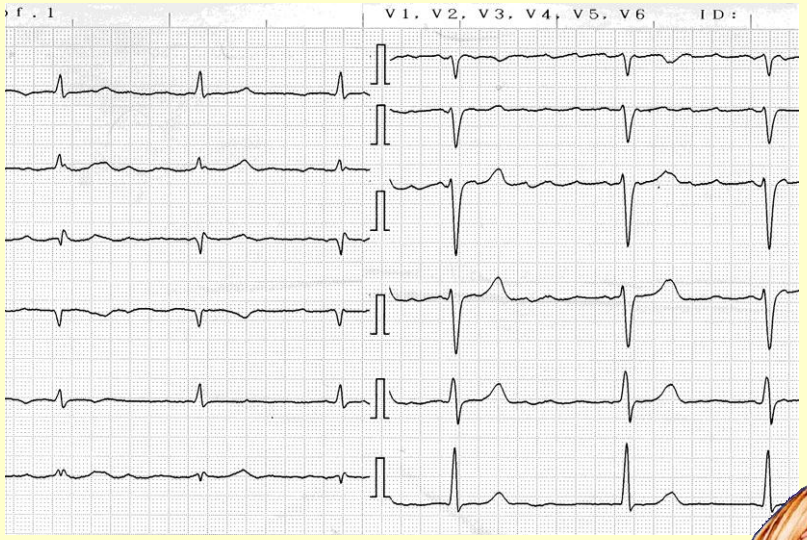
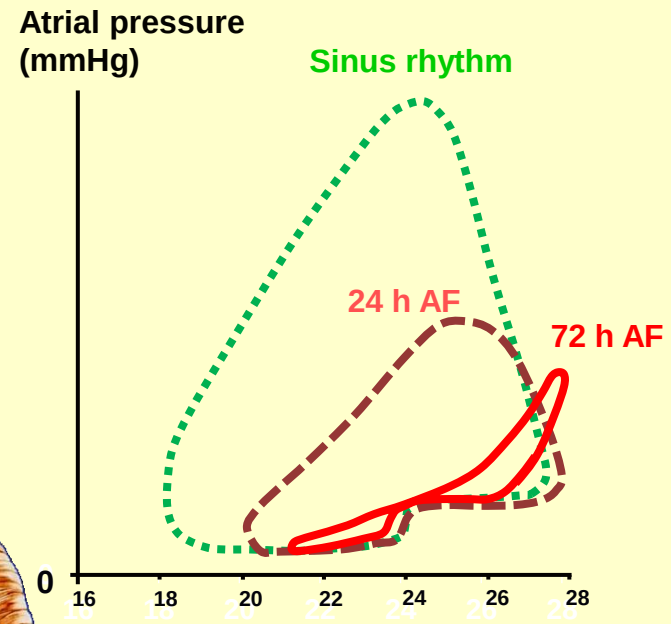
The latest findings from the RE-LY trial

