ATRIAL FIBRILLATION (AF)

Anticoagulant therapy, coumadines or direct antithrombins

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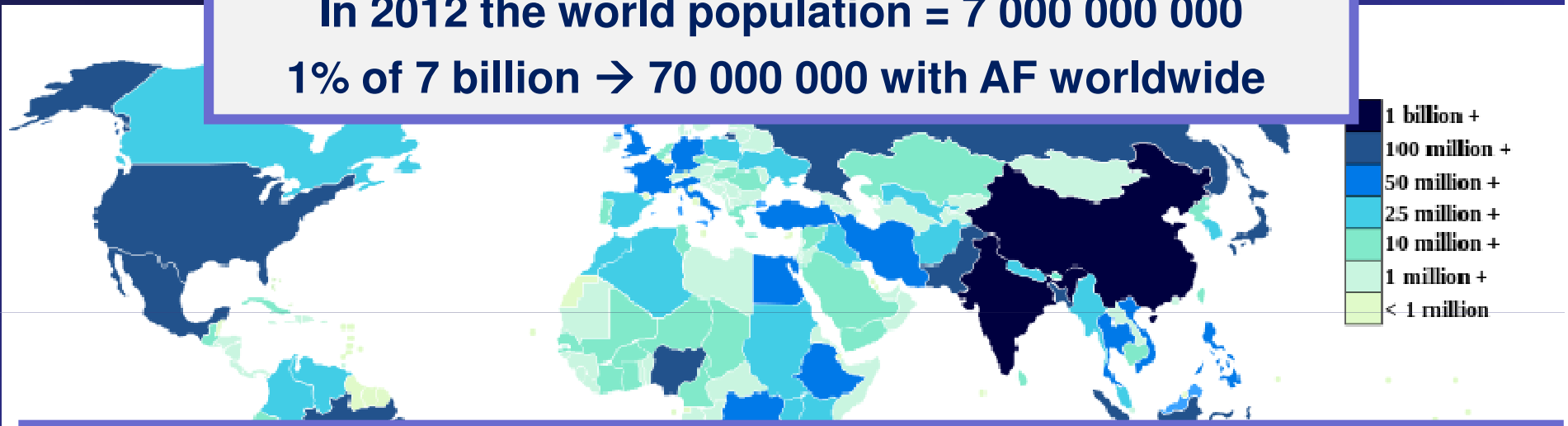
Global burden of AF and of AF-related strokes

1% of the general population is estimated to have AF

In 2012 the world population = 7 000 000 000

1% of 7 billion → 70 000 000 with AF worldwide



15 000 000 strokes per year worldwide

Up to ~1/5 of strokes are AF-related

1/5 of 15 000 000 → 3 000 000 AF-related strokes per yr

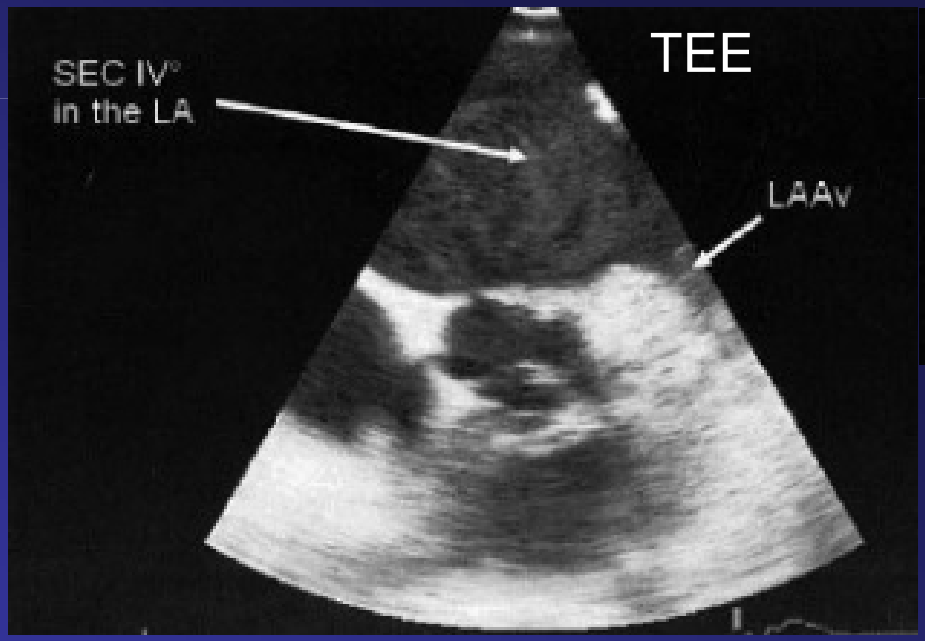
The average annual stroke rate in untreated nonvalvular (NV)AF is ~ 5%

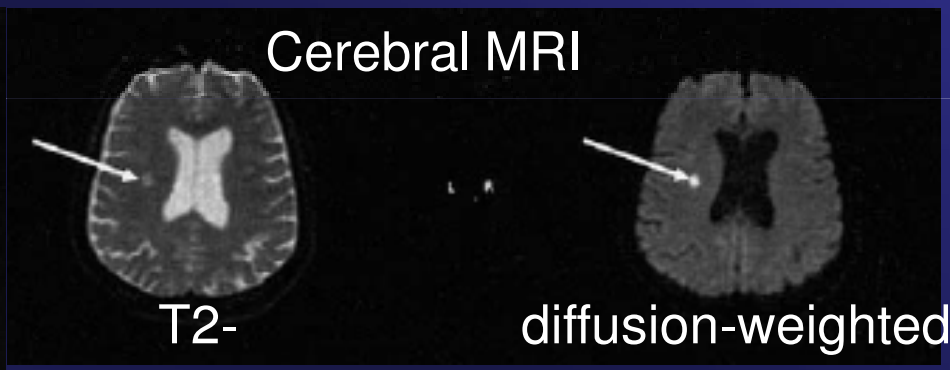
5% of 70 million → 3 500 000 AF-related strokes per yr

Camm et al. EHJ 2010;31:2369-429 - en.wikipedia.org/wiki/World_population
WHO world health report 2002 - 2011 Canadian AF Guidelines

AF-related strokes are serious

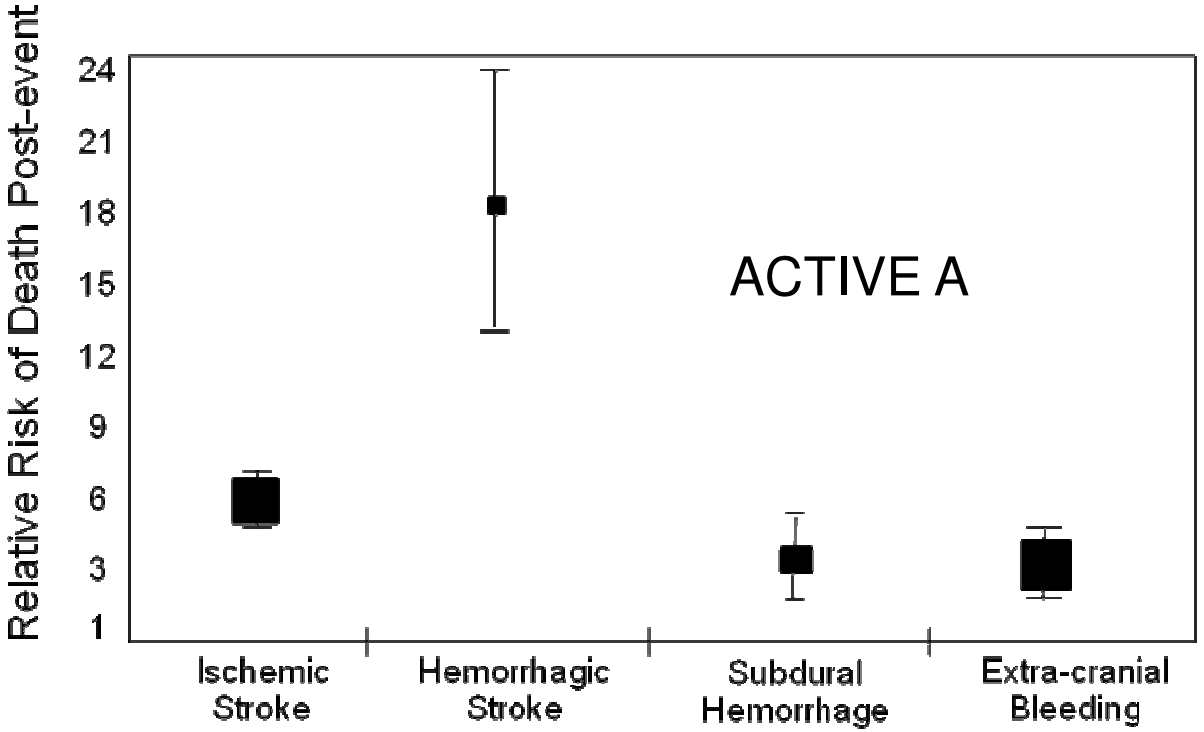
Ischemic strokes are more severe
with, than without, AF
Hemorrhagic strokes are the most dreaded





Steger et al. Eur Heart J 2004;25:1734-40 - Bernhardt et al. JACC 2005;45:1807-12

