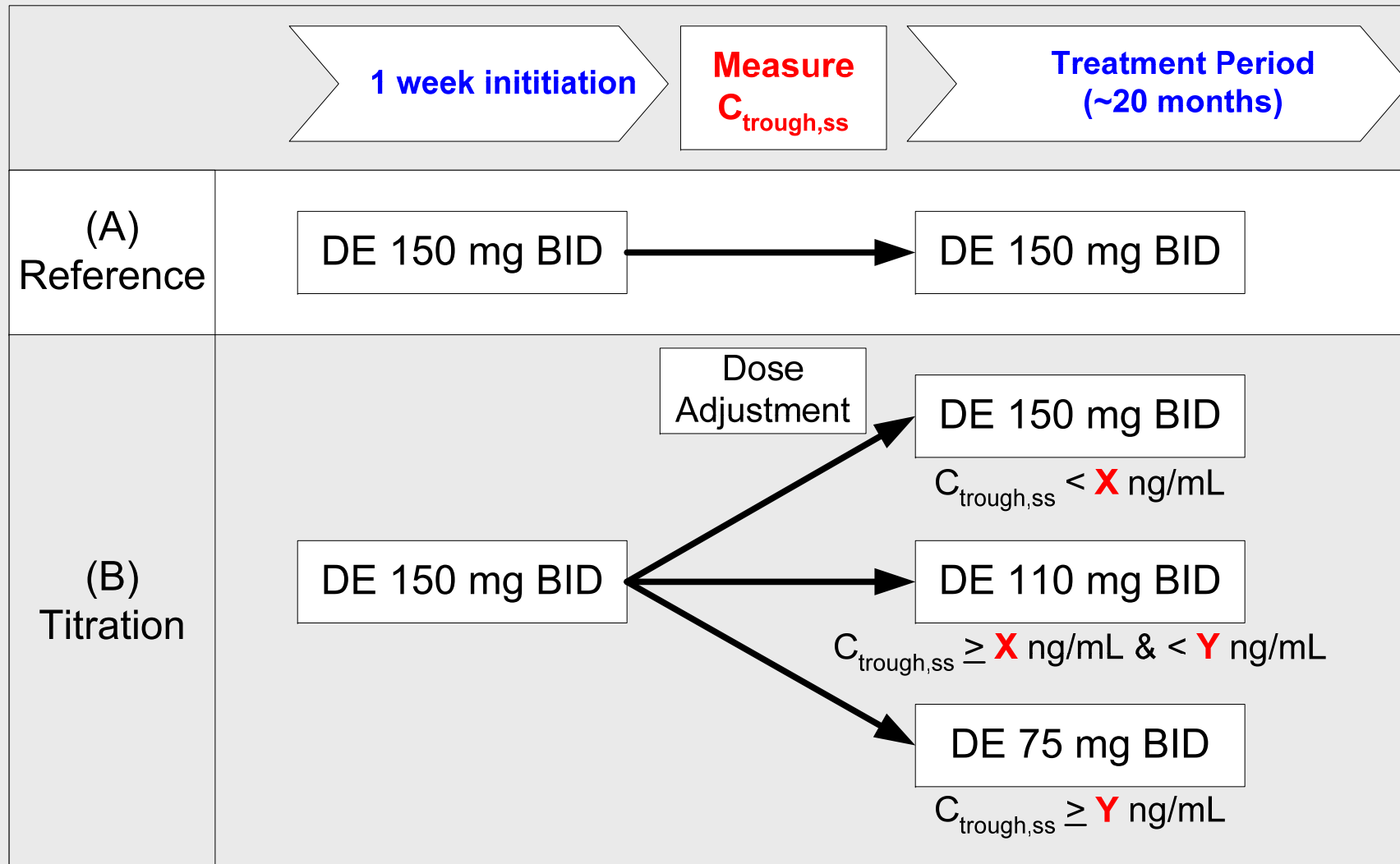
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Impact of Dabigatran Dose Adjustment on Clinical
Outcome in AF Patients

