



RELY[®]

Study of stroke prevention
in atrial fibrillation

Randomized Evaluation of Long-term anticoagulant therapy

Dabigatran Compared to Warfarin in 18,113 Patients with Atrial Fibrillation at Risk of Stroke

Sponsored by Boehringer-Ingelheim

Atrial Fibrillation and Stroke

- AF responsible for 1/6 of all strokes
- Warfarin reduces stroke in AF by 64%
 - significant increase in intracranial and other hemorrhage
 - Difficult to use
- Only 50% of eligible patients receive warfarin
- An alternative treatment is needed

Dabigatran

- Dabigatran Etexilate, a pro-drug, is rapidly converted to dabigatran
- 6.5% bioavailability, 80% excreted by kidney
- Half-life of 12-17 hours
- Phase 2 data identified 110 mg BID and 150 mg BID as viable doses

RE-LY: A Non-inferiority Trial

Atrial fibrillation
≥1 Risk Factor
Absence of contra-indications
951 centers in 44 countries

Blinded Event Adjudication.

R

Open

Blinded

Warfarin
adjusted
(INR 2.0-3.0)
N=6000

Dabigatran
Etexilate
110 mg BID
N=6000

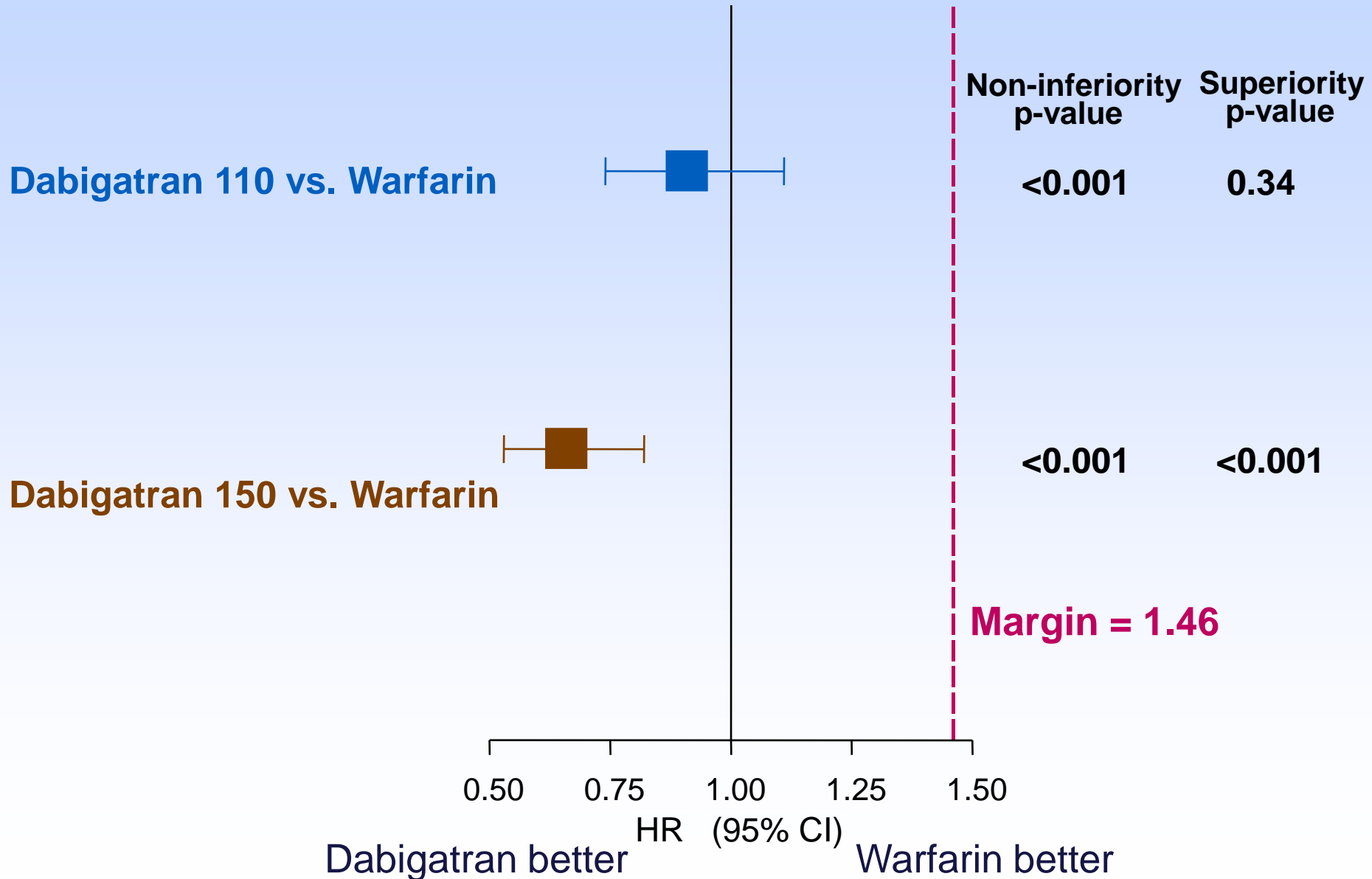
Dabigatran
Etexilate
150 mg BID
N=6000

- Performed December 2005-March 2009
- Median Follow up 2.0 years
- Follow up 99.9% complete
- Mean TTR = 64% (patients on warfarin)

Baseline Characteristics

Characteristic	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
Randomized	6015	6076	6022
Mean age (years)	71.4	71.5	71.6
Male (%)	64.3	63.2	63.3
CHADS2 score (mean)	2.1	2.2	2.1
0-1 (%)	32.6	32.2	30.9
2 (%)	34.7	35.2	37.0
3+ (%)	32.7	32.6	32.1
Prior stroke/TIA (%)	19.9	20.3	19.8
Prior MI (%)	16.8	16.9	16.1
CHF (%)	32.2	31.8	31.9
Baseline ASA (%)	40.0	38.7	40.6
Warfarin Naïve (%)	49.9	49.8	51.4