Relative risk of death post-event in ACTIVE A

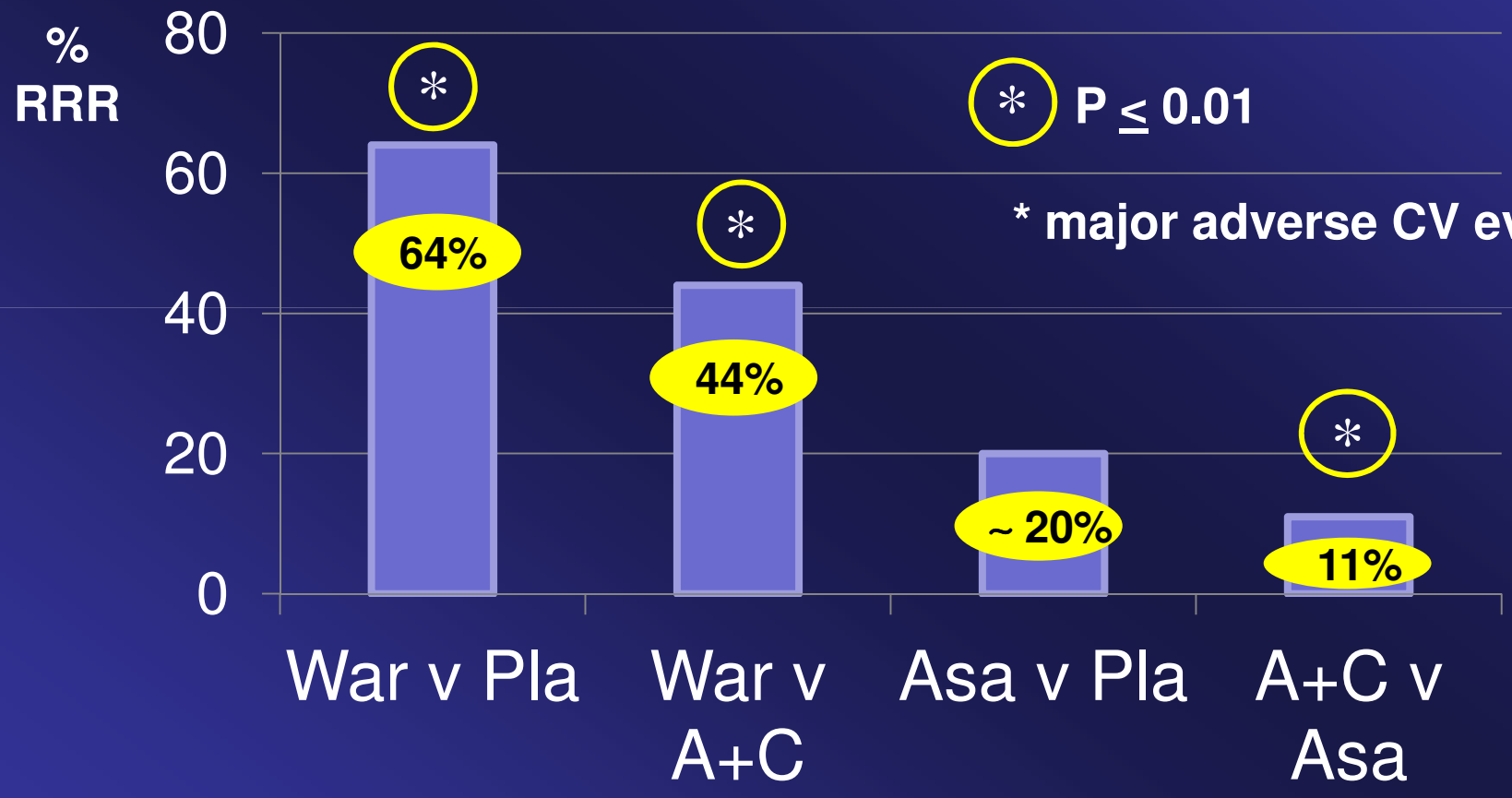


Event	Ischemic Stroke	Hemorrhagic Stroke	Subdural Hemorrhage	Extracranial Hemorrhage
Weighting	1.00	3.00	0.64	0.63

Connolly et al. Ann Intern Med 2011;155:579-86

Antithrombotic therapy in NVAF

% Relative risk reduction (RRR) of Stroke or MACE* in NVAF



Hart. J Thromb Tlysis 2008;25:26-32 – ACTIVE W. Lancet 2006;367:1903-12
ACTIVE A. NEJM 2009;360:2067-78

Risk of major bleeds with warfarin therapy

Annual risk of major bleed on warfarin ~2 - 3% per annum

Study	Year published	Population (*n*)	Major haemorrhage, % per year	ICH % per year	New to warfarin, %	Age, mean
Randomised trials						
AFI[18]	1994	AF ($n = 3691$)	1.3	0.3	100	69
SPAF II[19] (2 age strata)	1994	AF ($n = 715$)	1.7	0.5	100	NR
		AF ($n = 385$)	4.2	1.8	100	80
AFFIRM[20]	2002	AF ($n = 4060$)	2.0	0.6	NR	70
SPORTIF III[21]	2003	AF ($n = 3407$)	2.2	0.4	27	70
SPORTIF V[22]	2005	AF ($n = 3422$)	3.4	0.1	15	72
ACTIVE W[23]	2006	AF ($n = 6706$)	2.2	NR	23	71
RE-LY[24]	2009	AF ($n = 18006$)	3.4	0.74	51	72
ROCKET-AF[25]	Presented 2010	AF ($n = 14264$)	3.5	0.7	37	73
Inception cohort ARISTOTLE			1.7	0.8		
Landefeld and Goldman[26]	1989	All ($n = 565$)	7.4	1.3	100	61
Steffensen *et al.*[27]	1997	All ($n = 682$)	6.0	1.3	100	59F/66M
Beyth *et al.*[28]	1998	All ($n = 264$)	5.0	0.9	100	60
Pengo *et al.*[29]	2001	AF ($n = 433$)	Age ≥ 75: 5.1 Age < 75: 1.0	NA	100	68
Hylek *et al.*[30]	2007	AF ($n = 472$)	7.2	2.5	100	77
Non-inception cohort (prevalent warfarin use)						
Van der Meer *et al.*[31]	1993	All ($n = 6814$)	2.7	1.3	NR	66
Fihn *et al.*[32]	1996	All ($n = 928$)	1.0	1.3	NR	58
ATRIA[33]	2003	AF ($n = 6320$)	1.52	0.46	NR	71
Poli *et al.*[34]	2009	AF ($n = 783$)	1.4	2.5	NR	75
Rose *et al.*[35]	2009	AF ($n = 3396$)	1.9	NA	5	74

Lip et al. Europace 2011;13:723-46

Bleeding risk by HASBLED in AF patients

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

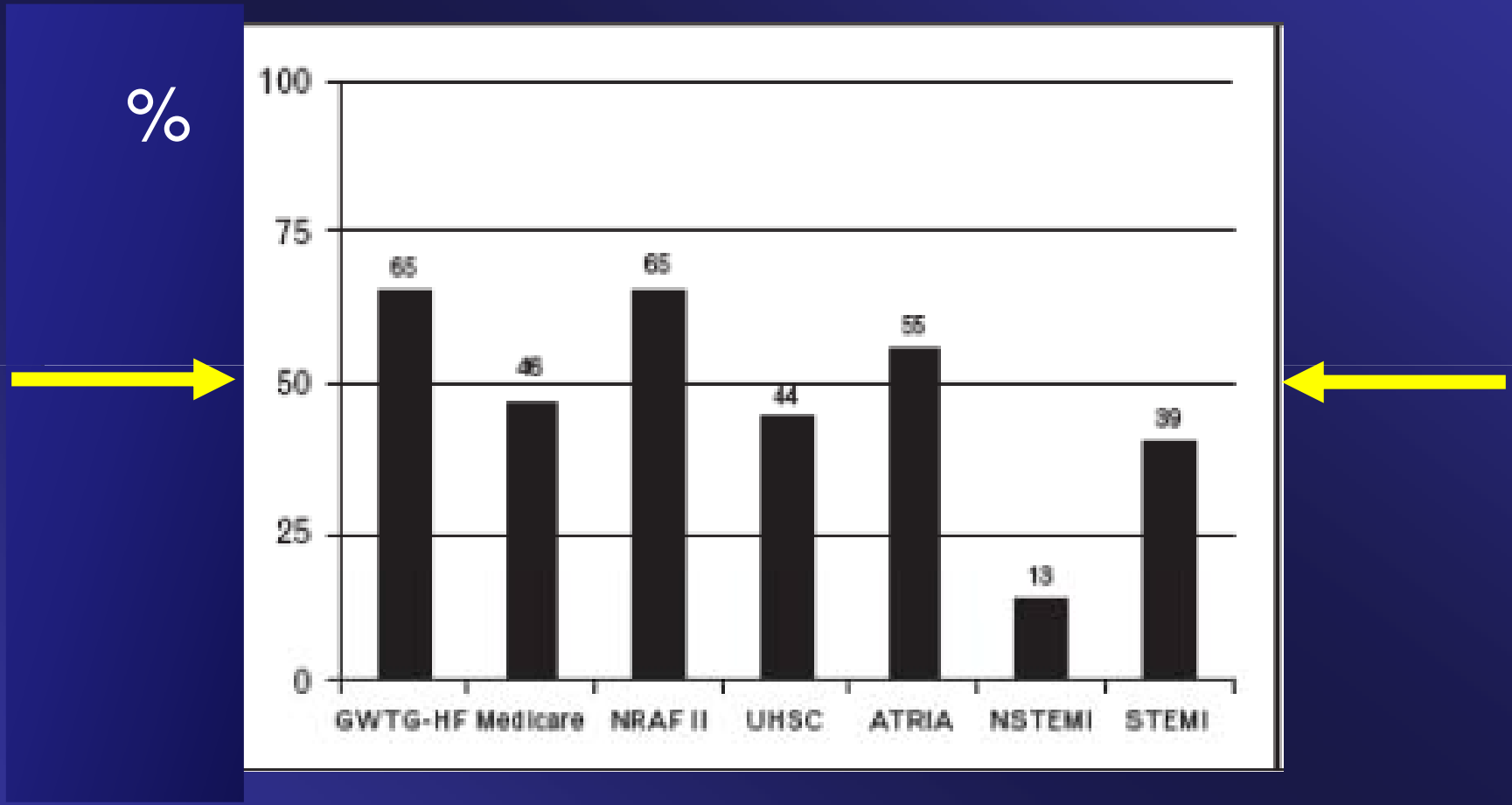
Score	Major bleeds %/y
0 very low	~ 1 % / yr
1 low	~ 2 % / yr
2 moderate	
≥ **3 high**	~ **5 % / yr**