A Clinical Trial Simulation Analysis

May 08, 2012

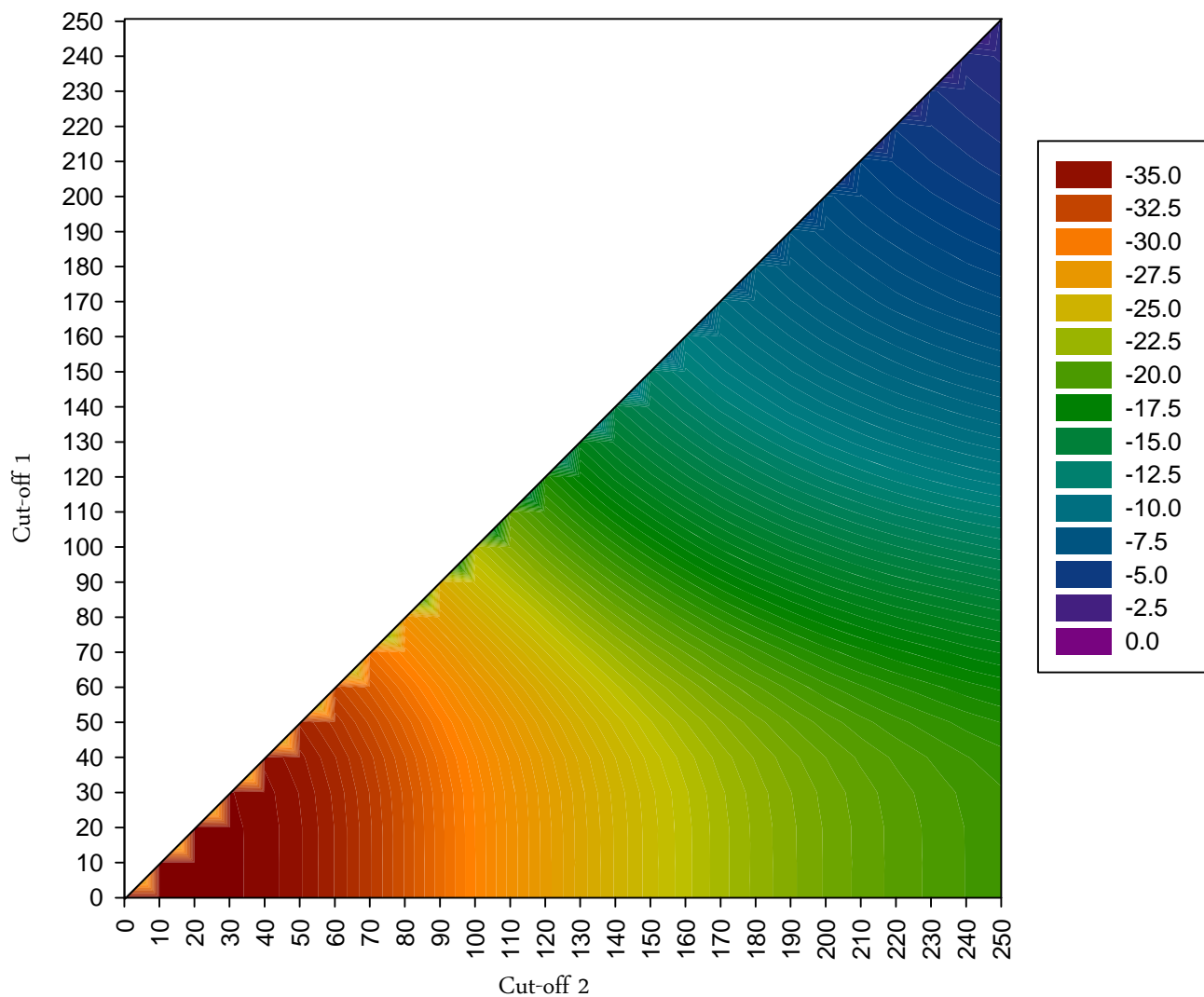




- Cut-off values ($C_{\text{trough,ss}}$) between 0 ng/mL and 250 ng/mL (step size 10 ng/mL) were assessed for both major bleeding and ischemic stroke/SEE prevention (352 different combinations)
- 500 clinical trials with 5000 patients each were simulated to evaluate each of the 352 cut-off combinations for both the safety and efficacy endpoints
- Patient characteristics were bootstrapped from RE-LY database

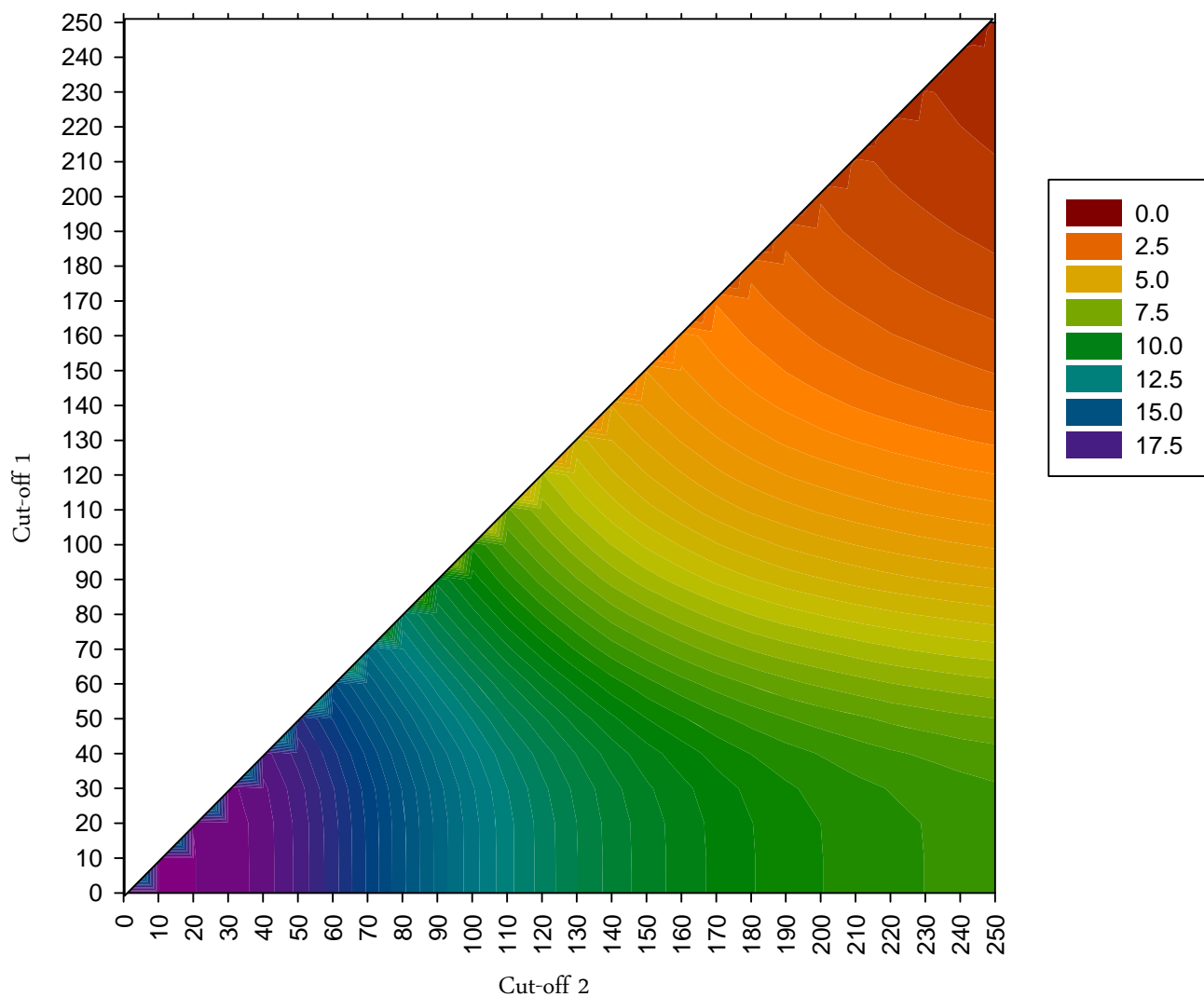
The goal was to identify the optimal trough dabigatran plasma cut-off values for a dose adjustment scheme which produces simulated results that are better (balancing ischemic stroke/SEE and major bleeding event rates) than a fixed dose Pradaxa regimen and a well-controlled warfarin regimen