Harald Darius, Berlin, Germany

KSC Congress, Daejeon, 03.12.2011

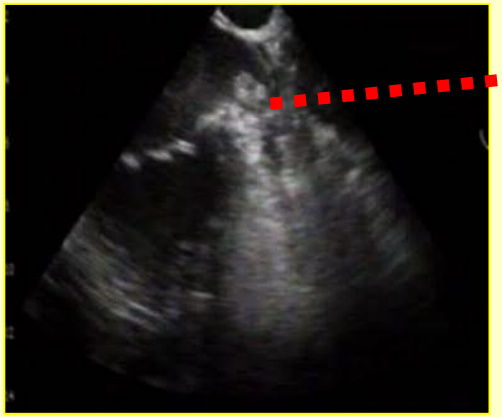
Atrial fibrillation and stroke

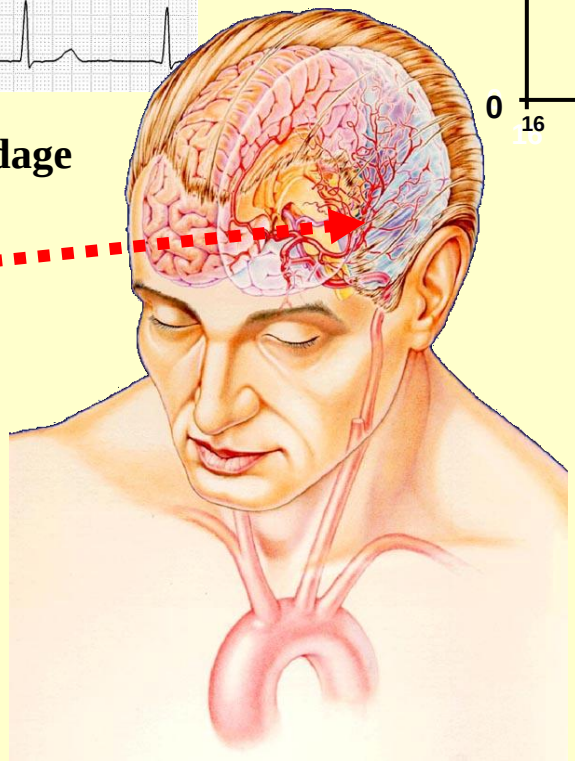




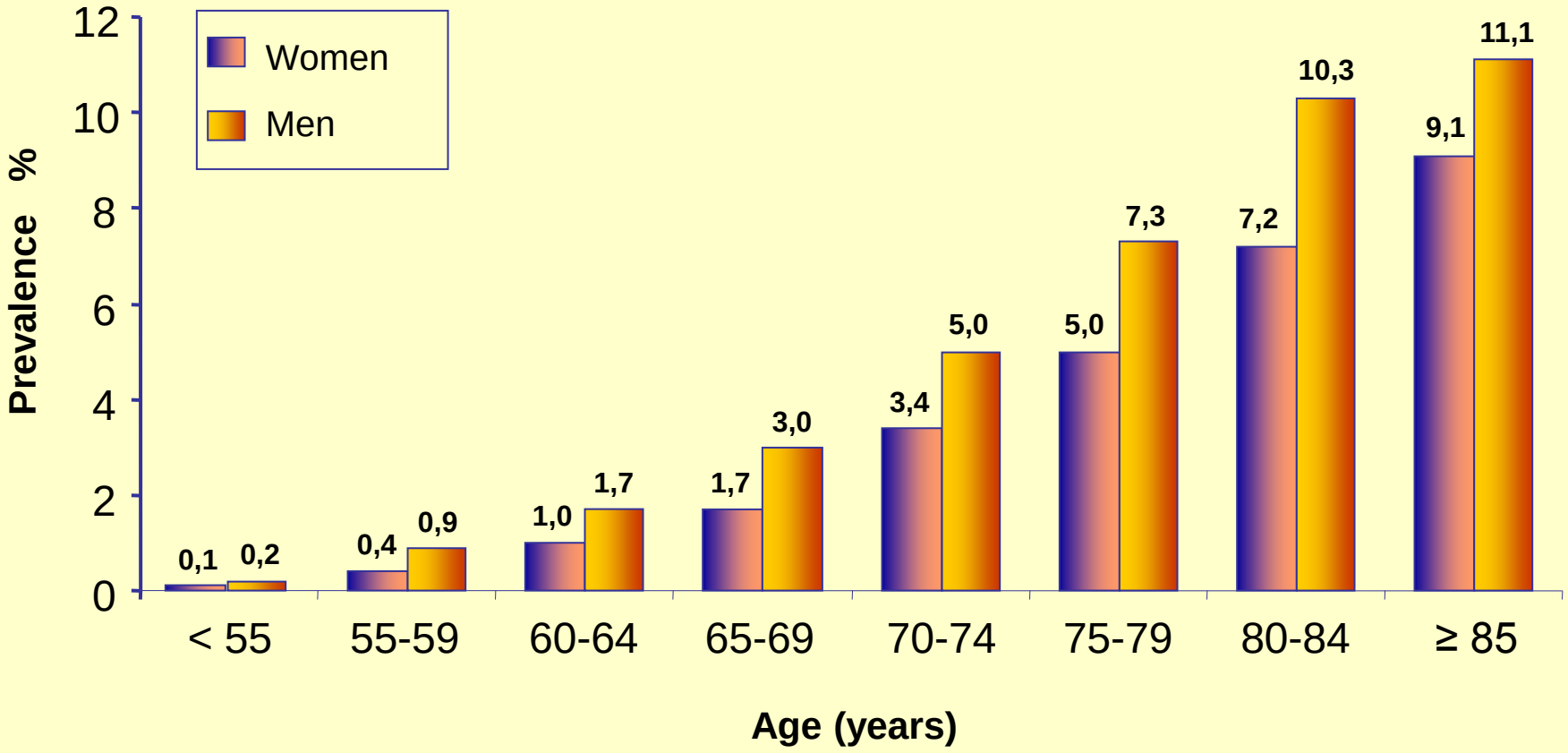
Am J Physiol 2004, 287:H2324-H2331

Thrombus in left atrial appendage





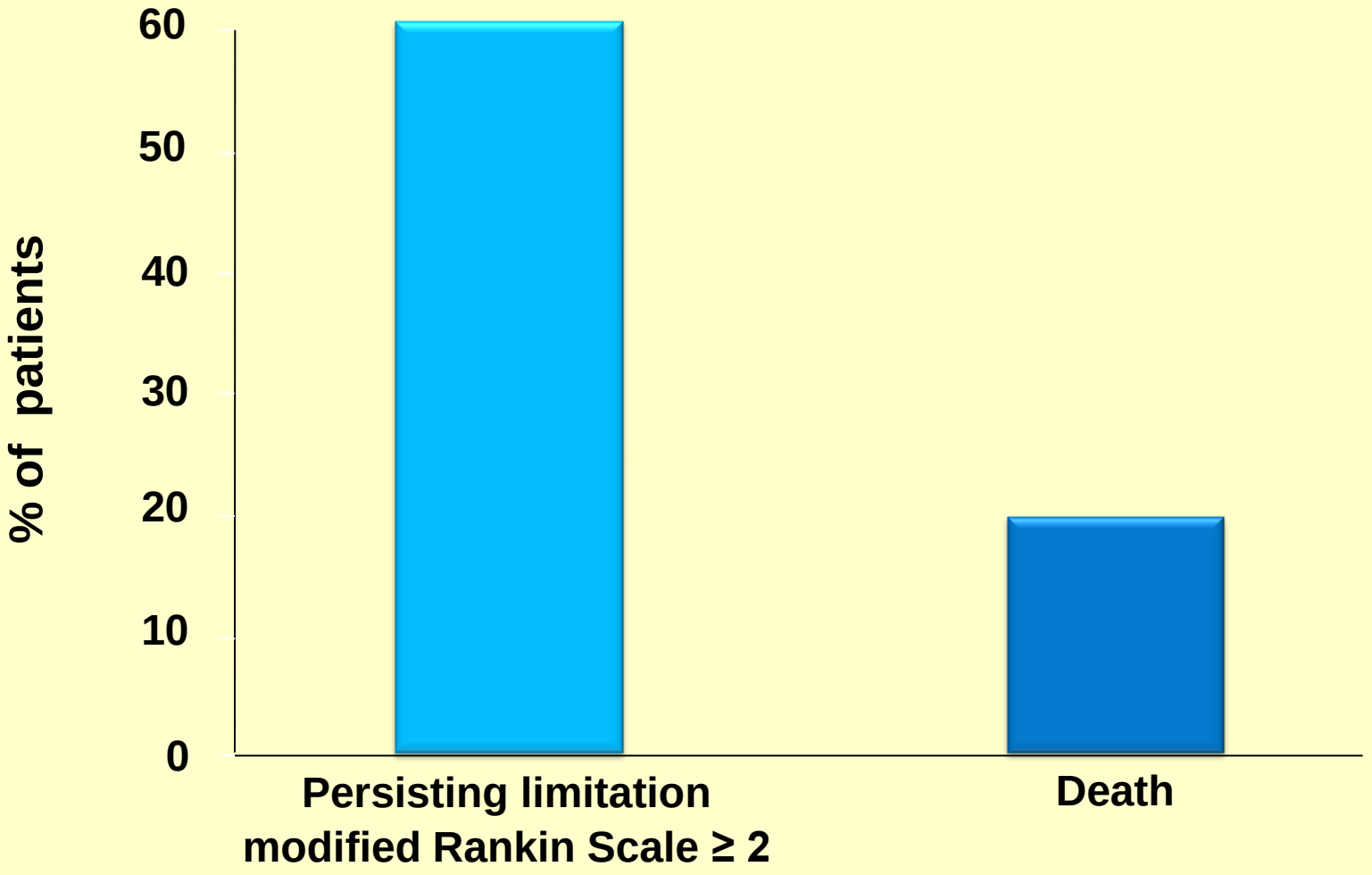
AF is a disease of older age patients



Go AS et al. JAMA 2001;285:2370-2375

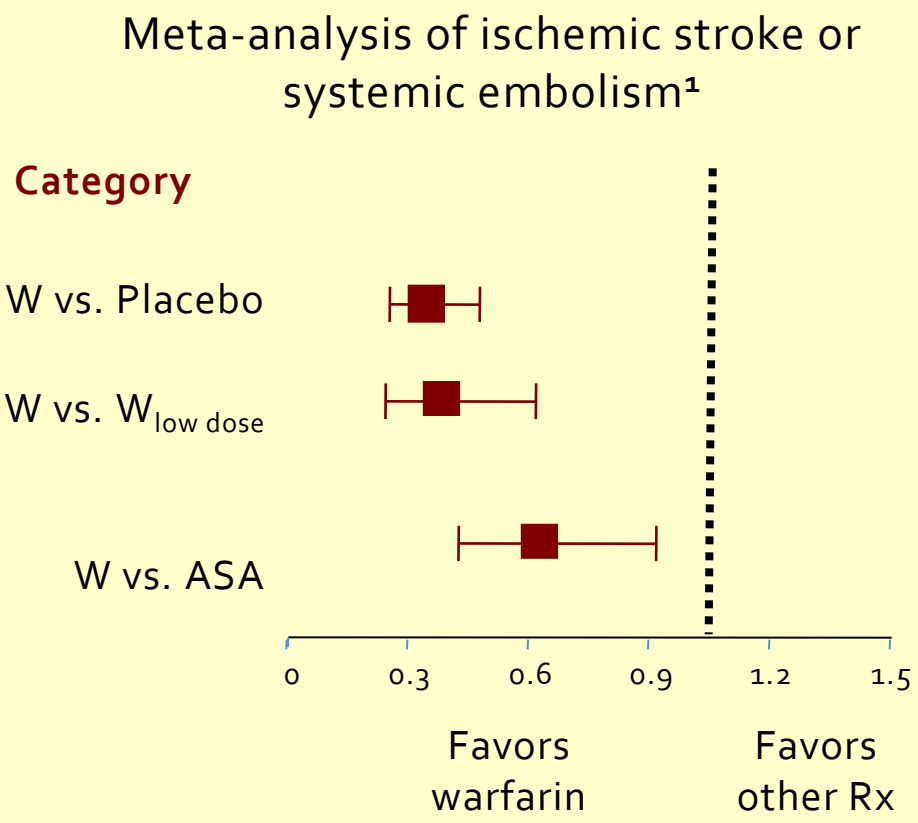
Severity of strokes in patients with AF

Clinical sequellae of a first ischemic stroke in AF patients (n=597)



Gladstone DJ et al. *Stroke*. 2009; 40: 235-240

Stroke Prevention with ASA and Warfarin: Meta-analysis

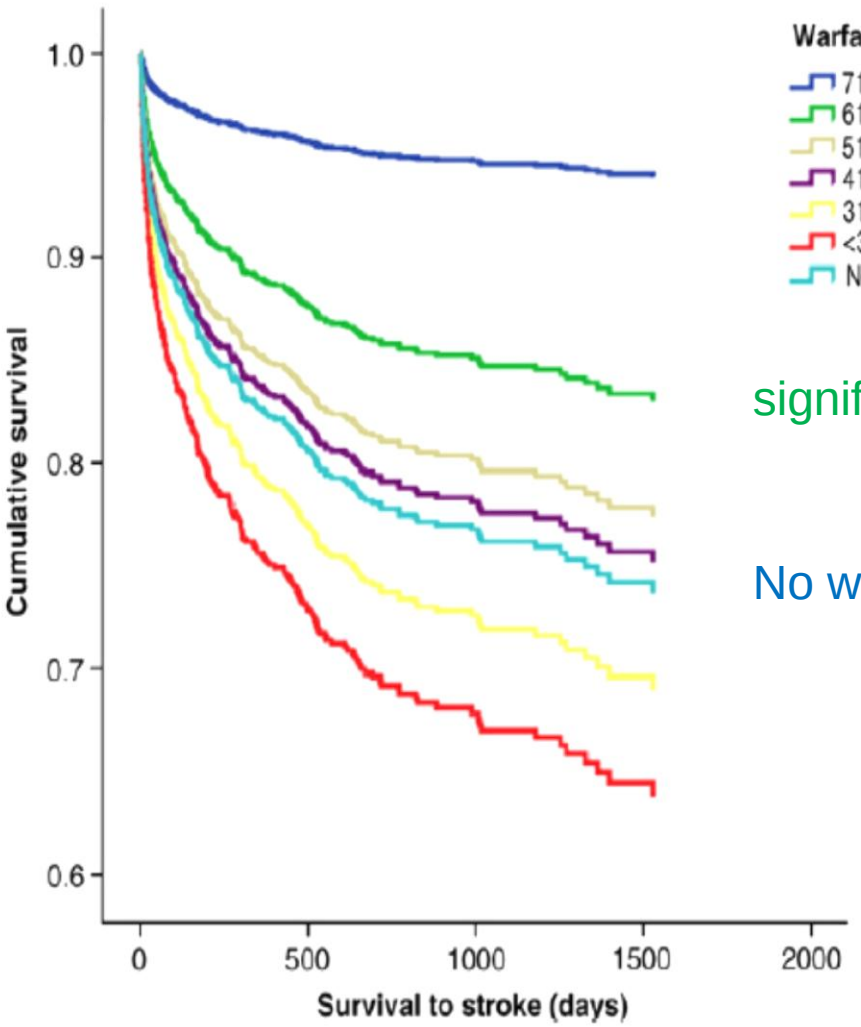


Study	Year	Size	Comparator	IS or SE
AFASAK-I	1989	1,007	W, A, P	44
BAATAF	1990	420	W, P	15
CAFA	1991	378	W, P	18
SPAF I	1991	421	W, P	24
SPINAF	1992	525	W, P	30
EAFT	1993	439	W, P	75
SPAF II	1994	715	W, A	35
SPAF II eld.	1994	385	W, A	32
SPAF III	1996	1,044	W, W_{ld}+A	55
AFASAK II	1998	677	W, A, W_{ld}, W_{ld}+A	26
MWNAF	1998	303	W, W_{ld},	7
PATAF	1999	394	W, A, W_{ld}	14
Evans	2001	386	W, A	52

ASA=acetylsalicylic acid; IS=ischemic stroke; SE=systemic embolism

Modif. after Lip GYH, et al. *Thromb Res.* 2006;118:321–333, with permission from Elsevier.

Time in Therapeutic Range (TTR)



signif. event reduction

No warfarin

Fig. 1. Cox proportional hazards model for survival to post atrial-fibrillation stroke for patients at moderate or high risk of stroke $CHADS_2 \geq 2$ by level of warfarin control.