Pisters et al. Chest 2010;138: 1093-100

Limitations of coumadines

1. Individual variability – Food & drug interactions
2. Dose adjustments - Slow onset/offset
3. Mandatory monitoring – Logistic difficulties

Warfarin use in eligible patients with AF

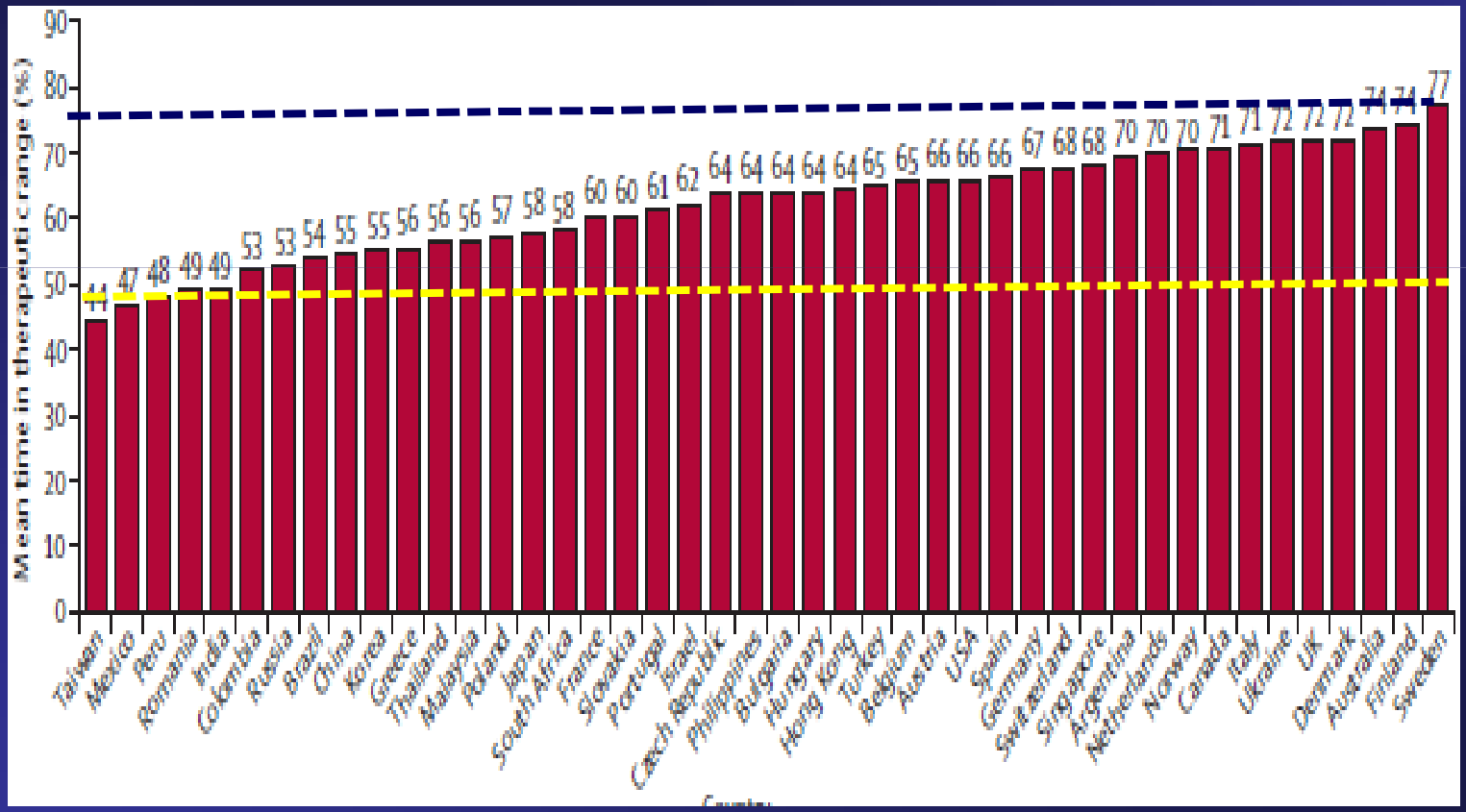


Piccini et al. Curr Opin Cardiol 2010;25:312-20

Optimal warfarin therapy in the setting of a RCT*

*** randomized controlled trial**

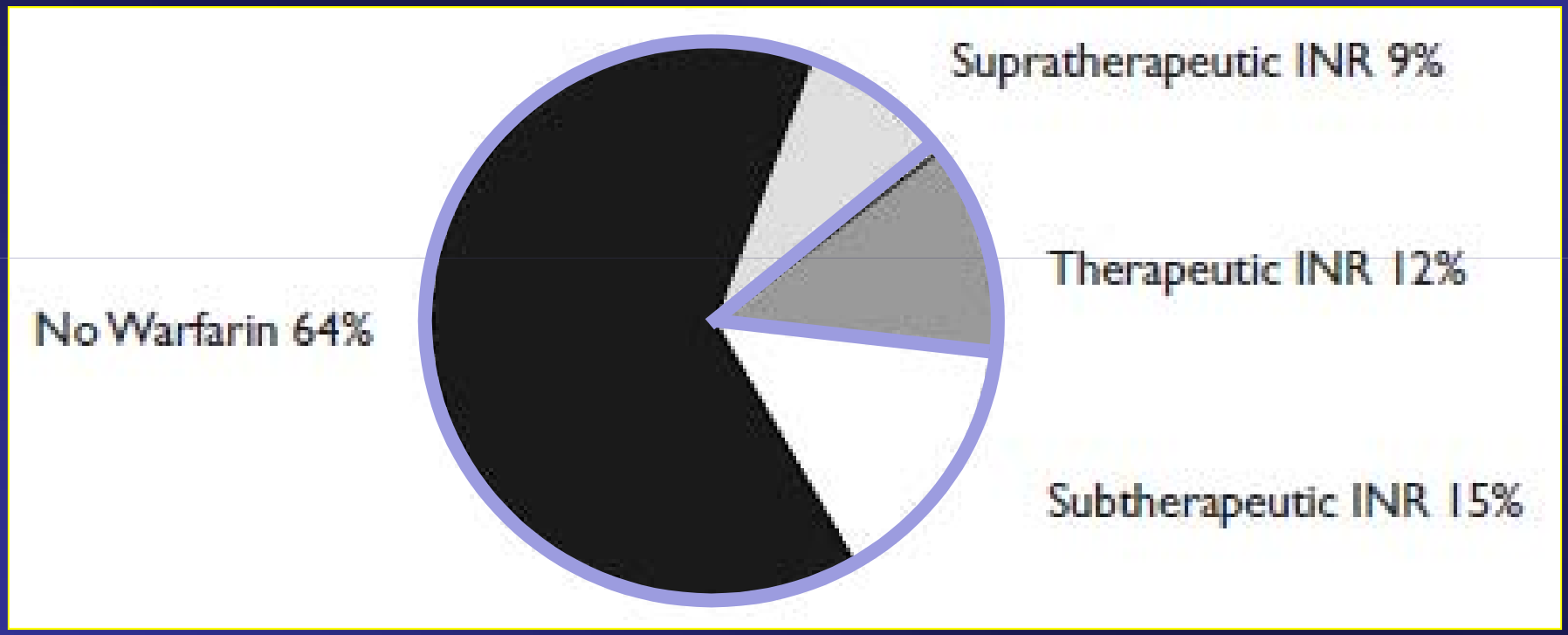
Mean time in therapeutic range (%)