% Change Compared to Reference (150 mg BID)



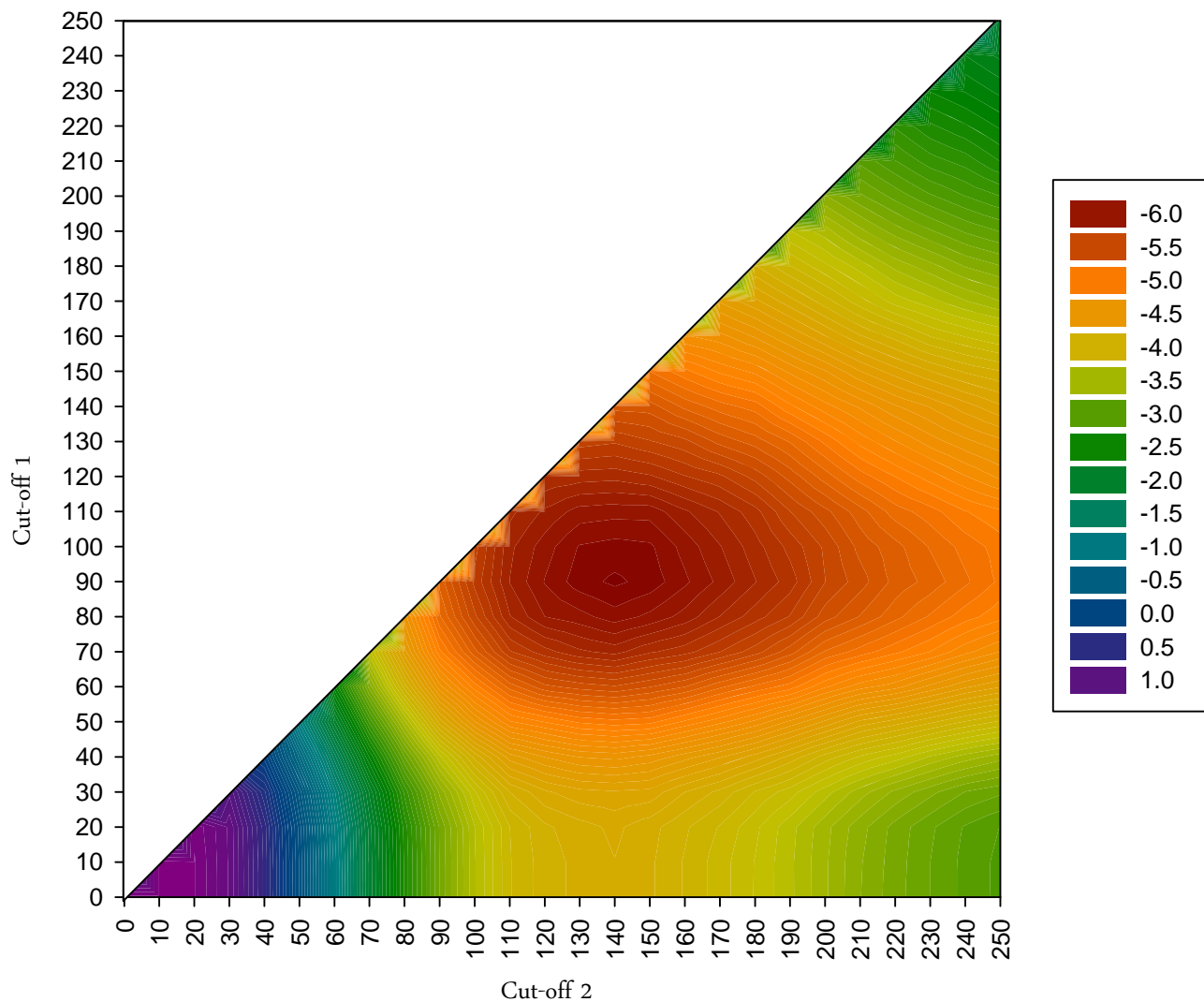
C _{trough,ss} [ng/mL]	Dosing
< Cut-off1	150 mg BID
Cut-off1 -< Cut-off 2	110 mg BID
≥ Cut-off 2	75 mg BID