Morgan et al. (2009) Thromb Res 124: 37-41

Expansion of the $CHADS_2$-Score

$CHADS_2 \rightarrow CHA_2DS_2VASc$

$CHADS_2$

Cardiac failure	1
Hypertension	1
Age > 75	1
Diabetes	1
Stroke or TIA	2

max. 6 points

Weak differentiation in

Low-Risk-Patients

Some risk factors not covered

CHA_2DS_2VASc

Cardiac failure or LVEF<=40%	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke/TIA/ Thromboembolism	2
Vascular disease	1
Age 65 - 74	1
Sex (female)	1

max. 9 points

European Heart Journal (2010) 31, 2369–2429

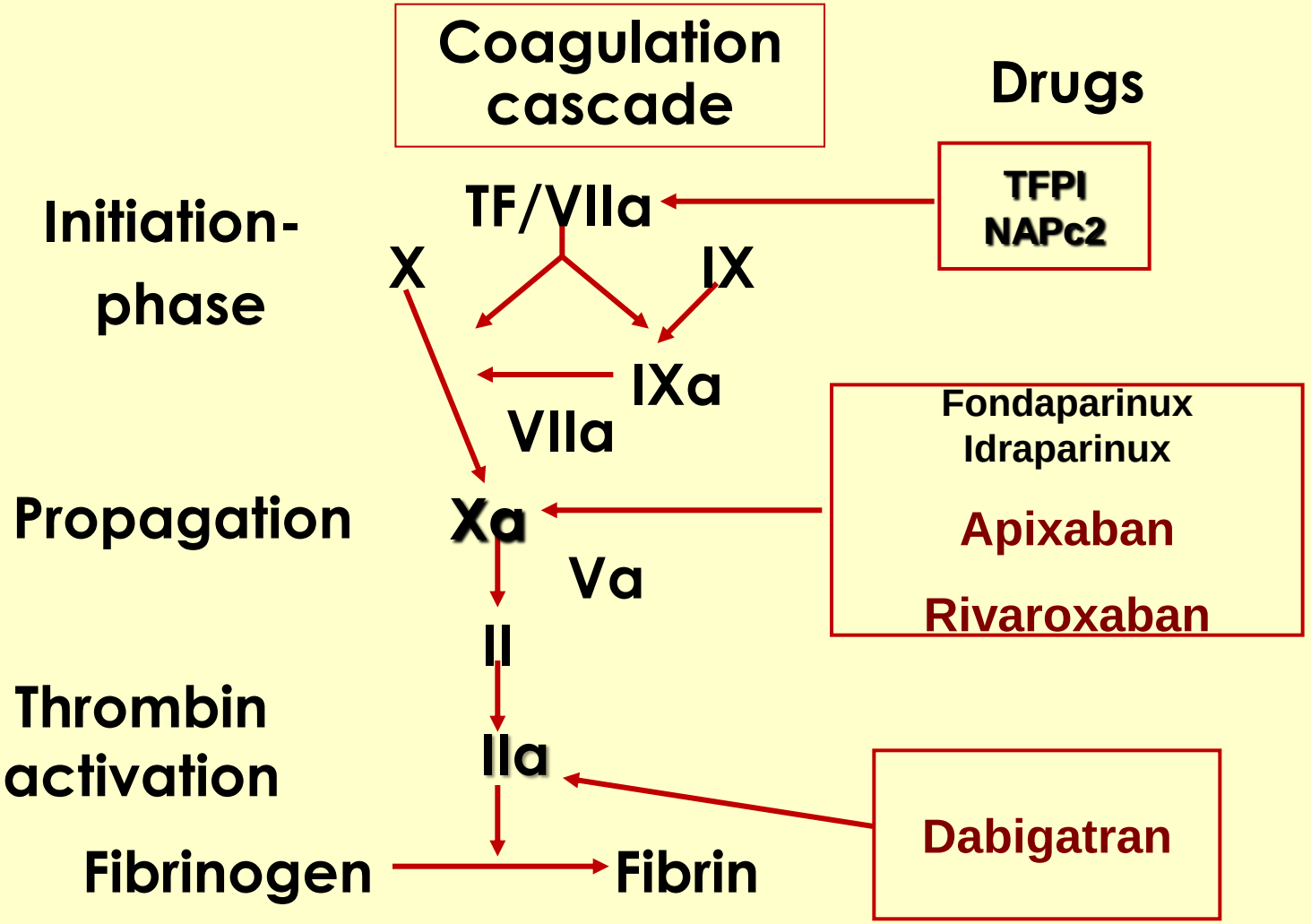
Limitations of VKA-therapy

VKA-therapy has severe limitations which hinder it's utilisation in clinical practical

- Non predictable individual sensitivity
- Narrow therapeutic window (INR-Bereich 2-3)
- Regular coagulation monitoring
- Slow onset / slow offset
- Frequent dose adaptations
- Multiple food interactions (salads, green vegetables)
- Multiple drug interactions
- Warfarin-resistance

Ansell J, et al. *Chest* 2008;133;160S-198S

Mechanism of Action of NOACs (New Oral AntiCoagulants)



Adapted accord. to Weitz I, Hirsh J. *Chest*. 2001;119:95S-107S.

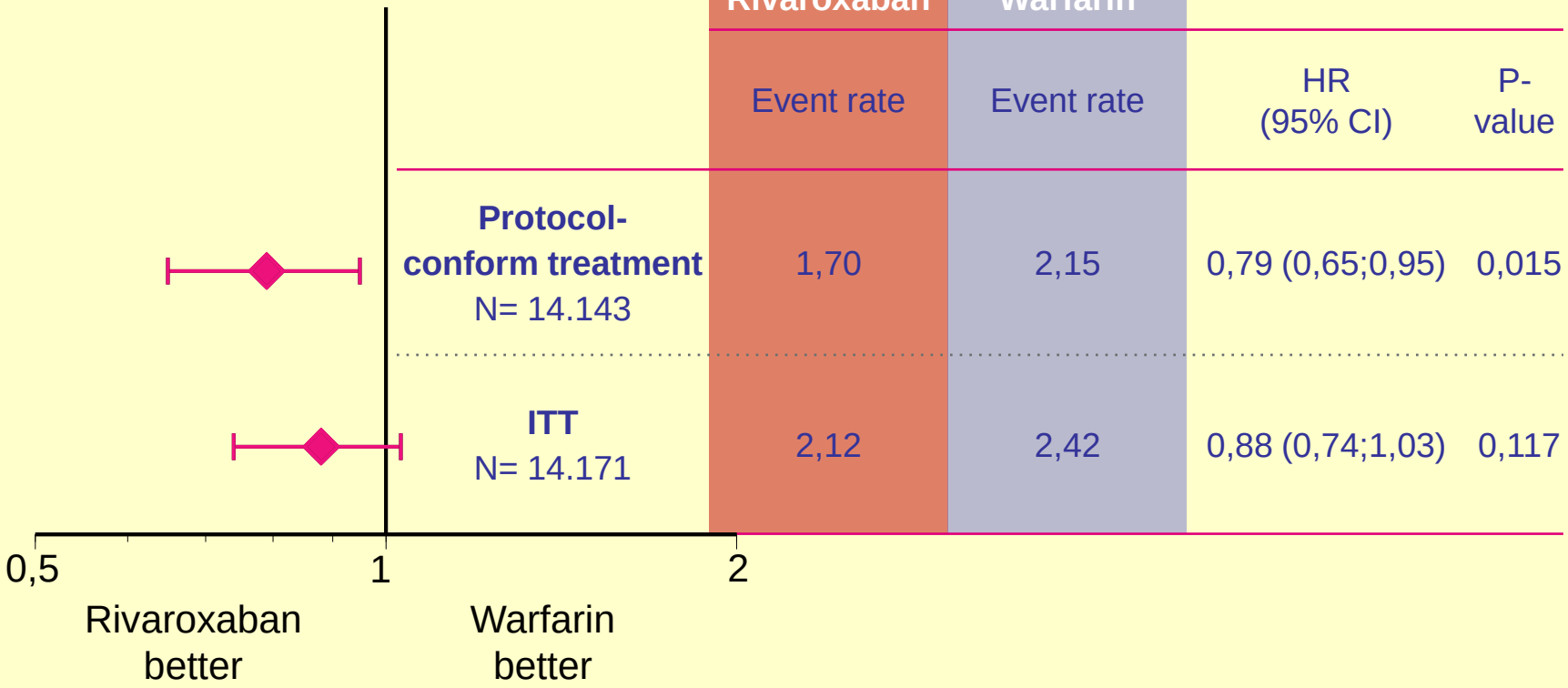
Pharmacology of novel anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Selective direct FIIa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor	Competitive inhibitor of FXa
Bioavailability	Oral prodrug with poor oral bioavailability	Good oral bioavailability	Good oral bioavailability	Good oral bioavailability
T½	12 - 14 hours (80% renal excretion)	6 - 9 hours	12 hours	9 -11 hours
Dosing	Twice daily	Once daily	Twice daily	Once daily
Time to max effect	1-4h	1-4h	1-4h	1-4 hr

Eriksson BI, et al. *Clin Pharmacokinet.* 2009;48:1-22.

ROCKET-AF

Primary Efficacy-Endpoint
Stroke and non-CNS embolism



	Rivaroxaban Event rate	Warfarin Event rate	HR (95% CI)	P-value
Protocol-conform treatment N= 14.143	1,70	2,15	0,79 (0,65;0,95)	0,015
ITT N= 14.171	2,12	2,42	0,88 (0,74;1,03)	0,117

Event rates per 100 patient years
Based on safety-cohort or Intention-to-Treat (ITT)