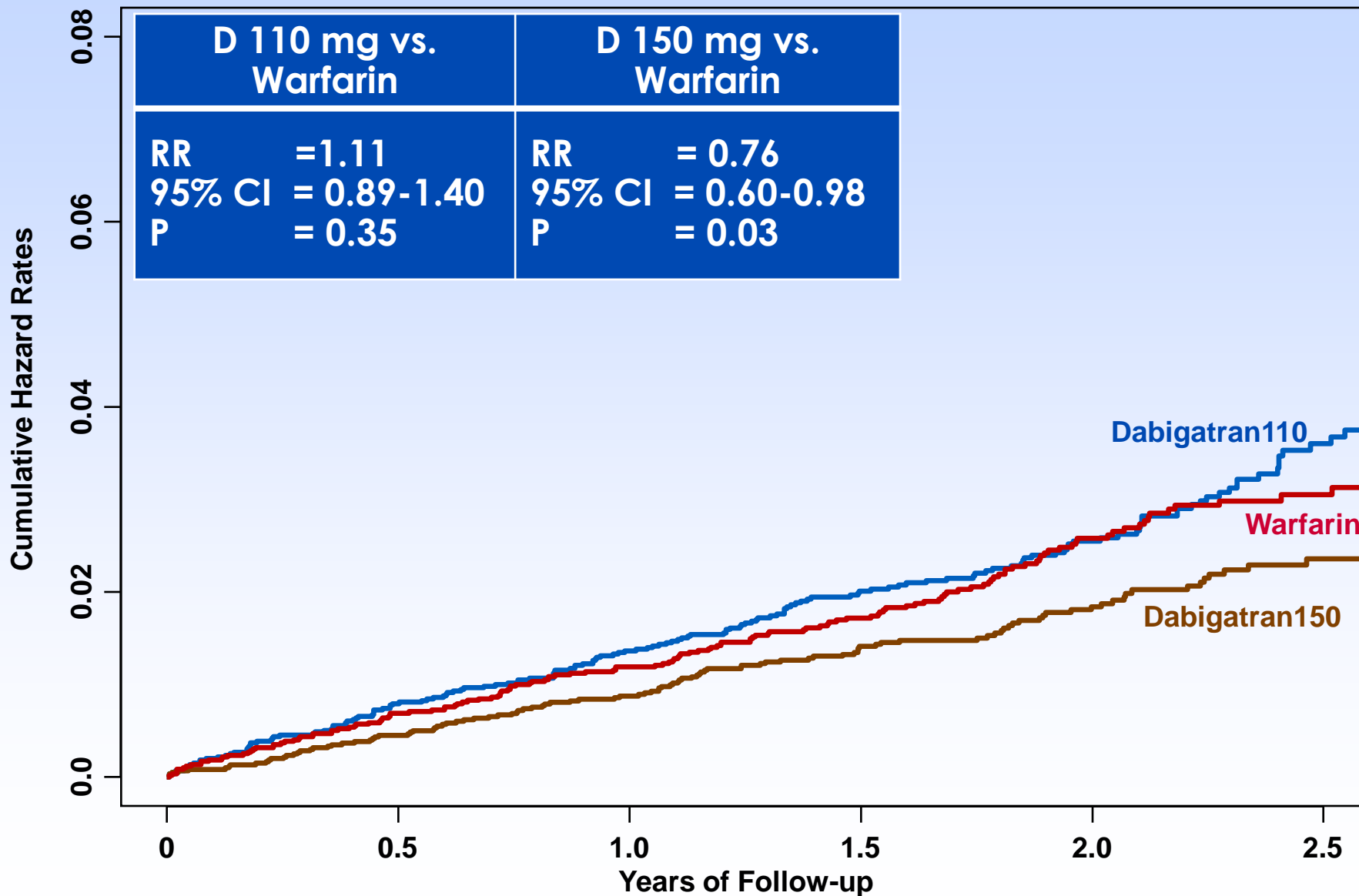
Stroke or Systemic Embolism



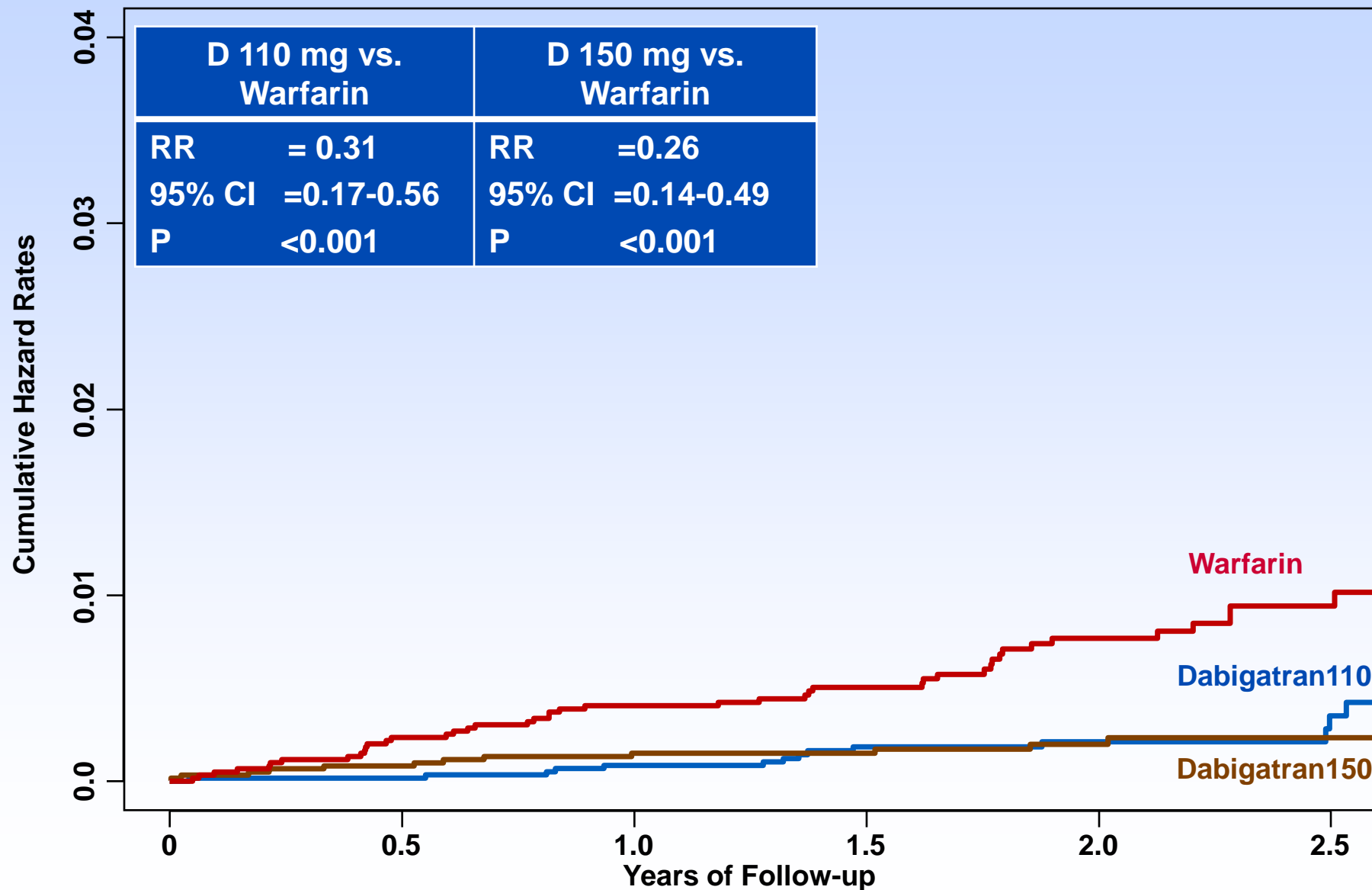
1^o Outcome: Superiority Analysis

	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR 95% CI	P*	RR 95% CI	P
Stroke or systemic Embolism	1.5 %	1.1 %	1.7 %	0.91 0.74-1.11	0.34	0.66 0.53-0.82	<0.001
Stroke	1.4 %	1.0 %	1.6 %	0.92 0.74-1.13	0.41	0.64 0.51-0.81	<0.001

Ischemic/Unspecified Stroke



Hemorrhagic Stroke



Bleeding

	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR 95% CI	p	RR 95% CI	p
Total	14.6%	16.4%	18.2%	0.78 0.74-0.83	<0.001	0.91 0.86-0.97	0.002
Major	2.7 %	3.1 %	3.4 %	0.80 0.69-0.93	0.003	0.93 0.81-1.07	0.31
Life- Threatening major	1.2 %	1.5 %	1.8 %	0.68 0.55-0.83	<0.001	0.81 0.66-0.99	0.04
Gastro- intestinal Major	1.1 %	1.5 %	1.0 %	1.10 0.86-1.41	0.43	1.50 1.19-1.89	<0.001

MI, Death and Net clinical Benefit

	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR 95% CI	p	RR 95% CI	p
MI	0.7%	0.7 %	0.5 %	1.35 0.98-1.87	0.07	1.38 1.00-1.91	0.048
Death	3.8 %	3.6 %	4.1 %	0.91 0.80-1.03	0.13	0.88 0.77-1.00	0.05
Net Clinical Benefit	7.1 %	6.9 %	7.6 %	0.92 0.84-1.02	0.10	0.91 0.82-1.00	0.04