% Change Compared to Reference (150 mg BID)



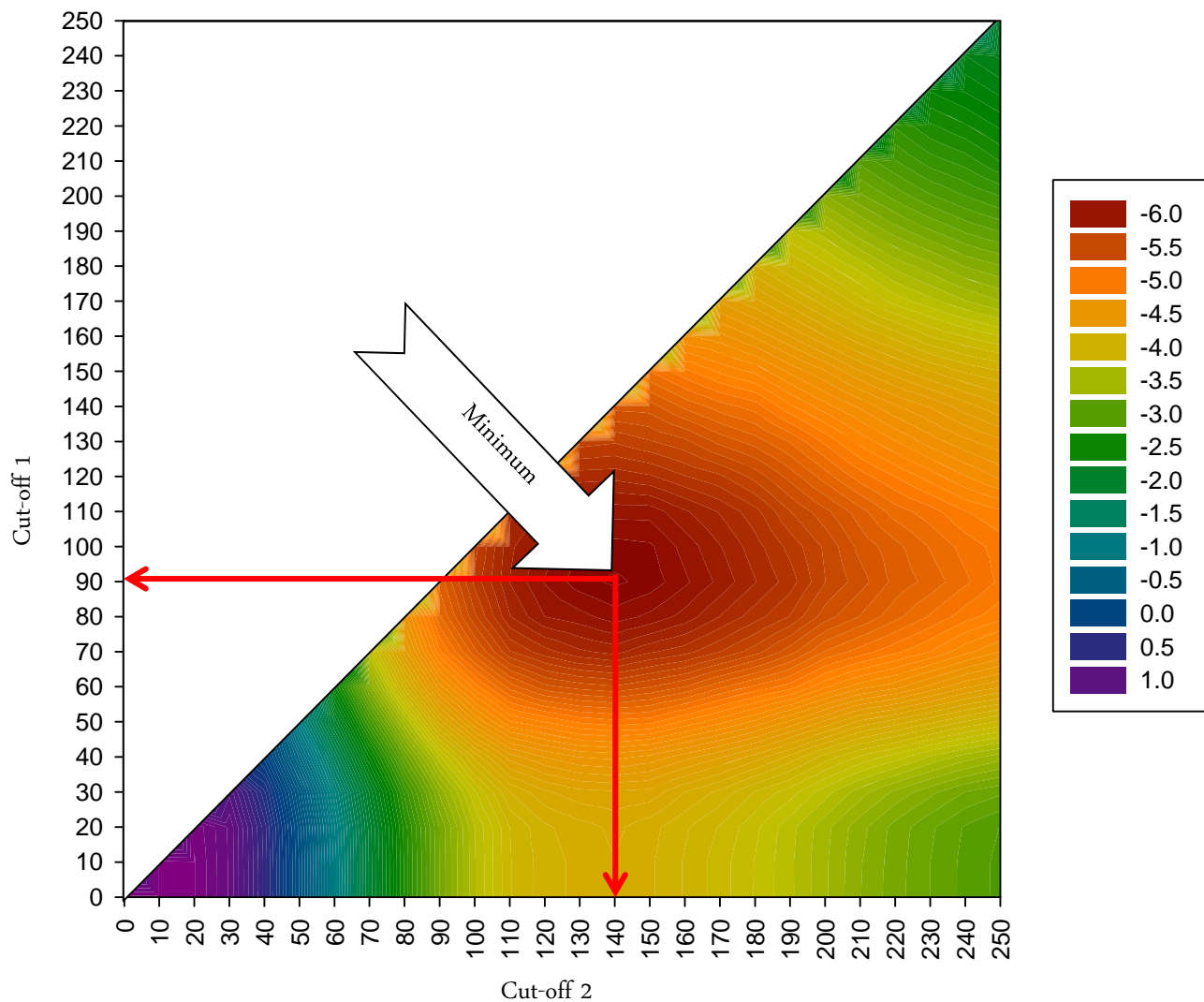
C _{trough,ss} [ng/mL]	Dosing
< Cut-off1	150 mg BID
Cut-off1 -< Cut-off 2	110 mg BID
≥ Cut-off 2	75 mg BID