KW Mahaffey, AHA Scientific Sessions Nov.. 2010

ROCKET-AF

Important secondary efficacy endpoints

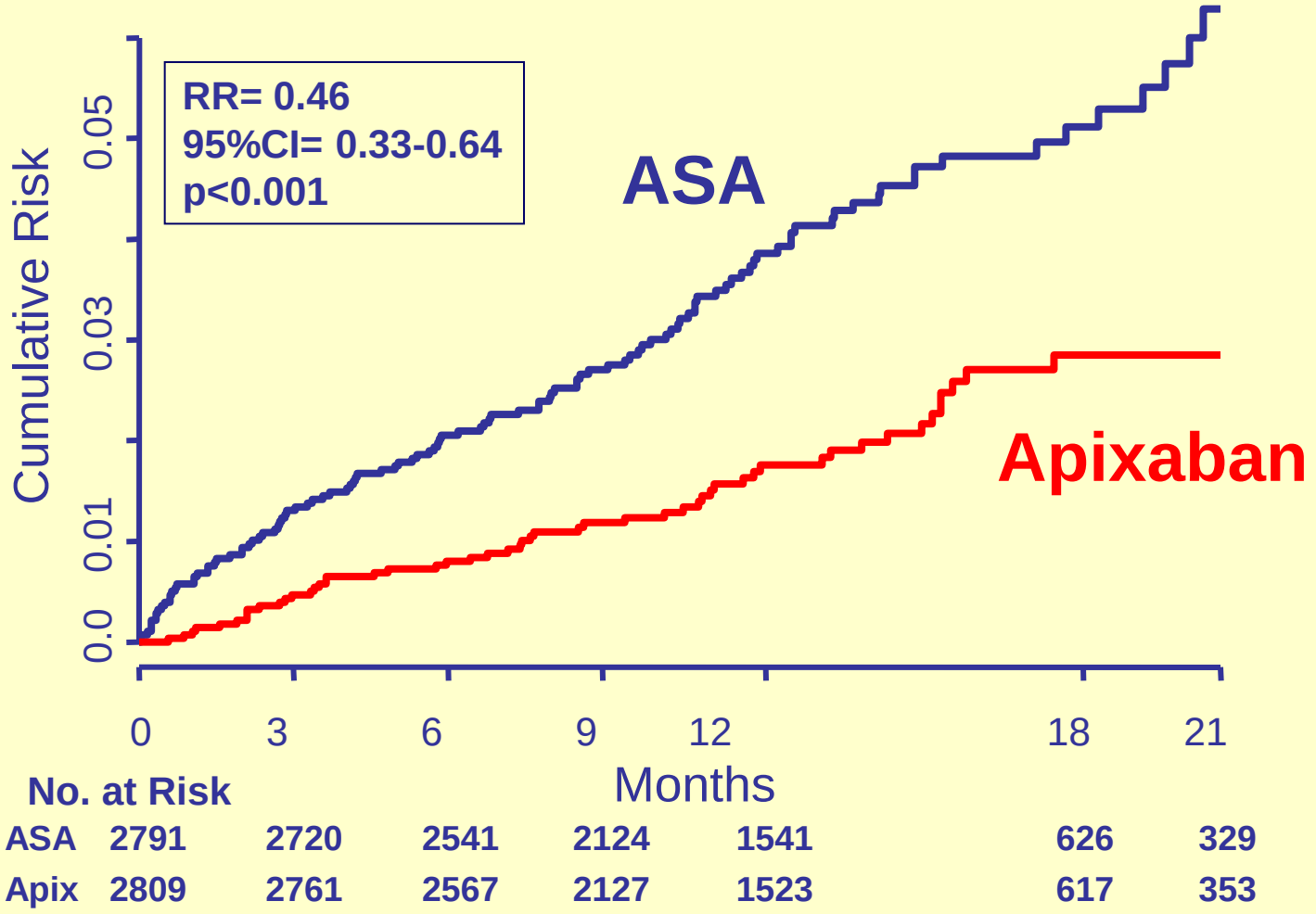
	Rivaroxaban event rate	Warfarin event rate	HR (95% CI)	p-value
Vascular death, stroke, embolism	4,51	4,81	0,94 (0,84; 1,05)	0,265
Stroke: hemorrhagic Ischemic unknown origin	 0,26 1,62 0,15	 0,44 1,64 0,14	 0,58 (0,38; 0,89) 0,99 (0,82; 1,20) 1,05 (0,55; 2,01)	 0,012 0,916 0,871
Non CNS embolism	0,16	0,21	0,74 (0,42; 1,32	0,308
Myocardial infarction	1,02	1,11	0,91 (0,72; 1,16)	0,464
Total mortality vascular non-vascular unknown cause	4,52 2,91 1,15 0,46	4,91 3,11 1,22 0,57	0,92 (0,82; 1,03) 0,94 (0,81; 1,08) 0,94 (0,75; 1,18) 0,80 (0,57; 1,12)	0,152 0,350 0,611 0,195