Wallentin et al. Lancet 2010;376:975-83

Real life anticoagulation with warfarin

Warfarin eligible patients with NVAF



Bungard et al. Pharmacotherapy 2000;20:1060-5

Multiple warfarin drug interactions

Specific Drugs Reported		
acetaminophen	fenoprofen	oxymetholone
alcohol†	fluconazole	pantoprazole
allopurinol	fluorouracil	paroxetine
aminosalicylic acid	fluoxetine	penicillin G, intravenous
amiodarone HCl	flutamide	pentoxifylline
argatroban	fluvastatin	phenylbutazone
aspirin	fluvoxamine	phenytoin†
atenolol	gefitinib	piperacillin
atorvastatin†	gemfibrozil	piroxicam
azithromycin	glucagon	pravastatin†
bivalirudin	halothane	prednisone†
capecitabine	heparin	propafenone
cefamandole	ibuprofen	propoxyphene
cefazolin	ifosfamide	propranolol
cefoperazone	indomethacin	propylthiouracil†
cefotetan	influenza virus vaccine	quinidine
cefoxitin	itraconazole	quinine
ceftriaxone	ketoprofen	rabeprazole
celecoxib	ketorolac	ranitidine†
cerivastatin	lansoprazole	rofecoxib
chenodiol	lepirudin	sertraline
chloramphenicol	levamisole	simvastatin
chloral hydrate†	levofloxacin	stanozolol
chlorpropamide	levothyroxine	streptokinase
cholestyramine†	liothyronine	sulfamethizole
cimetidine	lovastatin	sulfamethoxazole
ciprofloxacin	mefenamic acid	sulfinpyrazone
cisapride	methimazole†	sulfisoxazole
clarithromycin	methyldopa	sulindac
clofibrate	methylphenidate	tamoxifen
COUMADIN overdose	methylsalicylate ointment (topical)	tetracycline
cyclophosphamide†	metronidazole	thyroid
danazol	miconazole (intravaginal, oral, systemic)	ticarcillin
dextran	moricizine hydrochloride†	ticlopidine
dextrothyroxine	nalidixic acid	tissue plasminogen activator (t-PA)
diazoxide	naproxen	tolbutamide
diclofenac	neomycin	tramadol
dicumarol	norfloxacin	trimethoprim/sulfamethoxazole
diflunisal	ofloxacin	urokinase
disulfiram	olsalazine	valdecoxib
doxycycline	omeprazole	valproate
erythromycin	oxandrolone	vitamin E
esomeprazole	oxaprozin	zafirlukast
ethacrynic acid		zileuton
ezetimibe		
fenofibrate		

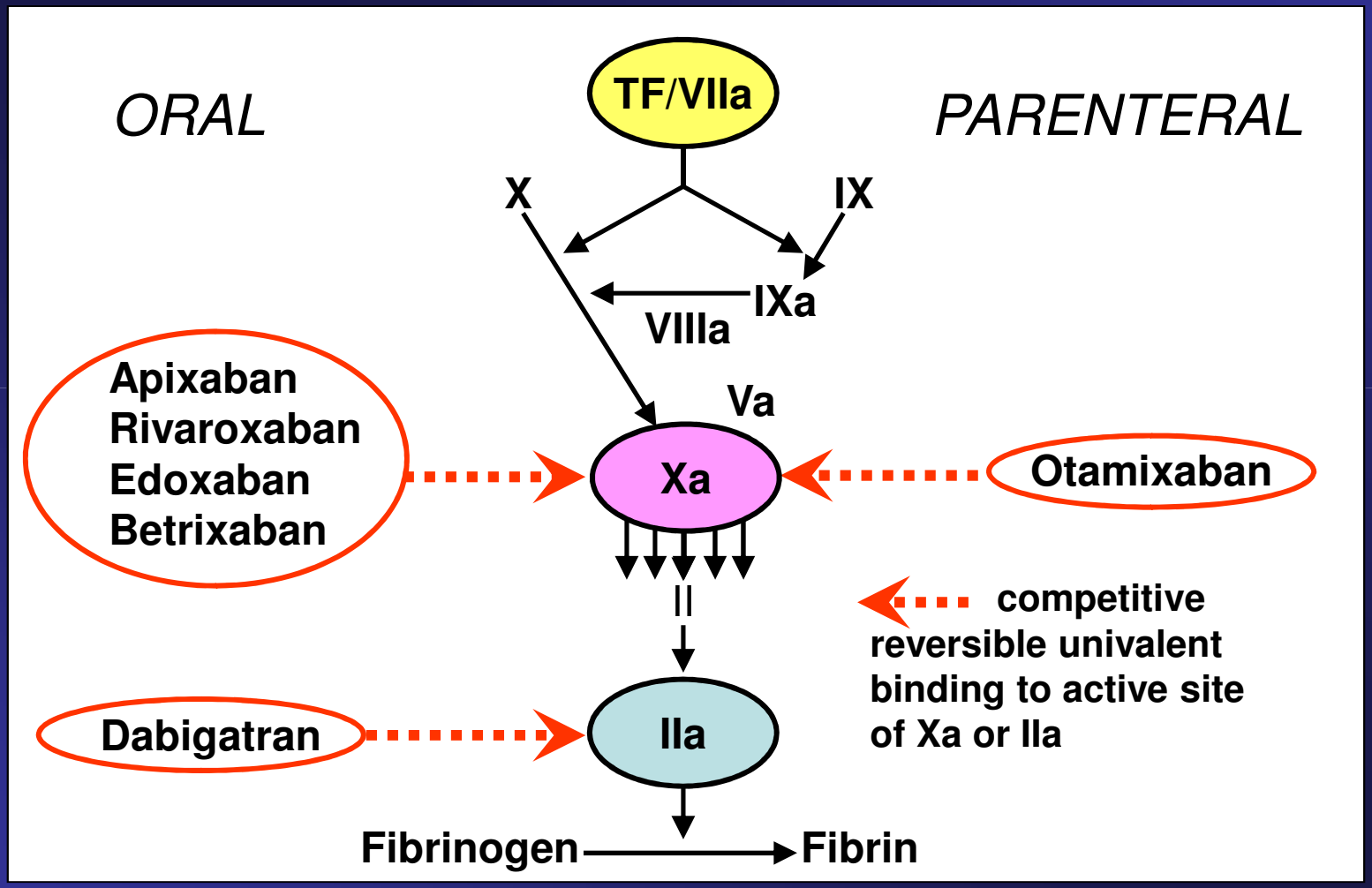
Increase INR

Decrease INR

Specific Drugs Reported		
alcohol†	COUMADIN underdosage	phenobarbital
aminoglutethimide	cyclophosphamide†	phenytoin†
amobarbital	dicloxacillin	pravastatin†
atorvastatin†	ethchlorvynol	prednisone†
azathioprine	glutethimide	primidone
butabarbital	griseofulvin	propylthiouracil†
butalbital	haloperidol	raloxifene
carbamazepine	meprobamate	ranitidine†
chloral hydrate†	6-mercaptopurine	rifampin
chlordiazepoxide	methimazole†	secobarbital
chlorthalidone	moricizine hydrochloride†	spironolactone
cholestyramine†	nafcillin	sucralfate
clozapine	paraldehyde	trazodone
corticotropin	pentobarbital	vitamin C (high dose)
cortisone		vitamin K

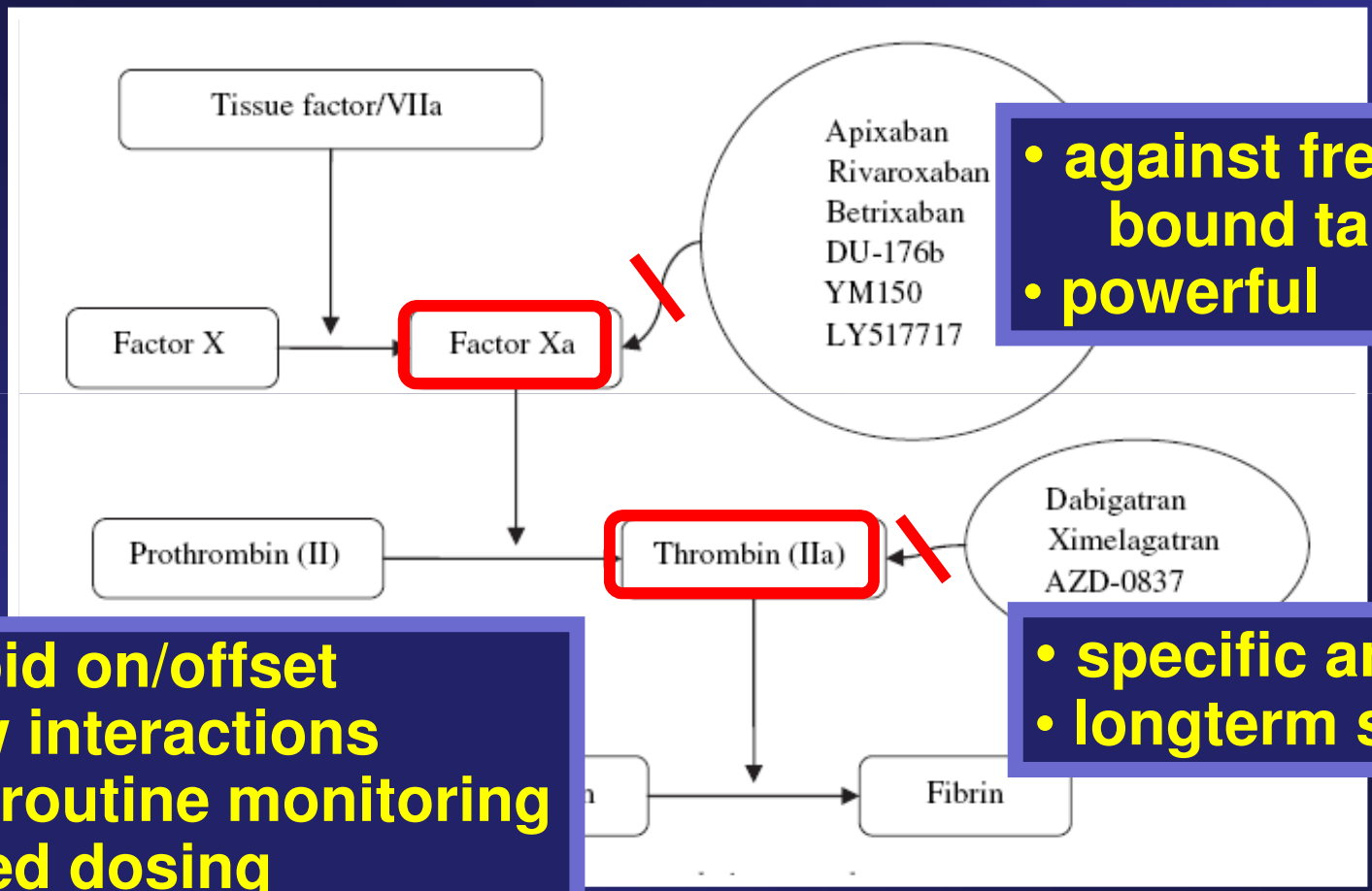
www.nhssb.n-i.nhs.uk

New anticoagulants



Adapted from Weitz & Bates, J Thromb Haemost 2005

Main features of new anticoagulants



- against free and bound targets
- powerful

- rapid on/offset
- few interactions
- no routine monitoring
- fixed dosing

- specific antidote?
- longterm safety?