= %Change Major Bleeds + 2x %Change Ischemic Stroke/SEE

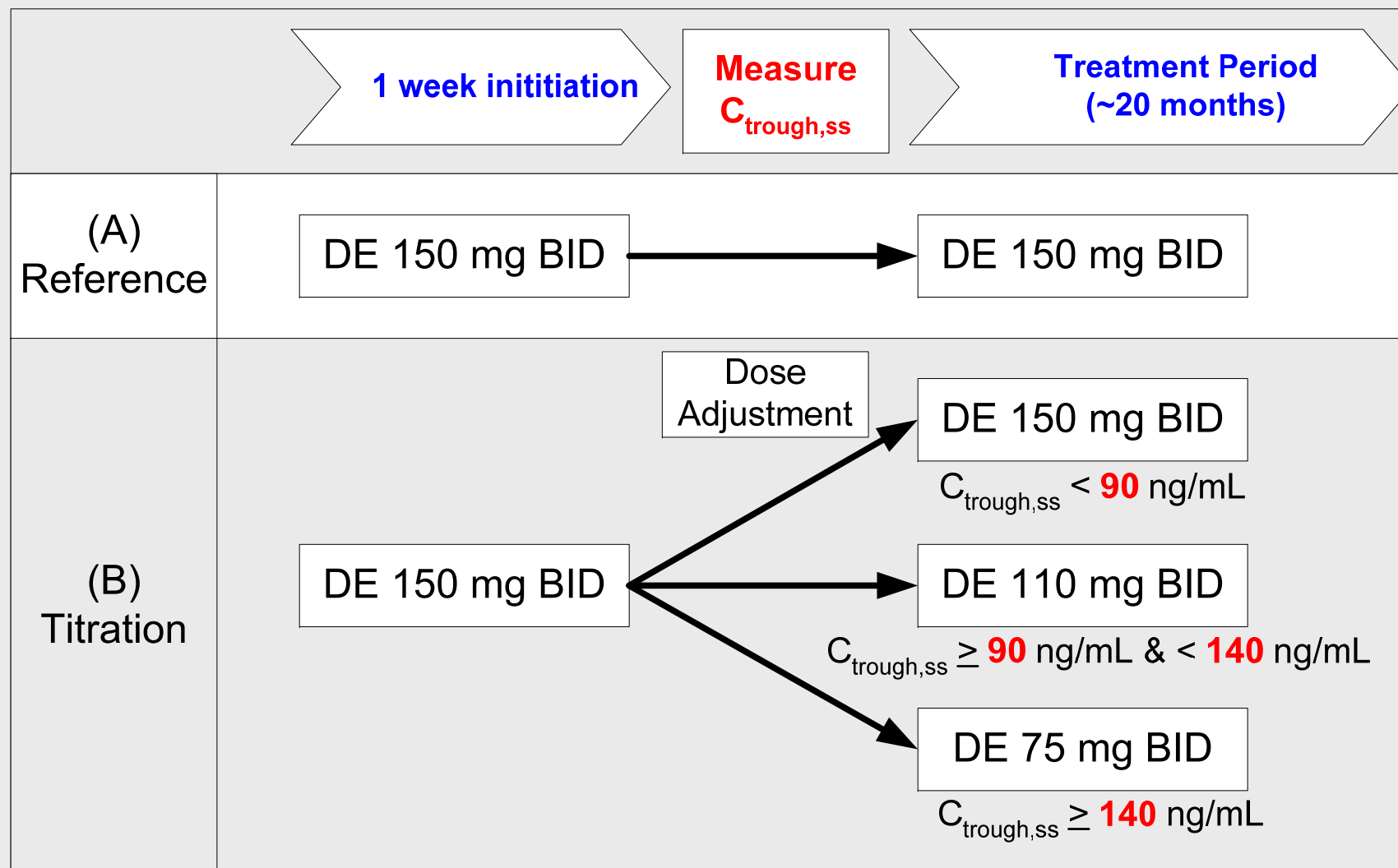


C _{trough,ss} [ng/mL]	Dosing
< Cut-off1	150 mg BID
Cut-off1 -< Cut-off 2	110 mg BID
≥ Cut-off 2	75 mg BID

= %Change Major Bleeds + 2x %Change Ischemic Stroke/SEE



C _{trough,ss} [ng/mL]	Dosing
< 90	150 mg BID
90 -<140	110 mg BID
≥140	75 mg BID



Distribution of Dabigatran Doses

Dabigatran Dose	(A) Reference	(B) Titration
75 mg bid	---	25.5%
110 mg bid	---	29.9%
150 mg bid	100%	44.6%

- Majority of patients eligible for 150 mg bid
- Significant amount assigned to 75 mg bid

Distribution of Dabigatran Exposure

N=5000	C _{trough,ss}	
	Median	P10 – P90
(A) Reference	97.1	48.6 – 199.4
(B) Titration	77.0	48.6 – 101.6

- Shift in exposure
- Median C_{trough,ss} ~21% reduced
- Minimum exposure levels maintained
- 90th percentile significantly reduced

Absolute Event Rates, not annualized

	Ischemic Stroke/SEE		Major Bleeding	
	Mean*	90% CI [§]	Mean*	90% CI [§]
(A) Reference	1.26	1.01 – 1.55	4.38	3.91 – 4.89
(B) Titration	1.34	1.08 – 1.63	3.49	3.08 – 3.96

Relative Risk

(B) Titration vs. (A) Reference	Rel. Risk	90% CI
Ischemic Stroke/SEE	1.06	(0.76 – 1.50)
Major Bleeding	0.80	(0.66 – 0.97)

*risk of event within median RE-LY duration [~20 months], not annualized;

[§] Clopper-Pearson (Exact); [§] Range 10th percentile – 90th percentile

Titration vs. Reference

- Risk of ischemic stroke/SEE events comparable (Relative Risk 1.06)
- Risk of major bleeding events significantly reduced (Relative Risk 0.8)