Event rate rates per 100 patients years
Based on Intention-to-Treat cohort

KW Mahaffey , AHA Scientific Sessions Nov.. 2010

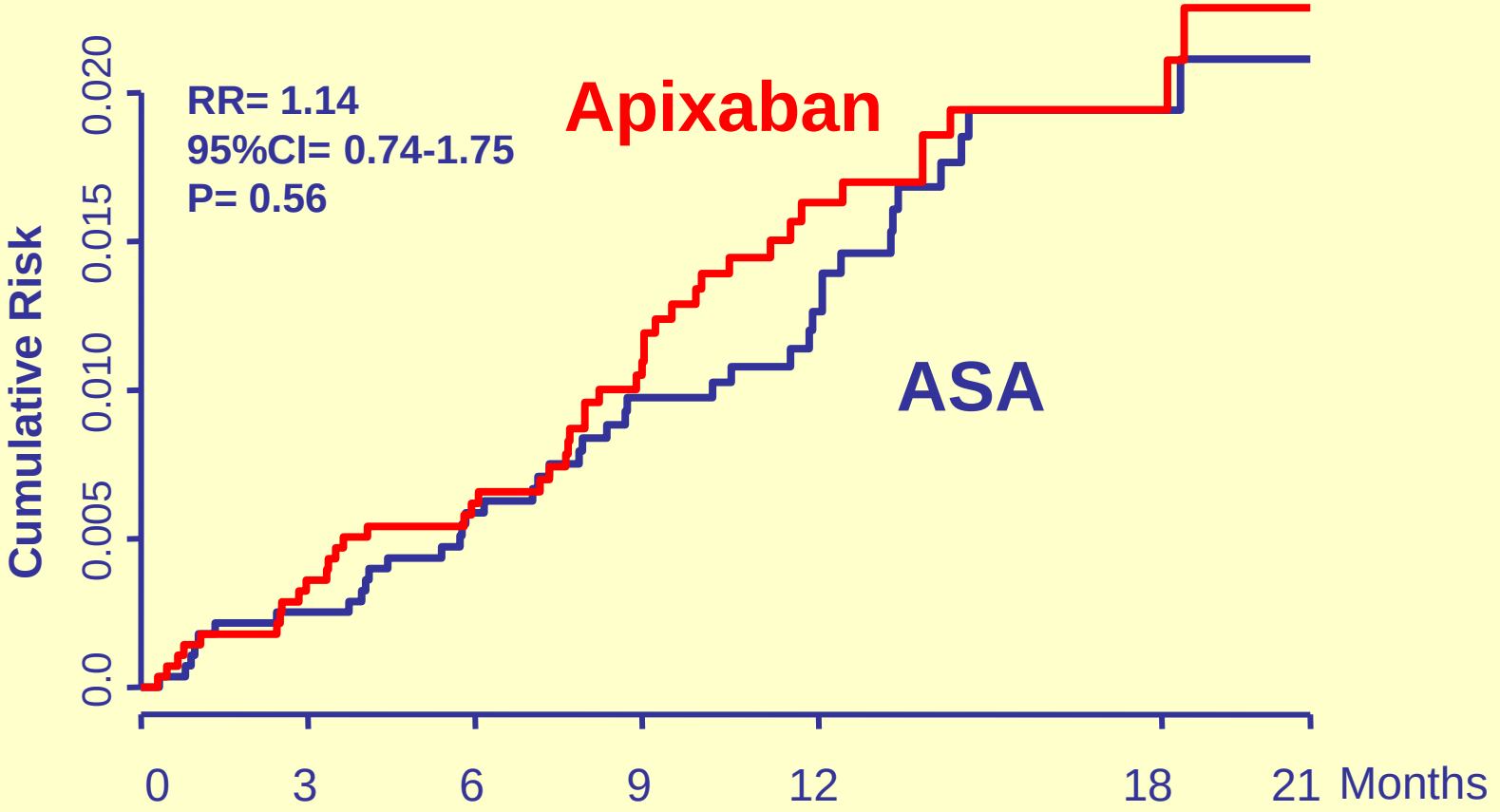
AVERROES

Stroke or Systemic Embolic Event



S. Connolly, ESC 2010

AVERROES
Major Bleeding



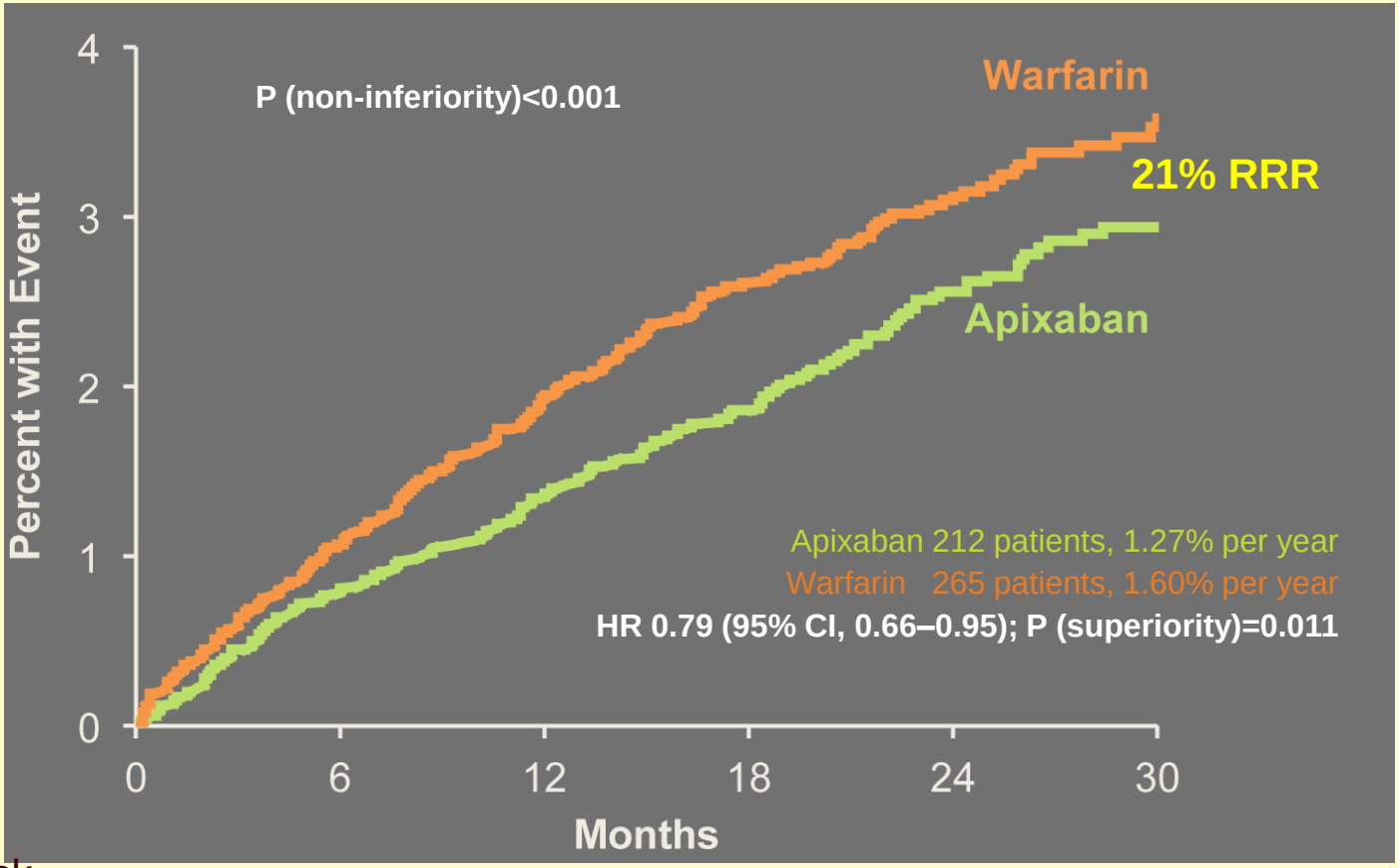
No. at Risk

ASA	2791	2744	2572	2152	1570	642	340
Apix	2809	2763	2567	2123	1521	622	357

S. Connolly, ESC 2010

ARISTOTLE: Primary Outcome

Stroke (ischemic or hemorrhagic) or systemic embolism

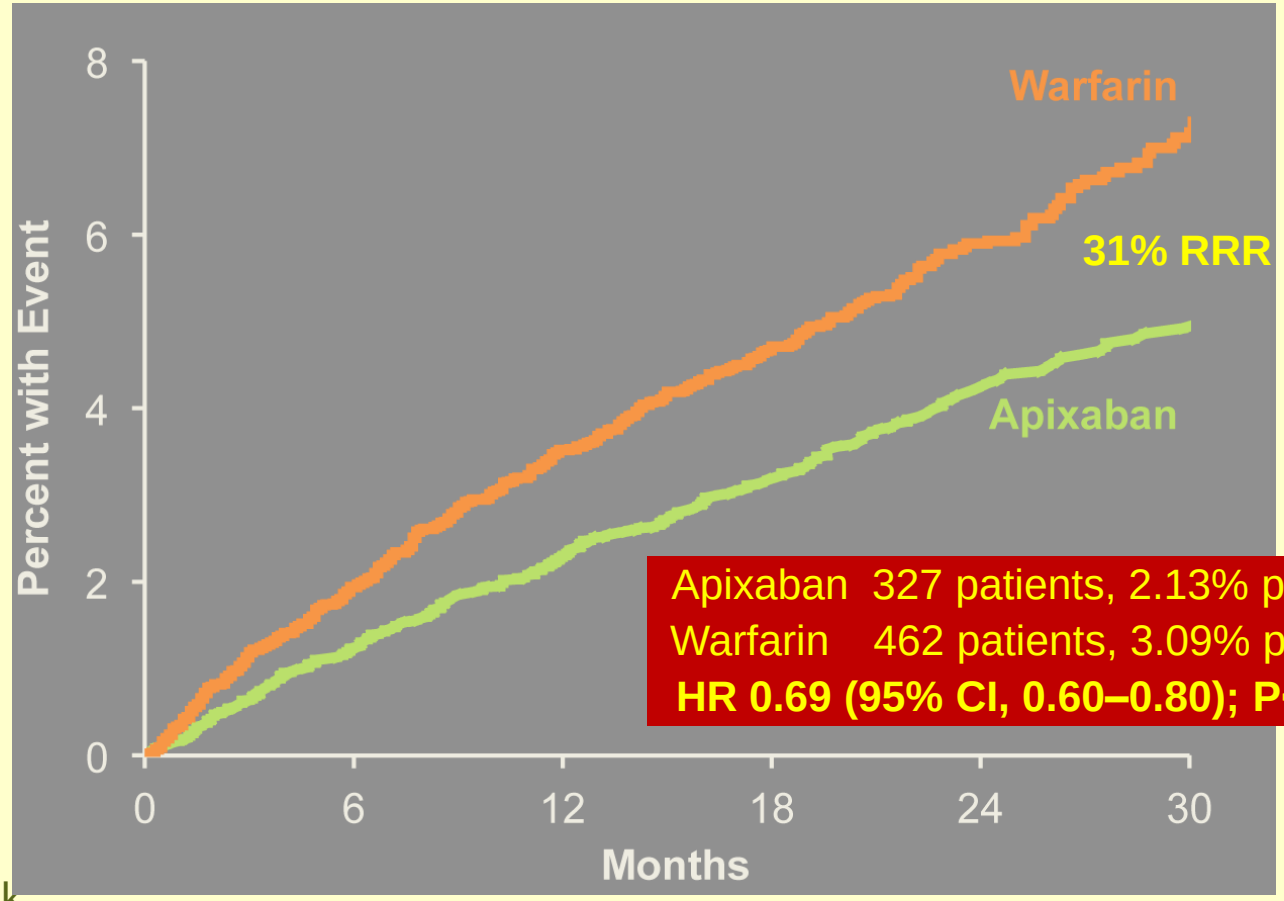


No. at Risk

Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

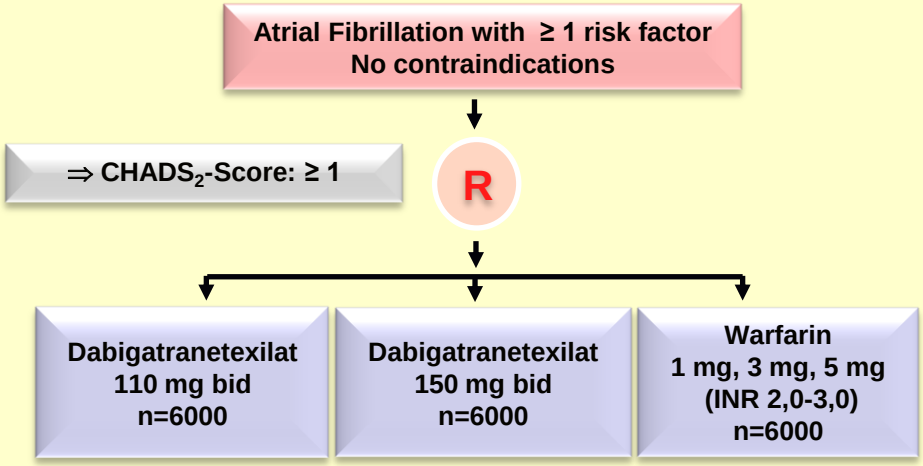
ARISTOTLE: Major Bleeding

ISTH definition

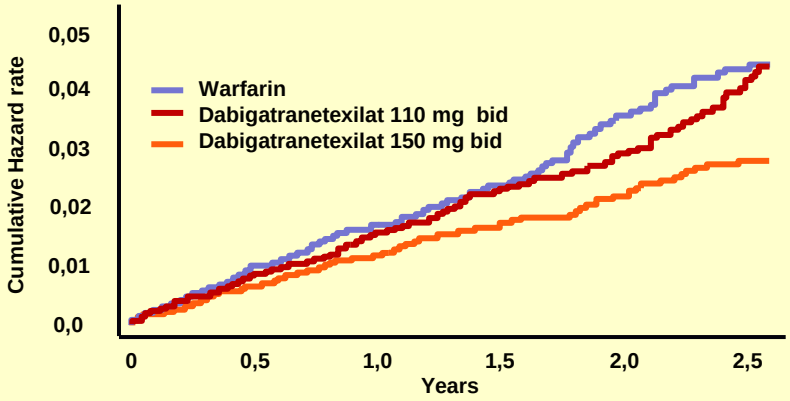


No. at Risk						
Apixaban	9088	8103	7564	5365	3048	1515
Warfarin	9052	7910	7335	5196	2956	1491

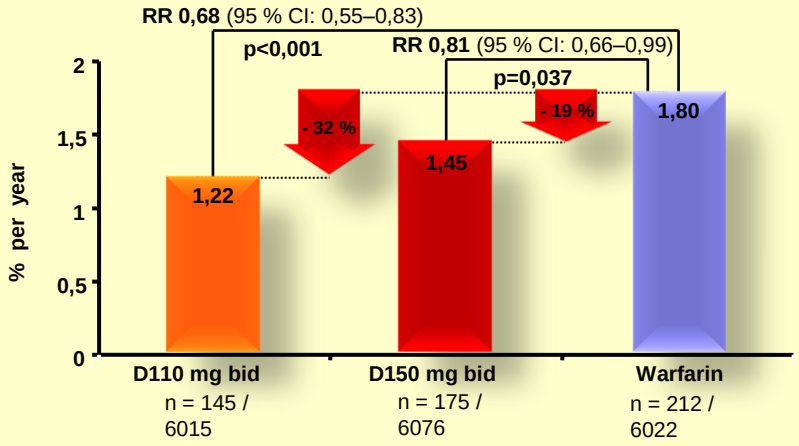
RE-LY Results



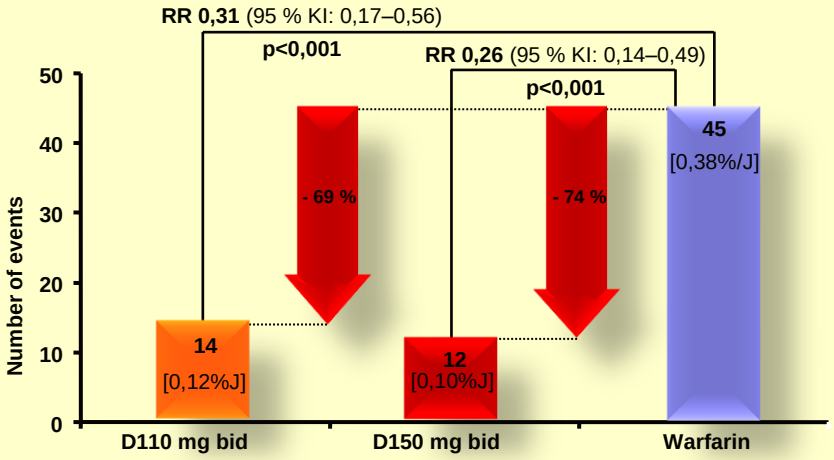
Primary Endpoint: Kaplan-Meier-Graph



Life threatening bleeding
[Component of the combined safety endpoint]