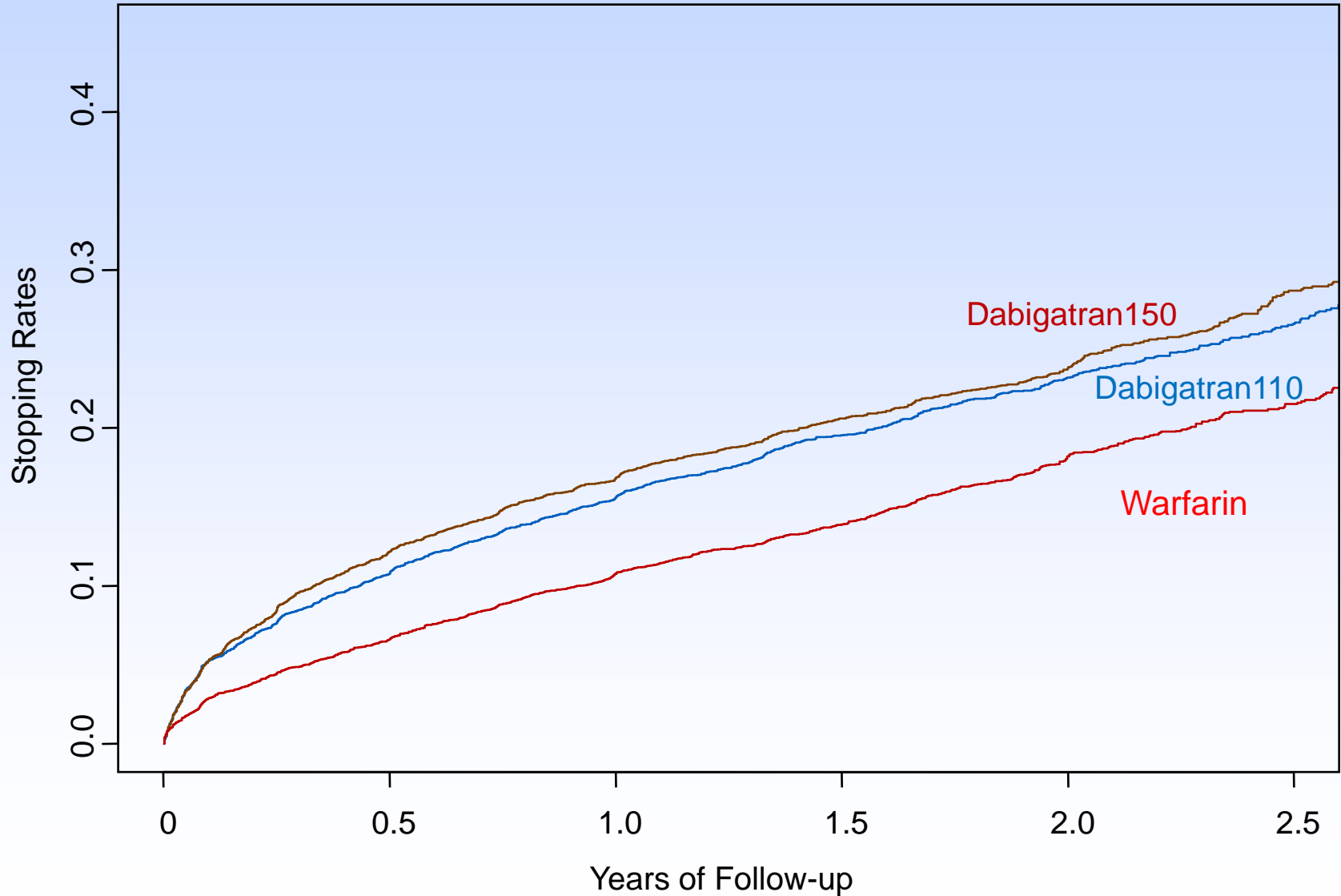
Net Clinical Benefit includes vascular events, death and major bleed