Absolute Event Rates, not annualized

	Ischemic Stroke/SEE		Major Bleeding	
	Mean [*]	90% CI [§]	Mean [*]	90% CI [§]
(B) Titration (n=5000)	1.34	1.08 – 1.63	3.49	3.08 – 3.96
(C) Warfarin (n=4597)	1.68	1.38 - 2.02	5.83	5.27 - 6.43

*risk of event within median RE-LY duration [~20 months], not annualized;

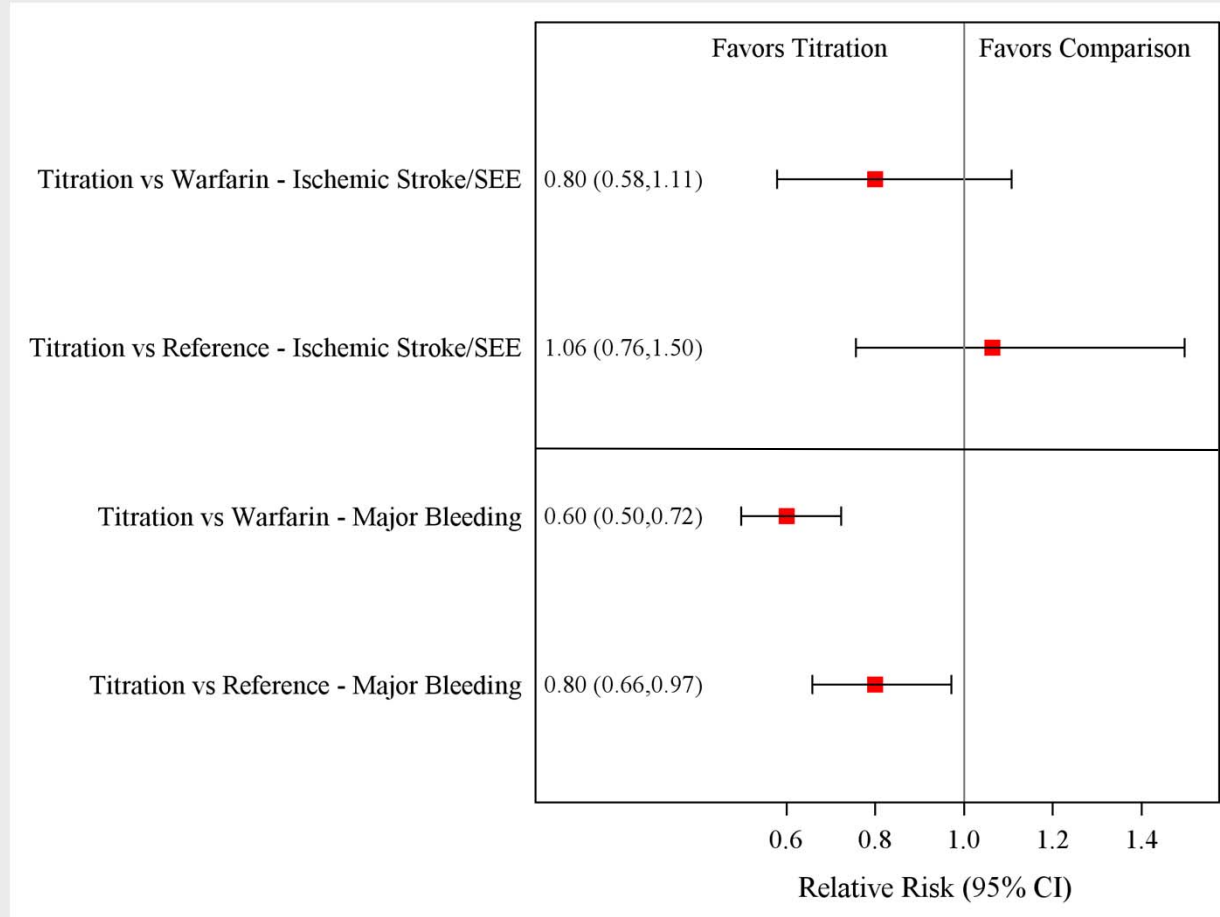
[§] Clopper-Pearson (Exact); [§] Range 10th percentile – 90th percentile

Relative Risk

(B) Titration vs. (C) Warfarin	Rel. Risk	90% CI
Ischemic Stroke/SEE	0.80	(0.58 – 1.11)
Major Bleeding	0.60	(0.50 – 0.72)

Titration vs. Warfarin

- Only RE-LY warfarin patients from centers that contributed PK measurements were considered (center matching)
- Risk of ischemic stroke/SEE events reduced (Relative Risk 0.8)
- Risk of major bleeding events significantly reduced (Relative Risk 0.6)
- Comparison needs to be handled with care. A potential bias can not be excluded due to the type of analysis.



- Extensive and comprehensive clinical trial simulation analyses were performed to investigate the impact of dabigatran dose titration on outcomes in AF patients.
- Dabigatran C_{trough,ss} values of 90 ng/mL and 140 ng/mL were identified as promising cut-off values to assign dabigatran doses of 150 mg bid, 110 mg bid and 75 mg bid.
- Compared to a reference treatment (=DE 150 mg bid), dose adjustment showed a significant reduction of major bleeding events (RR 0.8), while the ischemic stroke protection was maintained (RR 1.06).
- Compared to warfarin treatment, dose adjustment showed a significant reduction of ischemic stroke/SEE (RR 0.8) and major bleeding events (RR 0.6).