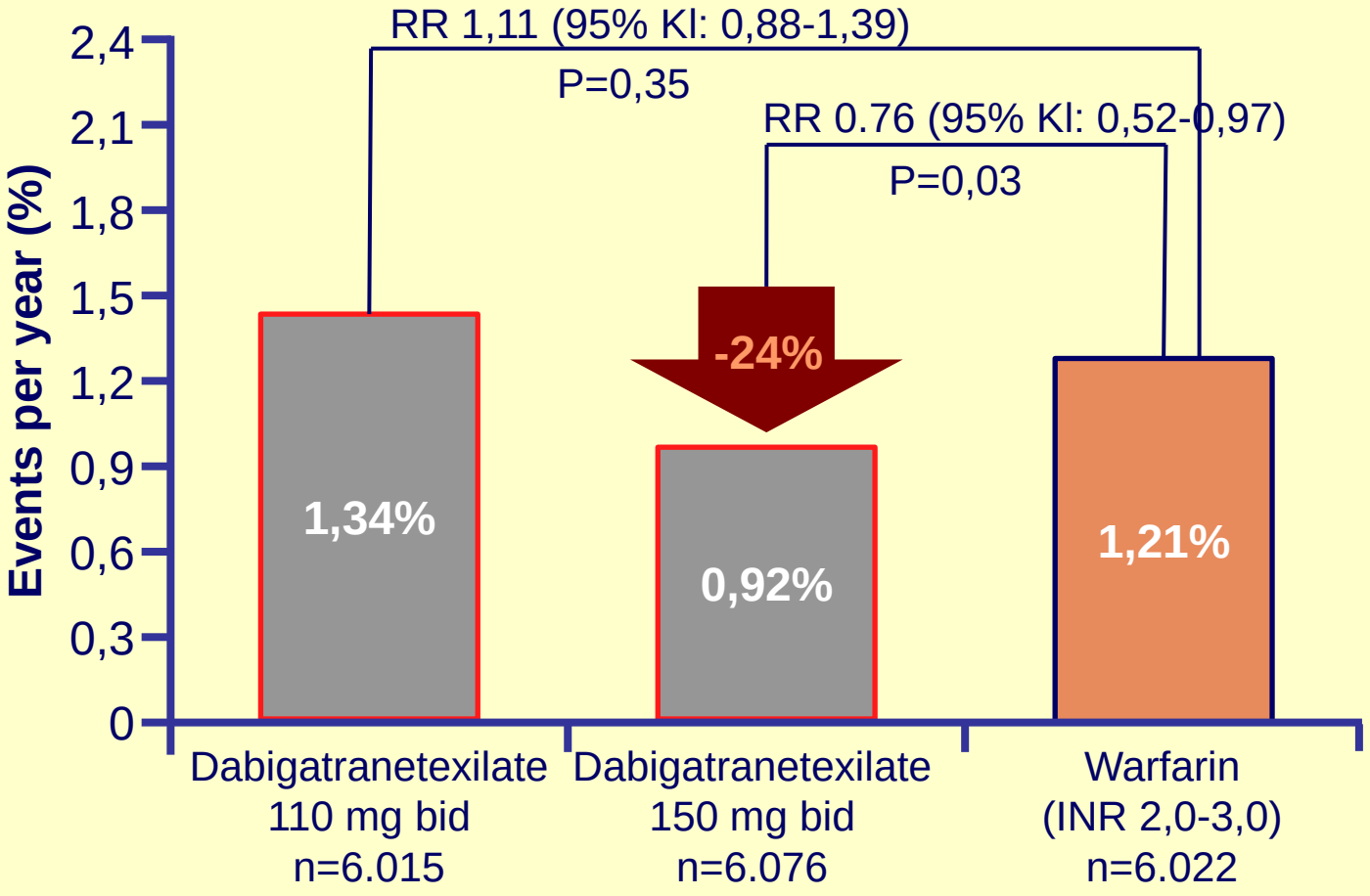
Intracerebral hemorrhages



NEJM, 2009, Volume 361:1139-1151

RE-LY® -Trial:

Prevention of ischemic strokes*

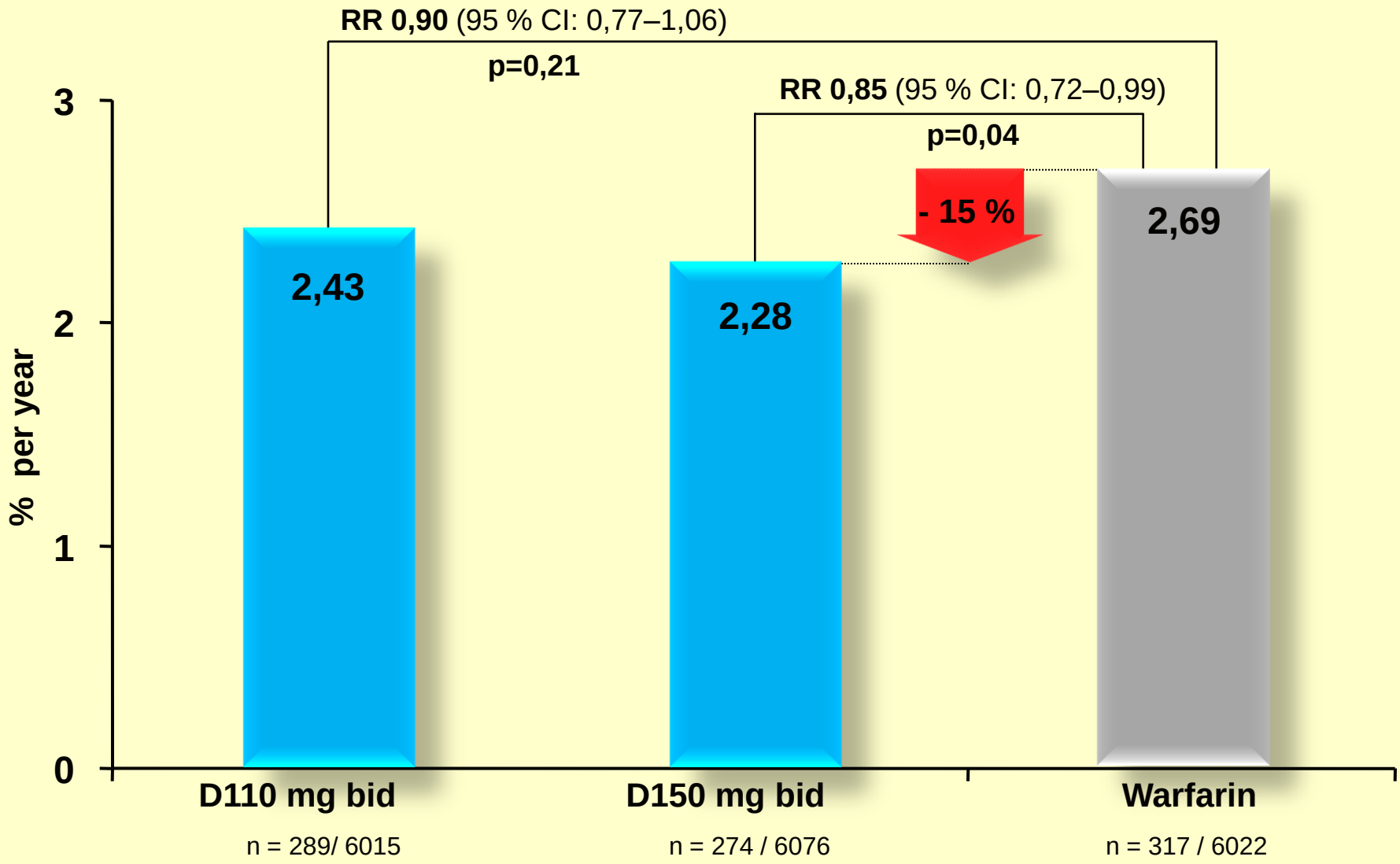


* Ischemic and non specified strokes

Connolly SJ et al. *N Eng J Med* 2009; 361: 1139-1151
Connolly SJ et al. *N Eng J Med* 2010; 363: 1875-1876