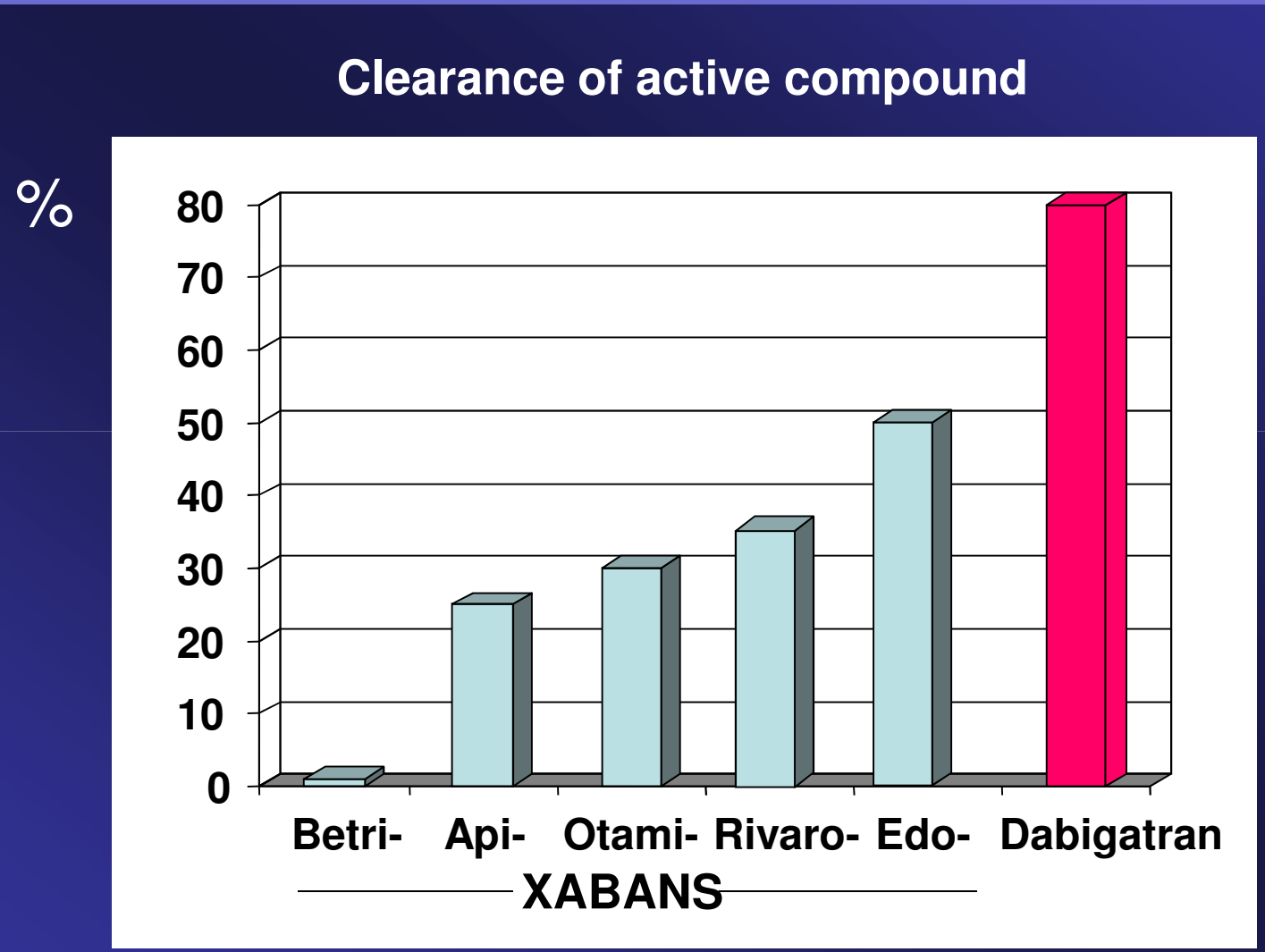
Khoo CW et al. Int J Clin Pract 2009;63:630-41

Clinical pharmacology of edoxaban, apixaban, rivaroxaban and dabigatran

	Edoxaban	Apixaban	Rivaroxaban	Dabigatran
Mechanism of action	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct Factor Xa inhibitor	Direct thrombin inhibitor
Availability	~60%	~50%	80–100%	6.5%
CYP 3A4 effect	No	Yes	Yes	No
P-GP effect	Yes	No	No	Yes
Pro-drug	No	No	No	Yes
Food effect	No	No	No	No
Protein binding		~87%	~66 %	80%
Mean $t_{1/2}$	6-11 h	~12 h	7–11 h	14–17 h (pts)
Tmax	1-2 h	3-4 h	2-4 h	0.5-2 h
Laboratory assay	Anti-FXa	Anti-FXa	Anti-FXa	Thrombin time

Eriksson et al. Clin Pharmacokinet 2009;41:1-22 – Andreotti, Pafundi. Rev Esp Cardiol 2010;63:1223-9 – De Caterina et al. JACC 2012

Renal clearance of new anticoagulants



Andreotti, Pafundi. Rev Esp Cardiol 2010;63:1223-9

Programs for the most advanced new oral anticoagulants (NOACs)

	Dabigatran Pradaxa®	Rivaroxaban Xarelto®	Apixaban Eliquis®	Edoxaban
VTE p Ortho	RE-MODEL RE-NOVATE RE-MOBILIZE	RECORD 1 RECORD 2 RECORD 3 RECORD 4	ADVANCE I ADVANCE 2 ADVANCE 3	STARS E3
VTE p M Ill	RE-SOLVE	MAGELLAN	ADOPT	—
VTE tx	RE-COVER RE-MEDY RE-SONATE	EINSTEIN-DVT EINSTEIN-PE EINSTEIN-EXT	AMPLIFY AMPLIFY-EXT	HOKUSAI
SPAF	RE-LY	ROCKET-AF	ARISTOTLE AVERROES	ENGAGE-TIMI48
ACS Secondary prevention	—	ATLAS 2	APPRAISE 2	XANADU-ACS

RE-LY®: study design

Atrial fibrillation with ≥1 risk factor
Absence of contraindications

Randomized Evaluation of Long-term anticoagulation therapY

Warfarin 1 mg, 3 mg, 5 mg (INR 2.0–3.0) N=6000	Dabigatran etexilate 110 mg BID N=6000	Dabigatran etexilate 150 mg BID N=6000

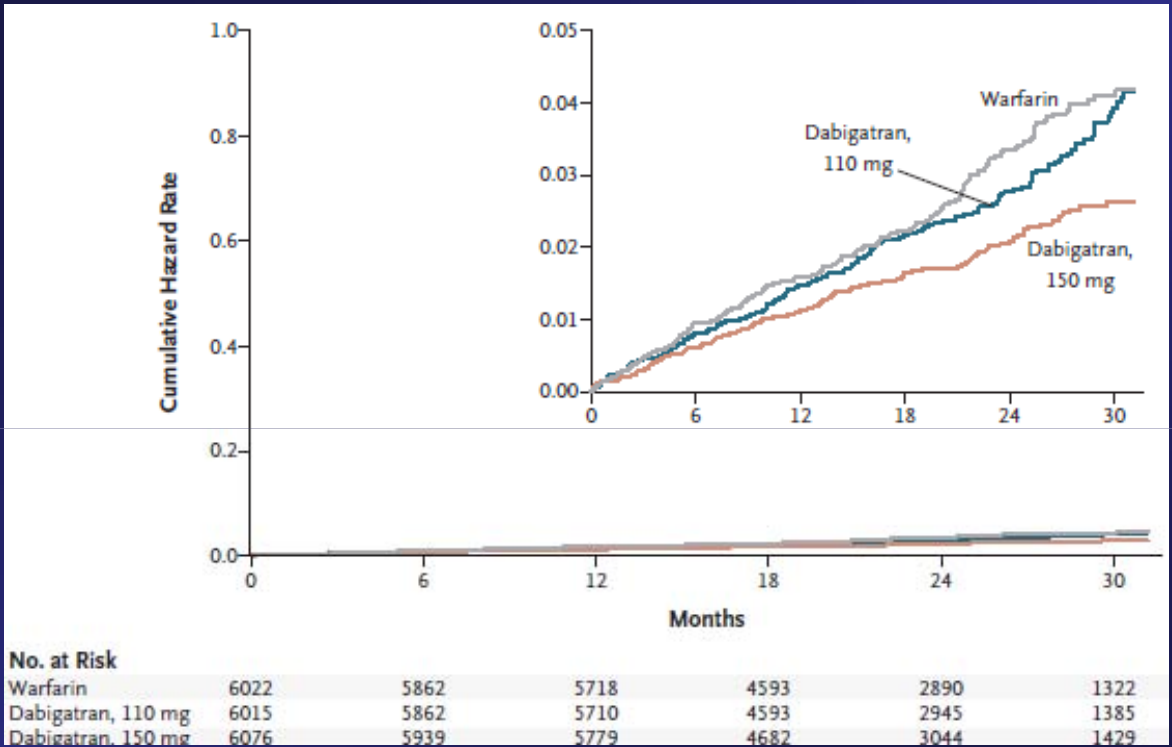
open

Primary endpoint: stroke or systemic embolism
2 year follow-up

Ezekowitz MD et al. Am Heart J 2009;157:805–10
Connolly SJ et al. N Engl J Med 2009;361:1139–51