Dabigatran 150 mg vs. 110 mg

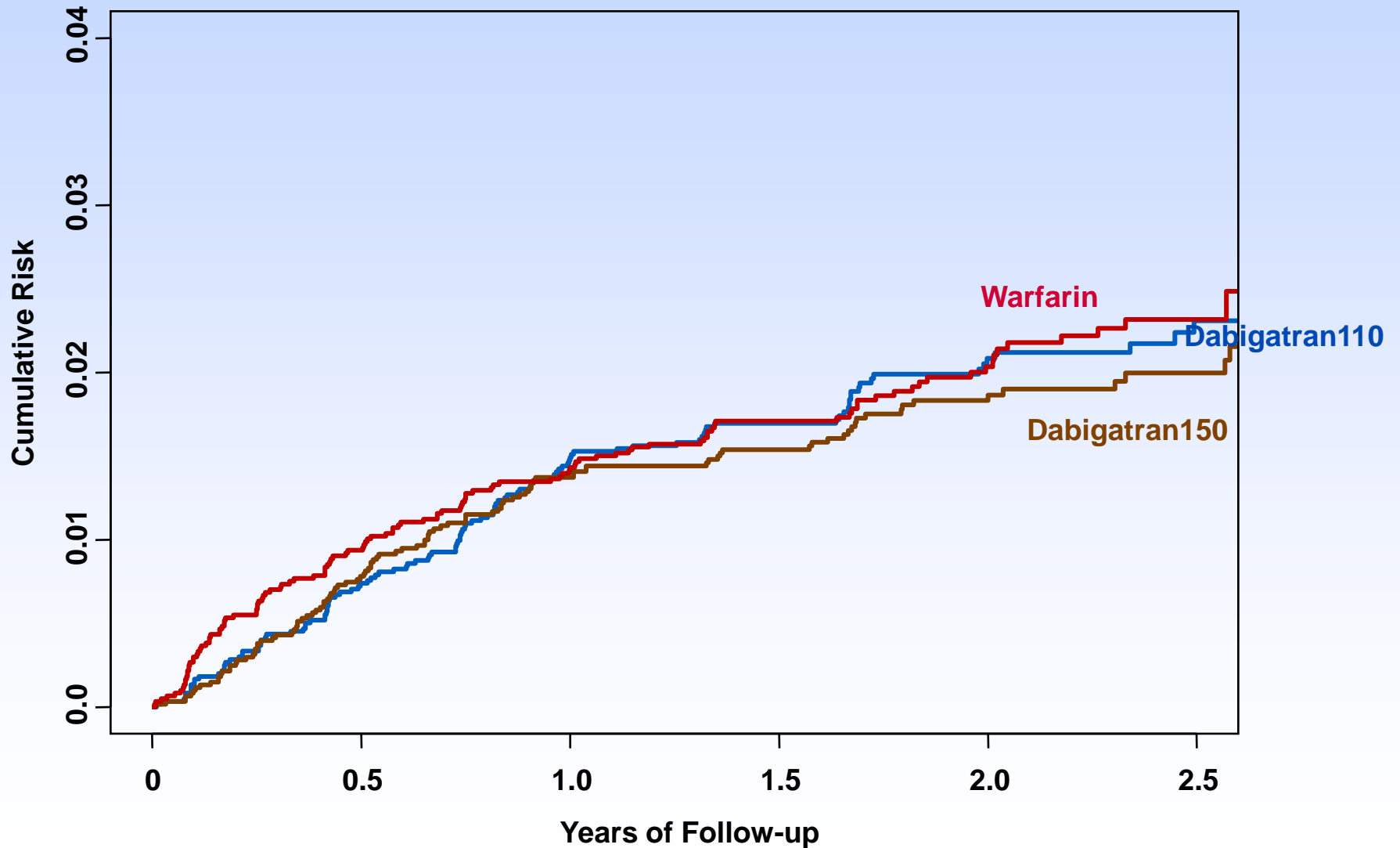
	Dabigatran 110mg	Dabigatran 150mg	D 150mg vs. D 110 mg	
	Number rate/yr	Number rate/yr	Relative Risk 95% CI	p
Stroke and systemic embolism	1.5%	1.1 %	0.73 0.58-0.91	0.005
Hemorrhagic stroke	0.1%	0.1 %	0.85 0.39-1.83	0.67
Major Hemorrhage	2.7 %	3.1 %	1.16 1.00-1.34	0.05
Net Clinical Benefit	7.1 %	6.9 %	0.98 0.89-1.08	0.66

***Net Clinical Benefit includes vascular events, death and major bleed**

Permanent Discontinuation



ALT or AST >3x ULN



Common Adverse Events

Adverse events occurring in >5% of any group	Dabigatran 110 mg %	Dabigatran 150 mg %	Warfarin %
Dyspepsia *	11.8	11.3	5.8
Dyspnea	9.3	9.5	9.7
Dizziness	8.1	8.3	9.4
Peripheral edema	7.9	7.9	7.8
Fatigue	6.6	6.6	6.2
Cough	5.7	5.7	6.0
Chest pain	5.2	6.2	5.9
Arthralgia	4.5	5.5	5.7
Back pain	5.3	5.2	5.6
Nasopharyngitis	5.6	5.4	5.6
Diarrhea	6.3	6.5	5.7
Atrial fibrillation	5.5	5.9	5.8
Urinary tract infection	4.5	4.8	5.6
Upper respiratory tract infection	4.8	4.7	5.2

*Occurred more commonly on dabigatran p<0.001

- Dabigatran 150 mg significantly reduced stroke compared to warfarin with similar risk of major bleeding
- Dabigatran 110 mg had a similar rate of stroke as warfarin with significantly reduced major bleeding
- Both doses markedly reduced intra-cerebral, life-threatening and total bleeding
- Dabigatran had no major toxicity, but did increase dyspepsia and GI bleeding

- Both Dabigatran doses offer advantages over warfarin
- Dabigatran 150 is more effective and dabigatran 110 has a better safety profile
- There is potential to tailor therapy to individual patient characteristics