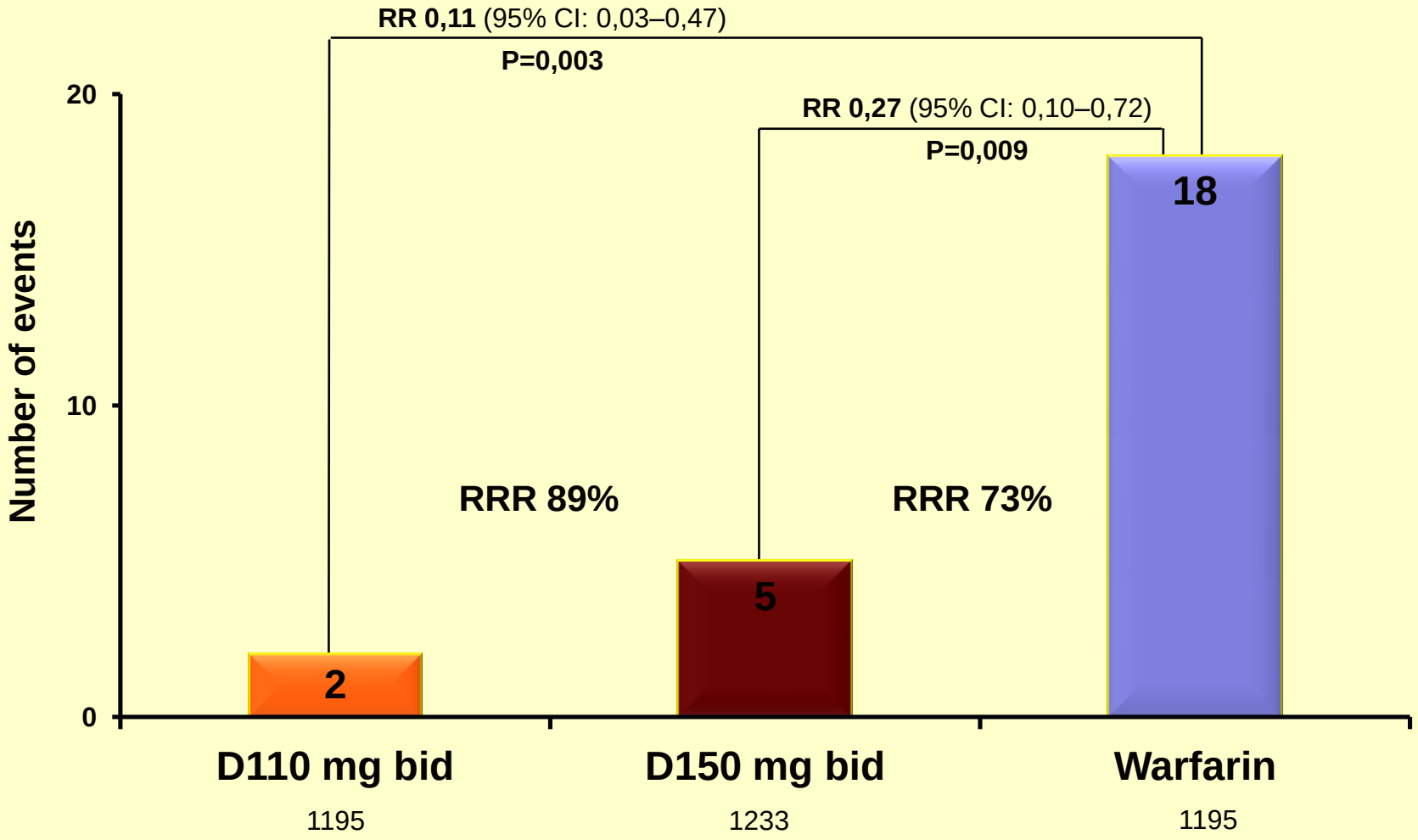
RE-LY® - Trial

Cardiovascular Mortality



N Engl J Med 2009; 361:1139-1151

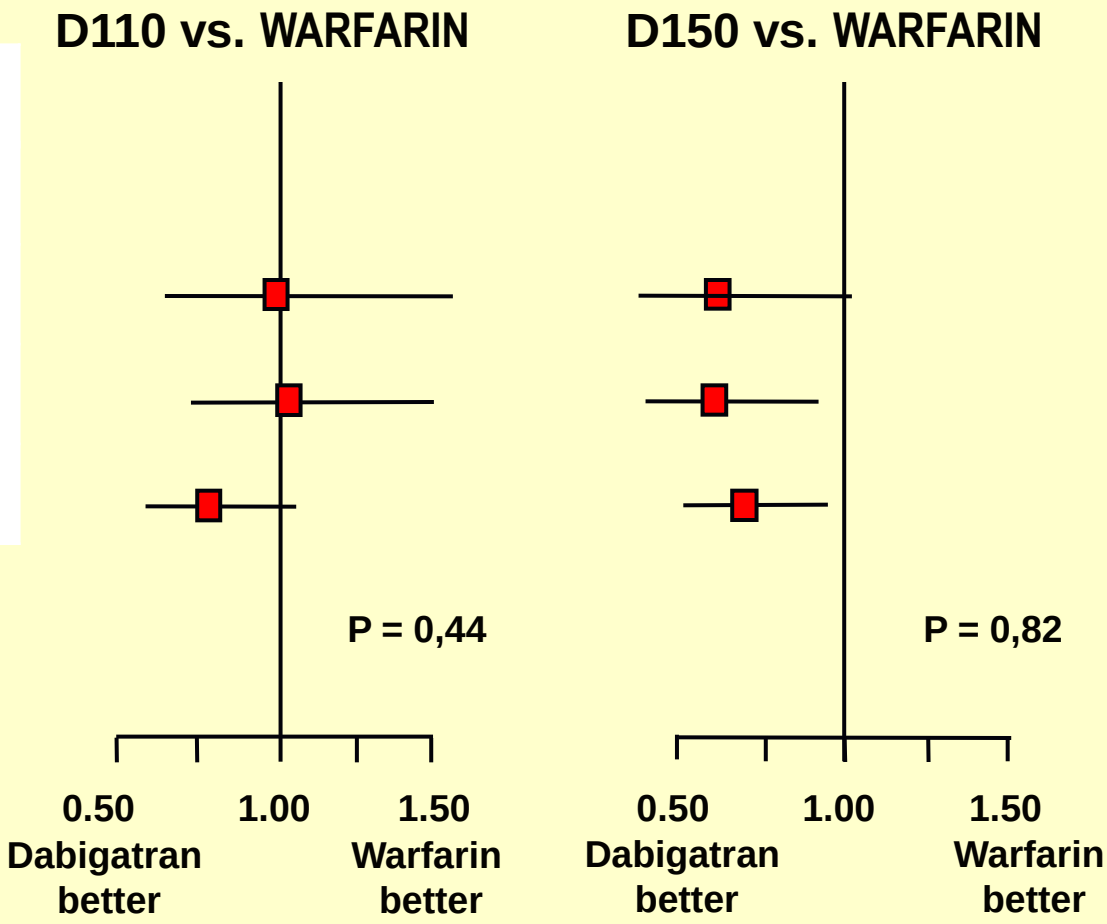
Hemorrhagic Stroke in Patients with a previous Stroke or TIA



N Engl J Med 2009; 361:1139-1151

$CHADS_2$ - Risk-Cohorts
Stroke and systemic embolism (SE)

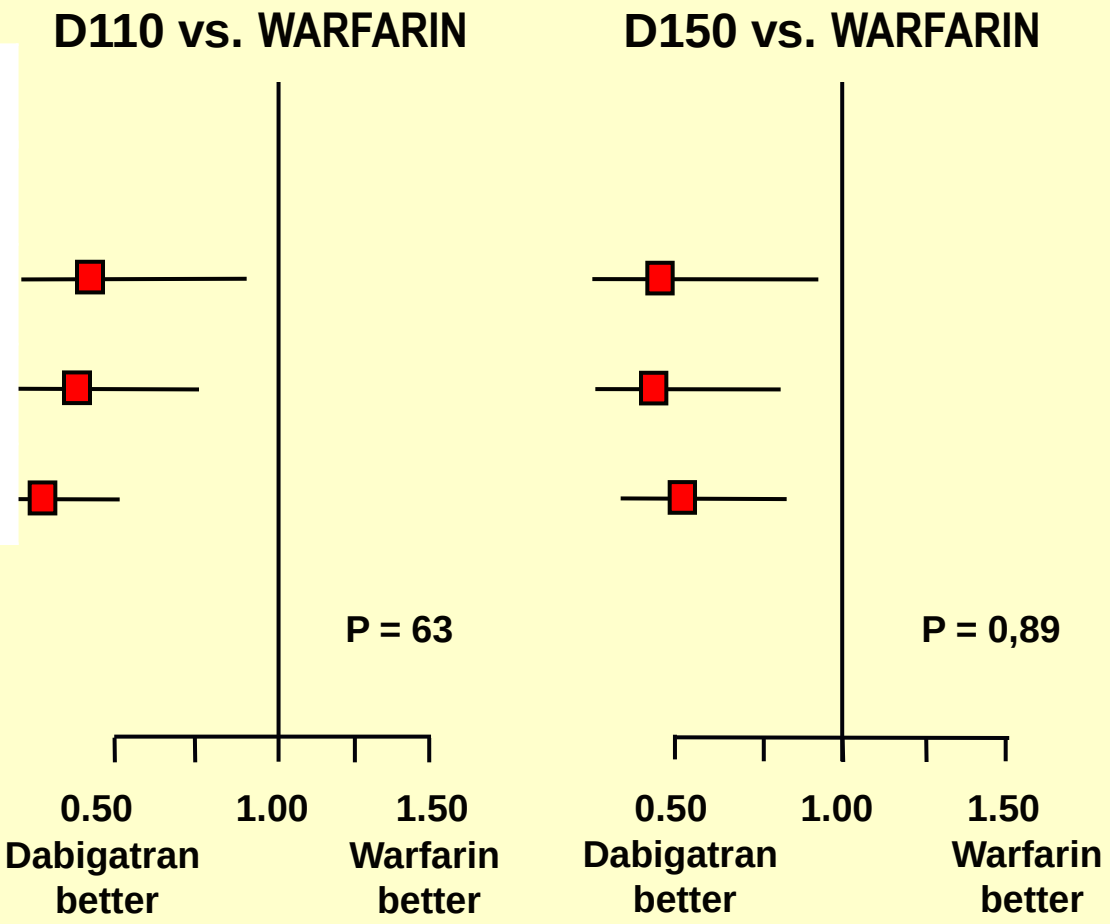
	Annual rate, %		
CHADS2	D110	D150	Warfarin
0-1	1,06	0,65	1,05
2	1,43	0,84	1,38
3-6	2,12	1,88	2,68



N Engl J Med 2009; 361:1139-1151

$CHADS_2$ - Risk-Cohortsn
Intracranial bleeding

	Annual rate, %		
CHADS2	D110	D150	Warfarin
0-1	0,20	0,20	0,51
2	0,22	0,24	0,64
3-6	0,26	0,49	1,07



N Engl J Med 2009; 361:1139-1151

RE-LY unwanted drug effects

	Dabigatran 110 mg bid (%)	Dabigatran 150 mg bid (%)	Warfarin (%)
Dyspepsia	11,8*	11,3*	5,8
Dyspnoe	9,3	9,5	9,7
Dzziness	8,1	8,3	9,4
Peripheral edema	7,9	7,9	7,8
Fatigue	6,6	6,6	6,2
HCough	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
Urinary tract infection	4,5	4,8	5,6
Atrial fibrillation	5,5	5,9	5,8
Upper respiratory tract infection	4,8	4,7	5,2

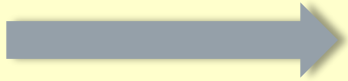
Unwanted side effect with a prevalence of > 5 %; *p<0,001 vs. Warfarin

N Engl J Med 2009; 361:1139-1151

Practical issues: Reduced kidney function

(CrCl 30-80 ml/min)

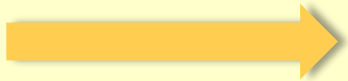
No dose adaptation



150 mg bid

(CrCl 30-50 ml/min) plus high bleeding risk

Dose adaptation may be considered



or

150 mg bid or 110 bid

(CrCl < 30 ml/min)