Efficacy, Safety and Mortality Outcomes

Stroke or Systemic Embolism in W v D110 v D150: 1.7 v 1.5 v 1.1* %/yr

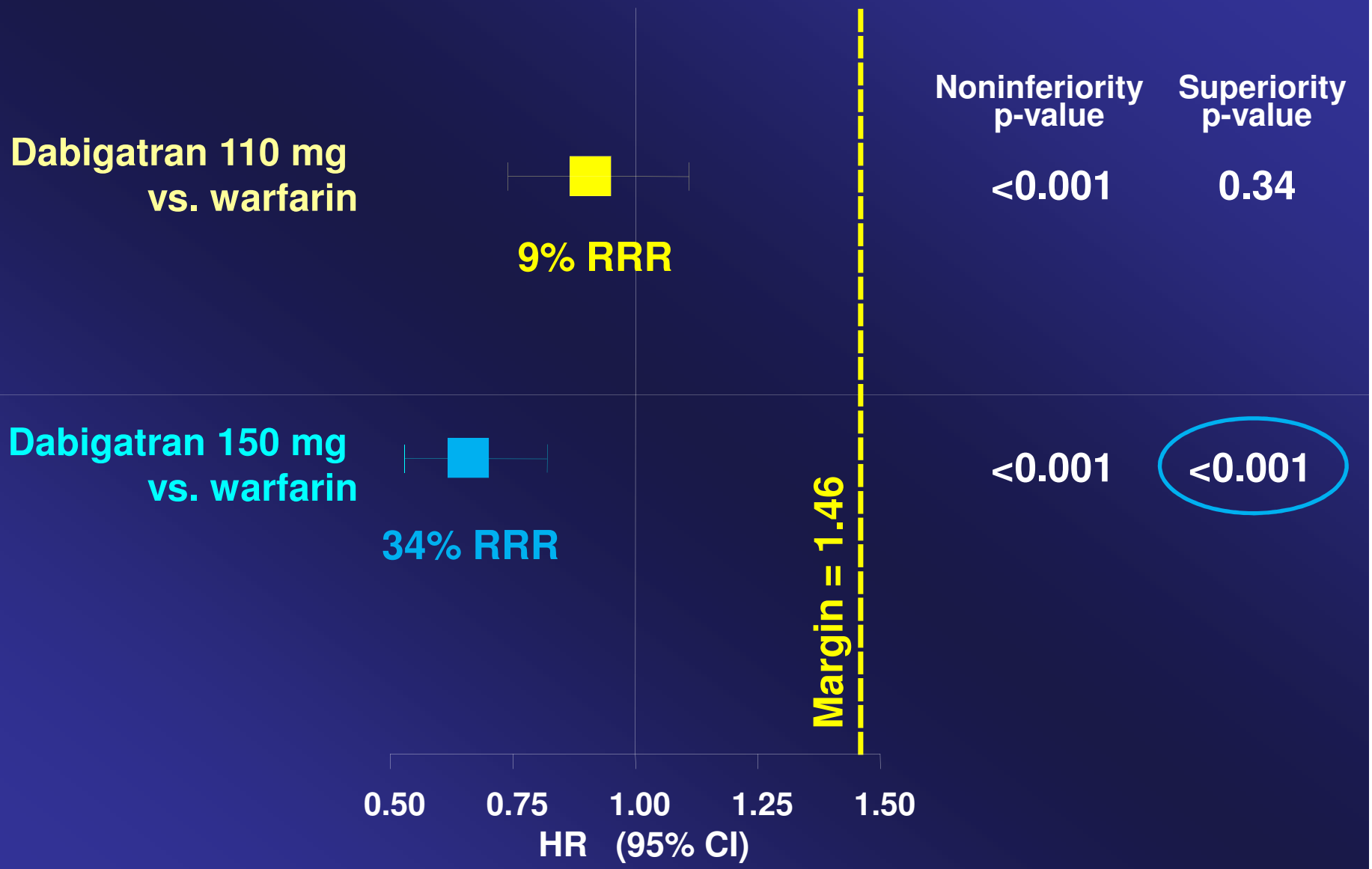


No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Study Major Bleeds: 3.4 v 2.7* v 3.1 %/y; HS: 0.4 v 0.1*. v 0.1* %/y
GI bleed: 1.0 v 1.1 v 1.5* %/y; MI: 0.5 v 0.7 v 0.7* %/y
CV death: 2.7 v 2.4 v 2.3* %/y; any death: 4.1 v 3.8 v 3.6 %/y

Connolly et al. NEJM 2009;361:1139-51

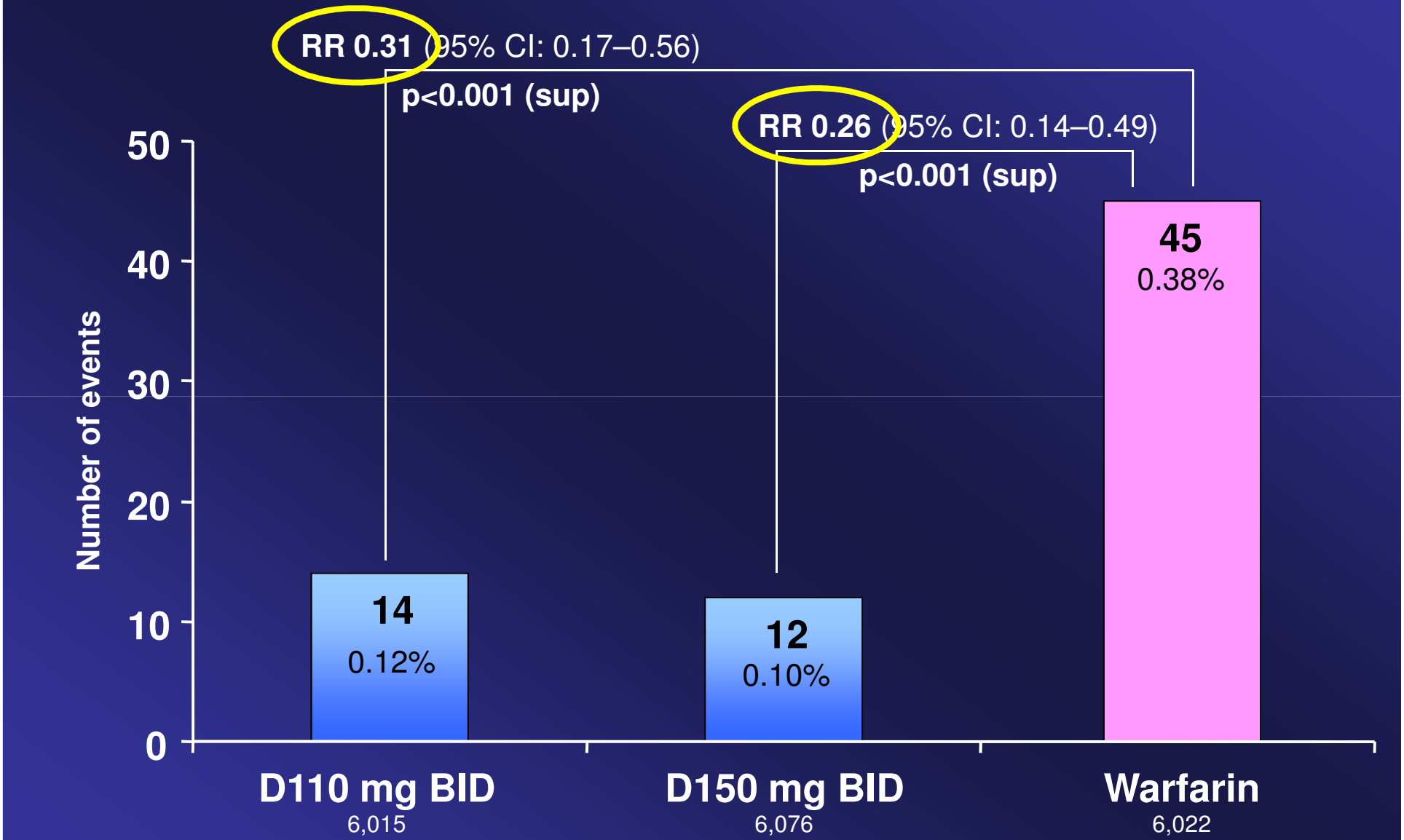
RE-LY stroke or systemic embolism



	Noninferiority p-value	Superiority p-value
Dabigatran 110 mg vs. warfarin	<0.001	0.34
Dabigatran 150 mg vs. warfarin	<0.001	<0.001