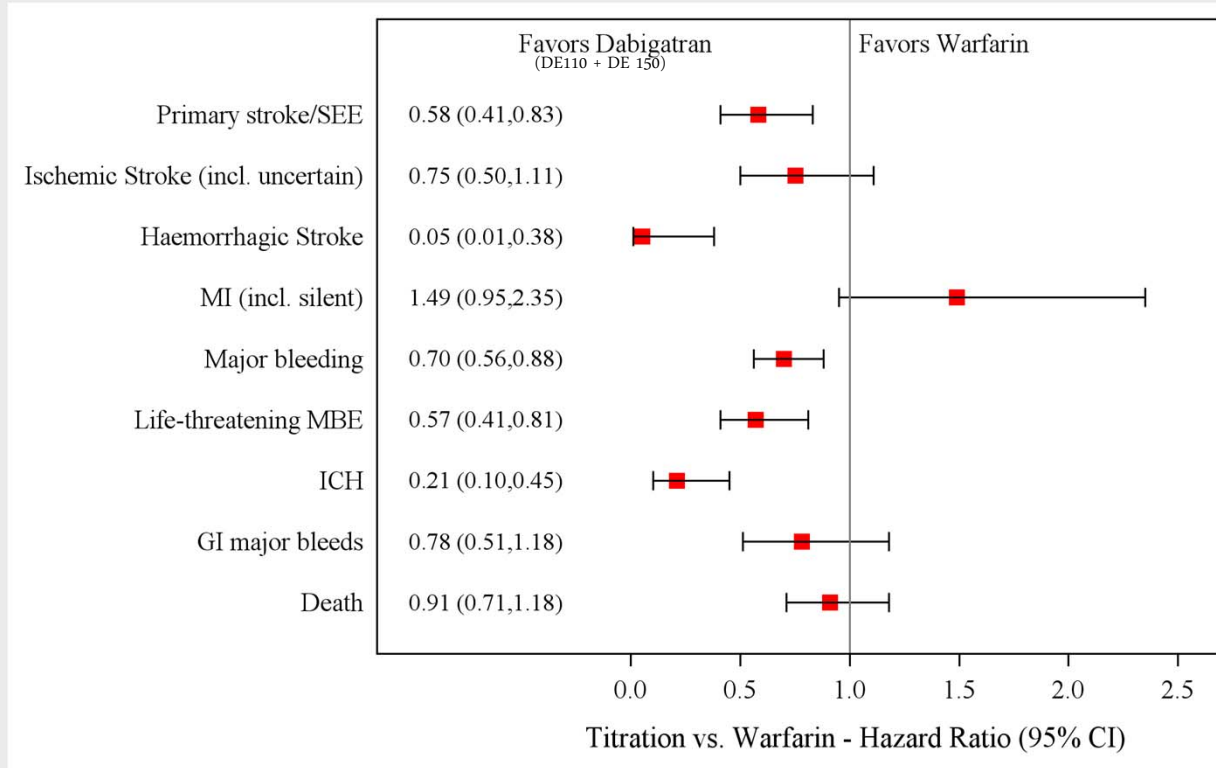
Impact of Dabigatran Dose Adjustment on Clinical Outcome in AF Patients

**COMPARISON OF OBSERVED DABIGATRAN VS. OBSERVED
WARFARIN OUTCOMES FROM RE-LY**

- The comparison of the projected dabigatran versus the observed warfarin outcome is not considered as ideal
- Solution: Comparison of observed dabigatran versus observed warfarin outcomes from RE-LY in a matching cohort
- Difficulty: Identification of the appropriate warfarin comparison group
 - ~26% of dabigatran treated patients are expected to be assigned to the 75 mg bid dose and are consequently not considerable for further analysis
 - These patients are expected to be patients at higher risk for outcome events due to their demographic characteristics
 - It is therefore important to remove this population also from the warfarin group to ensure a fair comparison between both groups

1. All dabigatran treated patients from RE-LY with valid C_{trough,ss} concentrations (n=8458) were assigned to their optimal target dose (75, 110, 150), based on their measured trough concentrations in RE-LY assuming dose proportionality. If more than 1 concentration was available, the median concentration was calculated.
2. A classification model was developed in dabigatran treated patients based on the propensity score method to identify with baseline characteristics the patients assigned to “DE 75 mg bid” versus “not DE 75 mg bid”.
3. The developed classification model was applied to center matching warfarin patients from RE-LY to identify those warfarin patients that are comparable to “optimal DE 75 mg” patients. Those patients were removed from the comparison with the observed DE group.
4. Selection of patients for statistical comparison from RE-LY safety dataset
 - a) Dabigatran: only patients who were treated “optimally” based on their trough concentration were included (i.e. predicted optimal dose = received dose in RE-LY)
 - b) Warfarin: only patients assigned to “not DE 75 mg bid” were included.