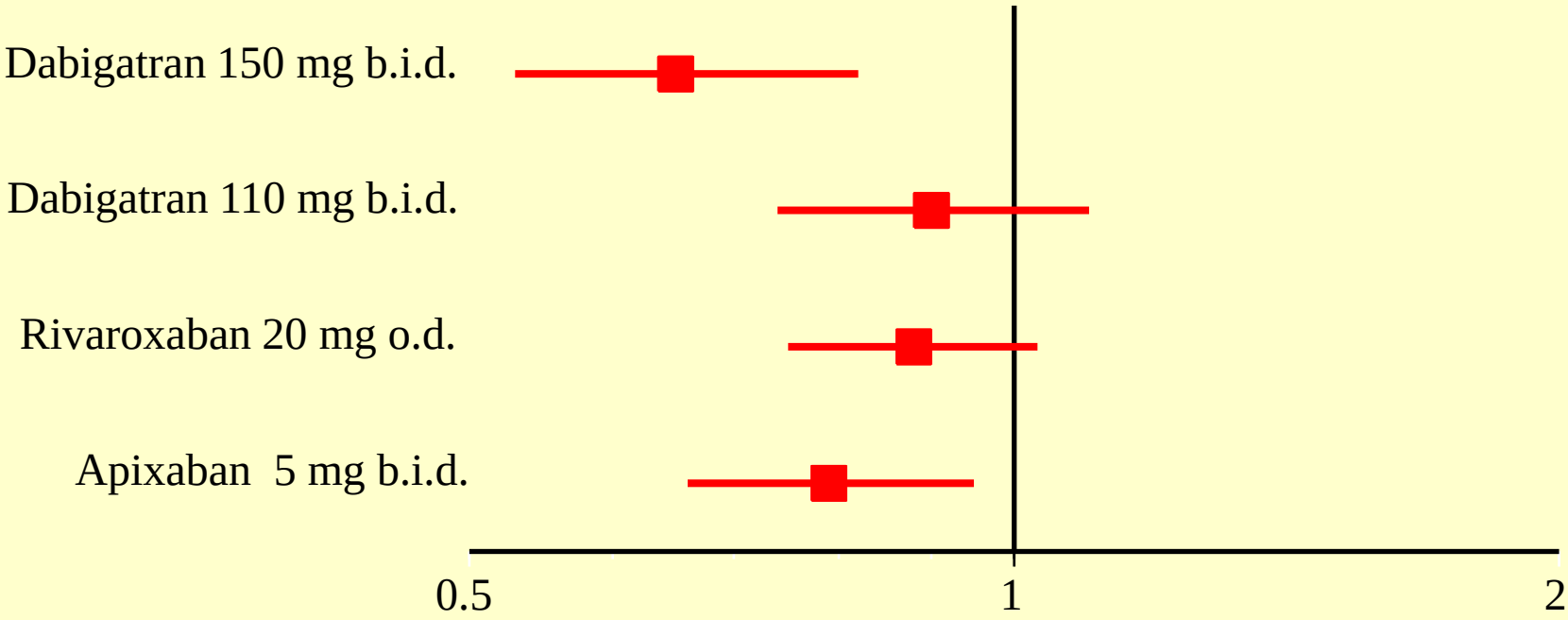
Contra indicated

Data per 100.000 patient years, from March 2008 – 31.10.2011	Cases calculated per 100.000 patient years according to the RE-LY* population		Registered suspected cases by per 100.000 patient years
	Pradaxa® bid 150mg (110mg)	Warfarin	
All severe bleeding events	3.320 (2.870)	3.570	594 (5,6 times less than expected accord. To Pradaxa 150 mg in RE-LY)
Myocardial infarction	810 (820)	640	31 (26 times lessthan expected)
Total deaths of any cause	3.640 (3.760)	4.130	169 (21,5 times less than expected)
From these fatal bleedings	230 (190)	330	63 (3,7 times less than expected)

Press release Boehringer Ingelheim, November 2011

New antithrombotic therapies compared to warfarin

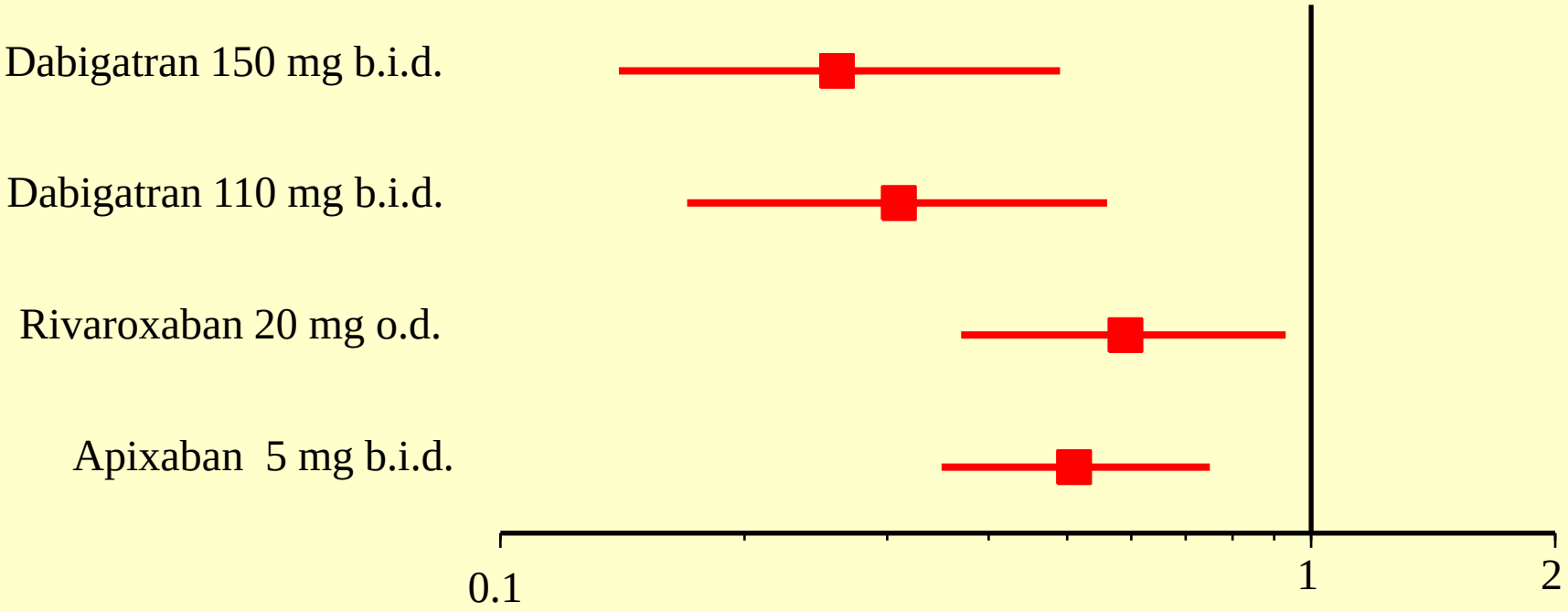
I° Endpoint:
Stroke or systemic embolism



Connolly S et al NEJM 2009; Patel M et al NEJM 2011; Granger C et al NEJM 2011

New antithrombotic therapies compared to warfarin

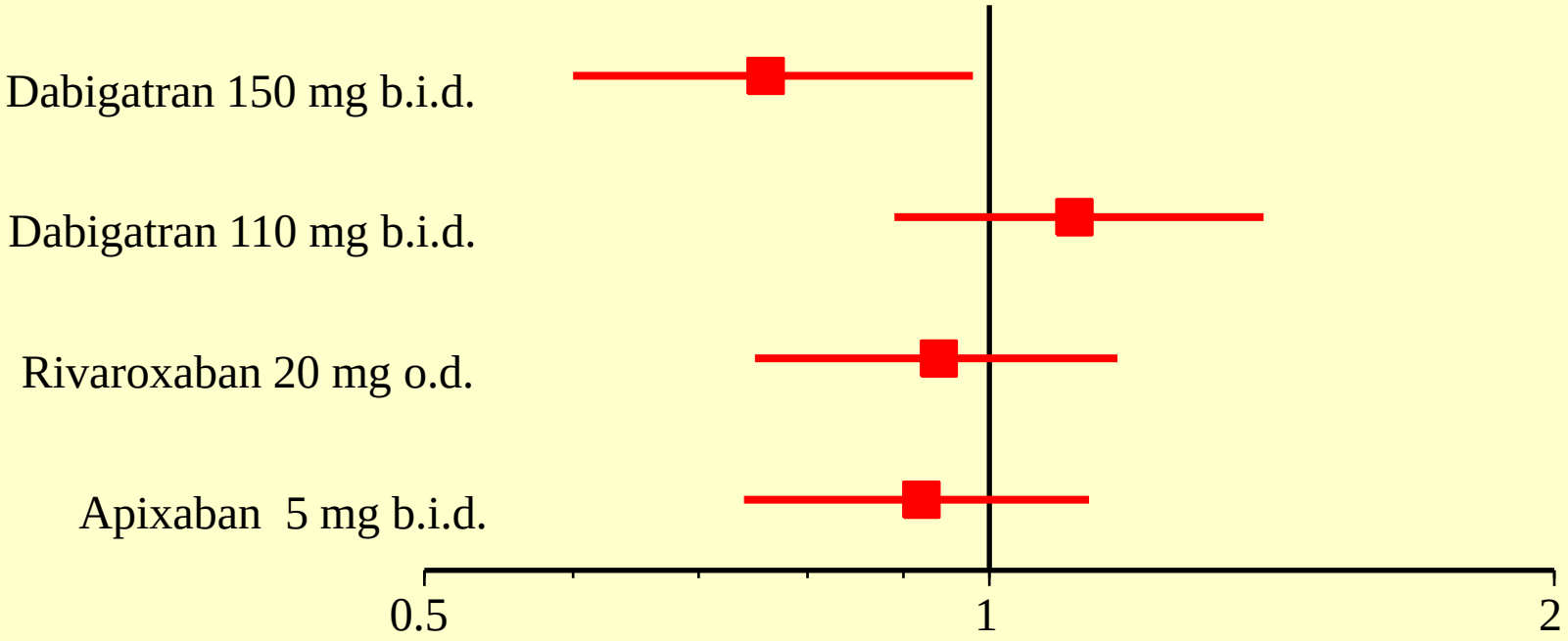
Hemorrhagic stroke



Connolly S et al NEJM 2009; Patel M et al NEJM 2011; Granger C et al NEJM 2011

New antithrombotic therapies compared to warfarin

Stroke of ischemic or unknown origin



Connolly S et al NEJM 2009; Patel M et al NEJM 2011; Granger C et al NEJM 2011

Direct Thrombin Inhibitors in Prevention of Ischemic Stroke

- New anticoagulants offer improved efficacy and improved safety as OAC
- OAC with VKA is problematic (Interactions, Monitoring, Onset-Offset)
- ESC AF-Guidelines: More patients with an indication for OAC- Tx
- F.Xa Antag. and thrombin antag. are already or soon available alternatives
- Dabigatran (150 mg bid) is superior to warfarin with significant decrease in ischemic strokes (-24%), CV mortality (-15%), ICH (-74%) and all bleedings (-9%)
- The bleedings observed in clinical practice are below the range of statistical expectations and very often result from off-label therapy (hemodialysis patients, CrCl < 30 ml/Min (Warning Letter stressing the known limitations for renal failure patients)

Best regards from Berlin