Connolly et al. NEJM 2009;361:1139-51

RE-LY hemorrhagic stroke



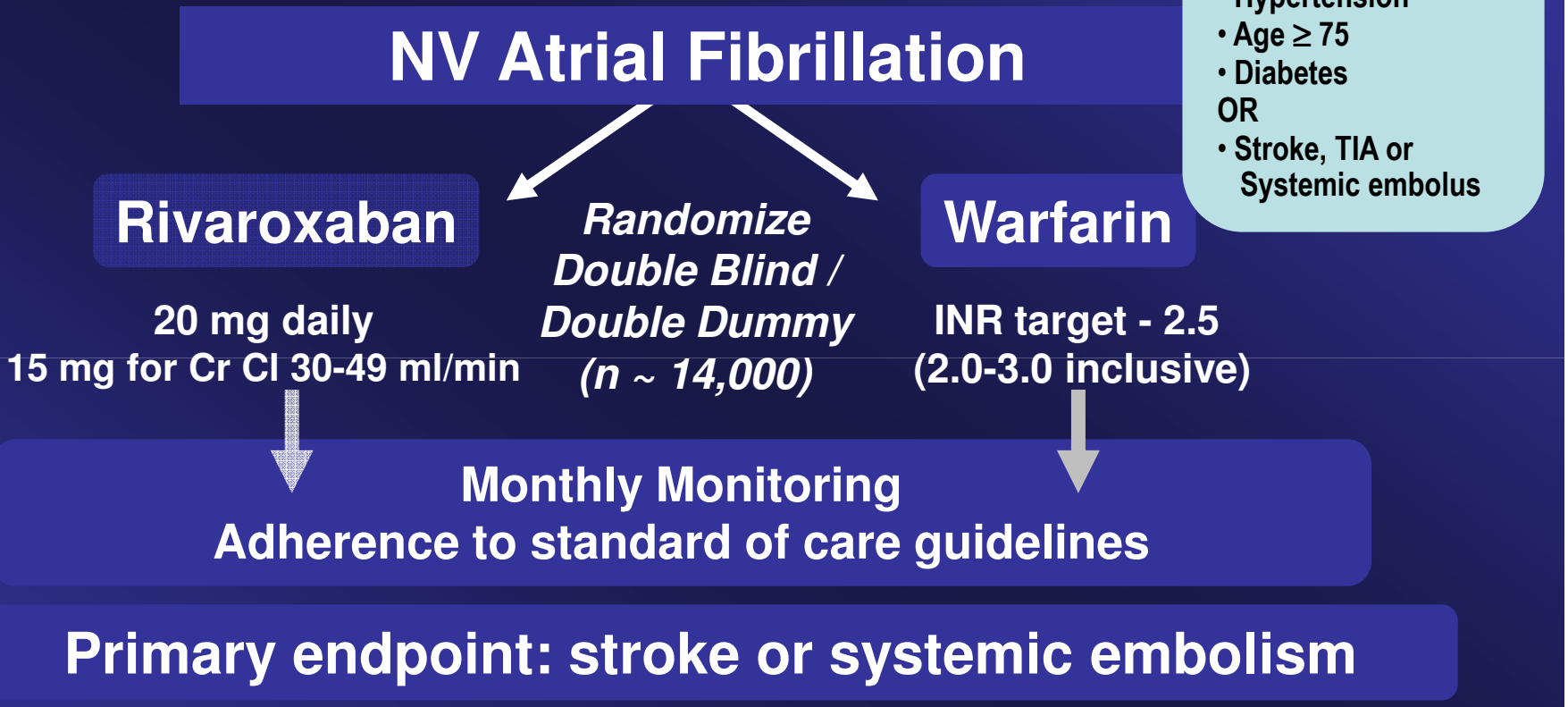
Connolly et al. NEJM 2009;361:1139-51

NOAC perform BETTER than WAR regardless of INR quality

Compared with warf, benefits of dabig 150 in reducing stroke, of dabig 110 in reducing bleeds, and of both regimens in reducing ICH were found regardless of INR quality

Wallentin L et al. Lancet 2010;376:975-83

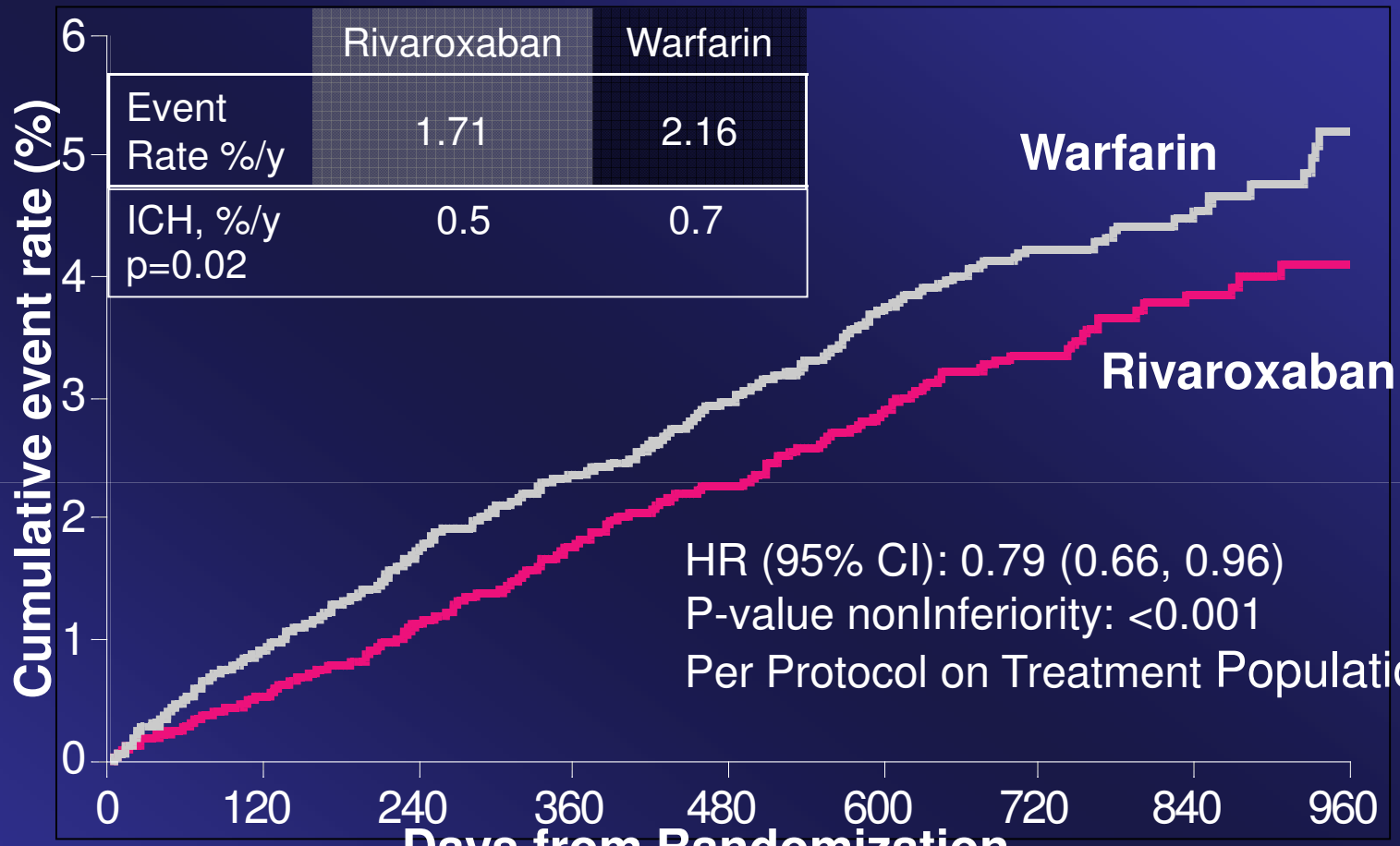
ROCKET design



* Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%

Patel et al. NEJM 2011;365:883-91

ROCKET stroke and systemic embolism



No. at risk:

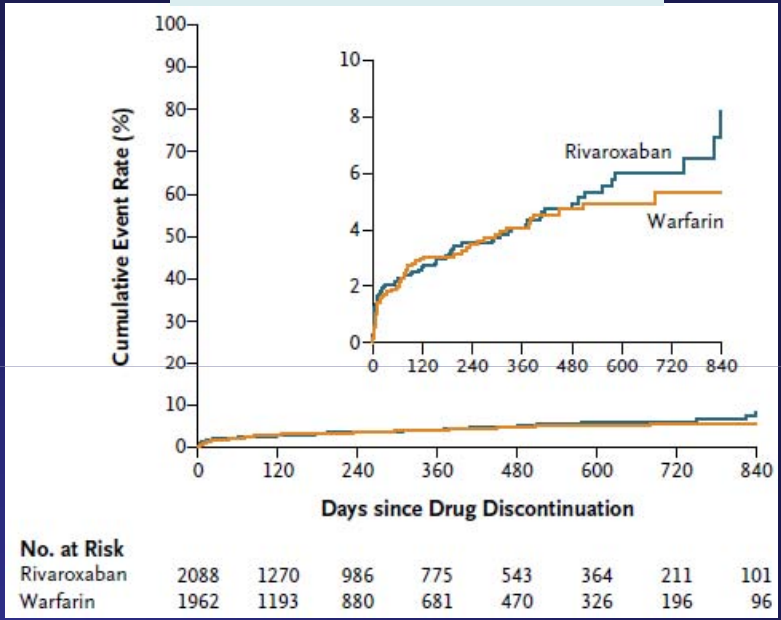
Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