- From the 8458 dabigatran treated RE-LY patients with valid C_{trough,ss} values, 25.6%, 25.8% and 49.6% were assigned to 75 mg, 110 mg and 150 mg bid as their “optimal” dose.
- From these 8458 patients, **ONLY** 3086 patients (36.5%) received the “optimal” dabigatran dose in RE-LY.
- A propensity score classification model was successfully developed.
 - 1340 of 5301 center matching warfarin patients (25.3%) were identified as “75 mg patients” and excluded
 - In depth comparison of patient characteristics of excluded dabigatran and excluded warfarin patients showed no relevant difference in any of the relevant factors (e.g. CHADS₂, CHADS VASc, HAS-BLED, age, etc.)
 - Dabigatran and warfarin patients included in these analysis showed no relevant differences in any relevant patient characteristics



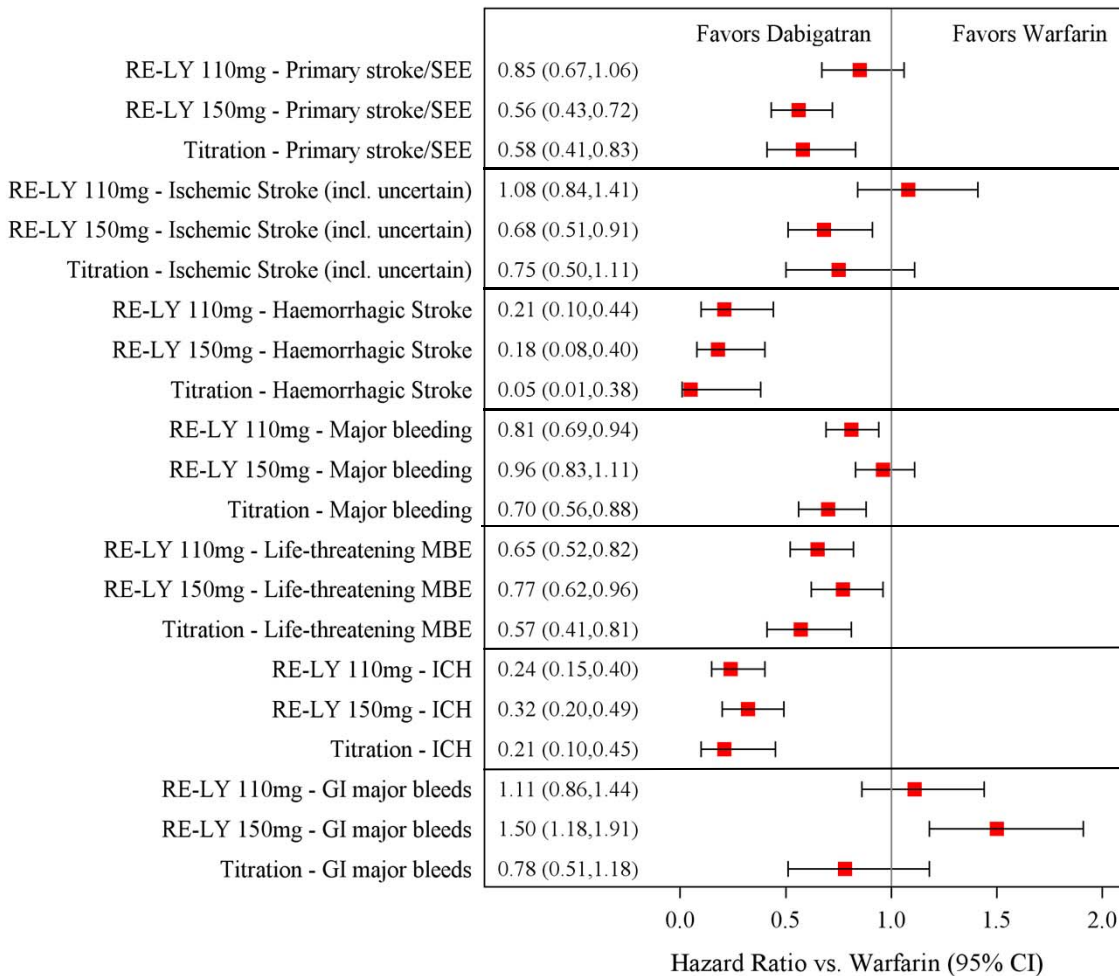
Number of patients

Treatment	Titration
DE 110 mg	1081
DE 150 mg	2005
Warfarin	3961
Total	7047

Optimally treated (=titrated) dabigatran patients reveal a promising efficacy and safety profile compared to matched warfarin group.

Results – Clinical Outcome

“Titration vs RE-LY” – Safety Dataset



Number of patients

Treatment	Titration	RE-LY
DE 110 mg	1081	5983
DE 150 mg	2005	6059
Warfarin	3961	5998
Total	7047	18040

Titration patients have an efficacy profile that is comparable to the RE-LY DE 150 mg group and a safety profile that is comparable to the RE-LY DE 110 mg group

- A complex propensity score classification model was developed and provided an appropriate and well matched titration vs warfarin comparison
- Optimally treated (=titrated) dabigatran patients could have a better efficacy and safety profile compared to a well-controlled and matched warfarin group:
 - Efficacy profile comparable to DE 150 mg group from RE-LY
 - Safety profile comparable to DE 110 mg group from RE-LY

- Comprehensive clinical trial simulation analyses identified promising cut-off values to assign optimal dabigatran doses of 150, 110 and 75 mg bid.
- Optimally used (=titrated) dabigatran has the potential to provide patients an even better efficacy and safety profile than fixed dose dabigatran and also a better safety and efficacy profile than a matched warfarin group.
- **Dose titration based on exposure is a promising approach to significantly reduce major bleeding events while maintaining stroke prevention in AF patients; however, this strategy would need to be validated in a reasonable number of patients**