Patel et al. NEJM 2011;365:883-91

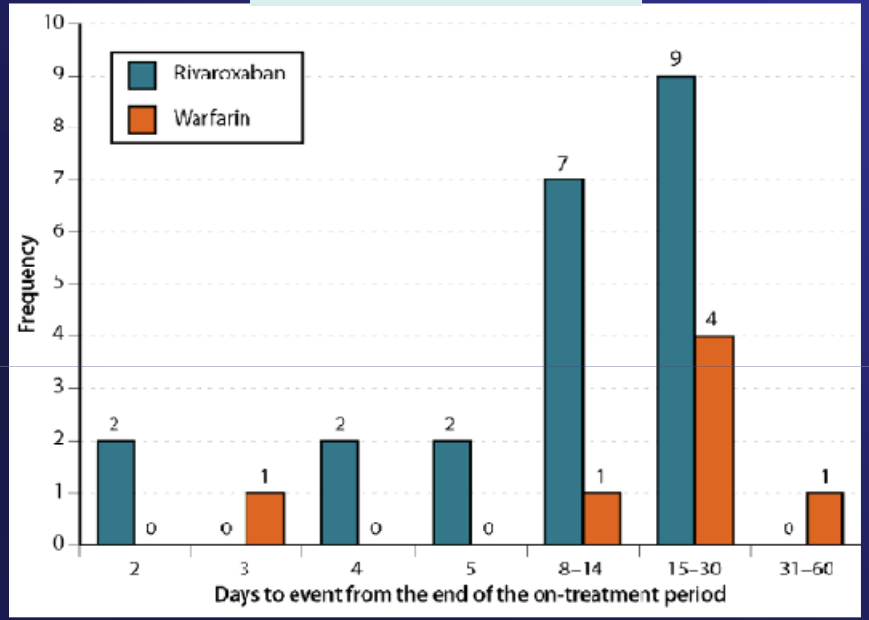
Events after Discontinuation in ITT population

Stroke or Systemic Embolism

Before end of study



At end of study



	Rivaroxaban	Warfarin
Event Rate %/y	2.1	2.4

HR (95% CI): 0.88 (0.74, 1.03)
P-value nonInferiority: <0.001
Intention to treat (ITT) analysis

Patel et al. NEJM 2011;365:883-91

ARISTOTLE design

Inclusion risk factors
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Randomize
double blind, double dummy
(n = 18,201)

Major exclusion criteria
- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine

Apixaban 5 mg oral twice daily (2.5 mg BID in selected patients)

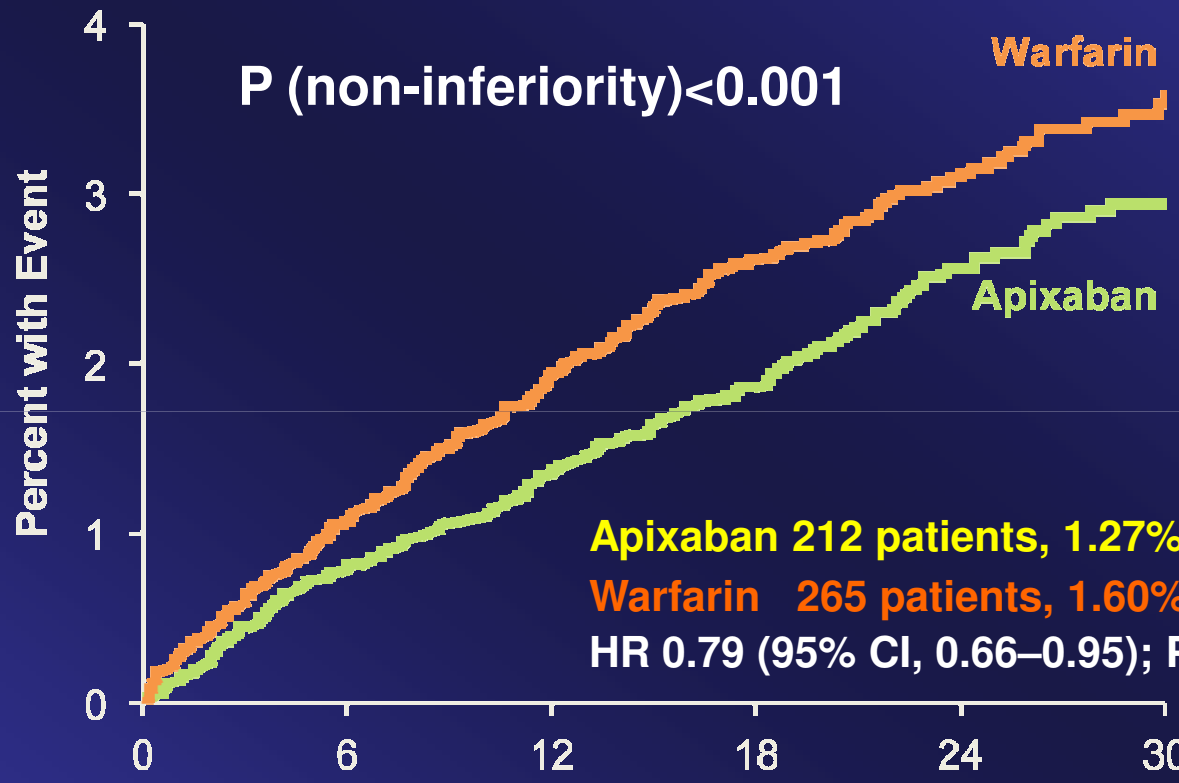
Warfarin (target INR 2-3)

Primary outcome: stroke or systemic embolism

Hierarchical testing: non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death

Granger et al. NEJM 2011;365:981-92

ARISTOTLE stroke (ischemic or hemorrhagic) or systemic embolism

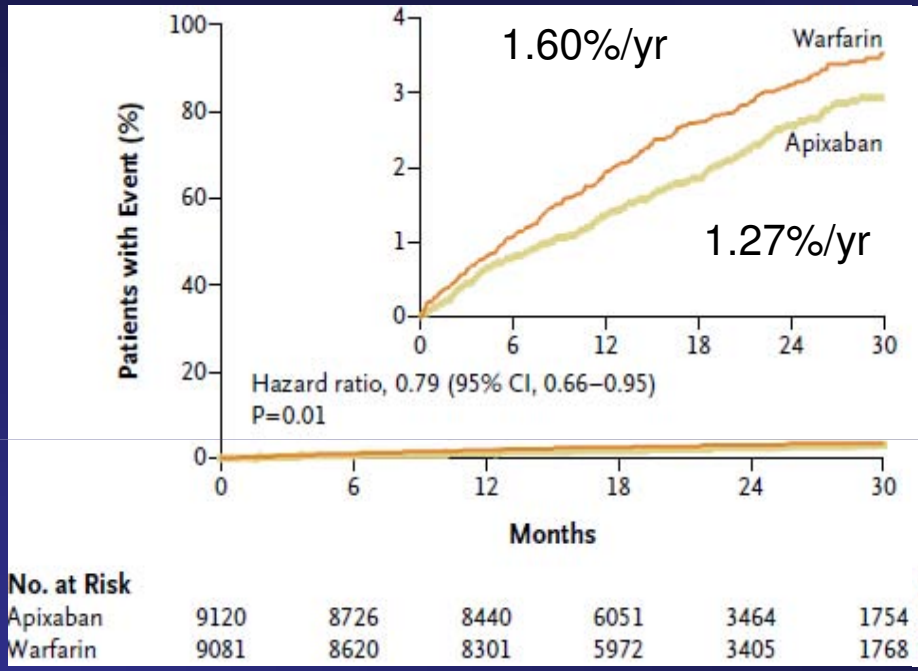


No. at Risk						
Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

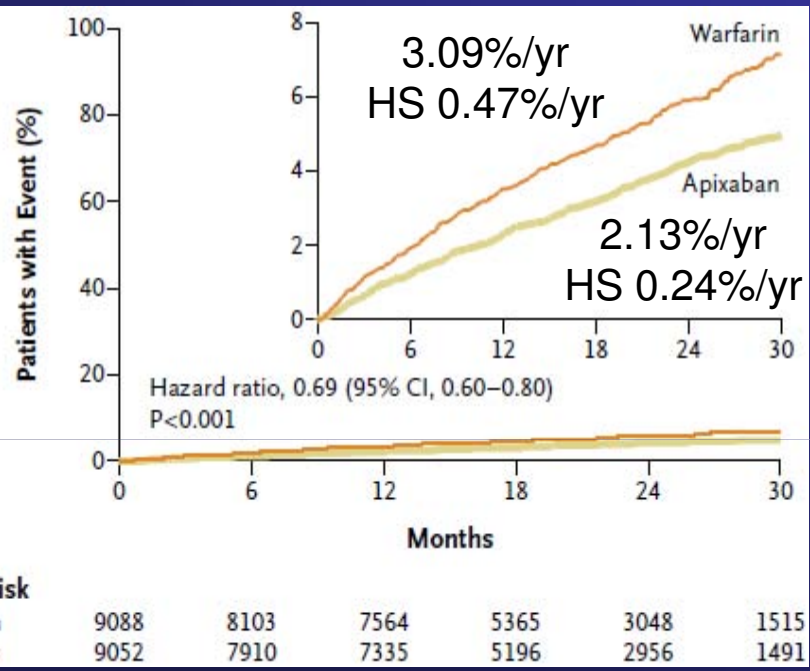
Granger et al. NEJM 2011;365:981-92

Efficacy, Safety and Net Clinical Outcomes

Stroke or Systemic Embolism



ISTH Major Bleeding

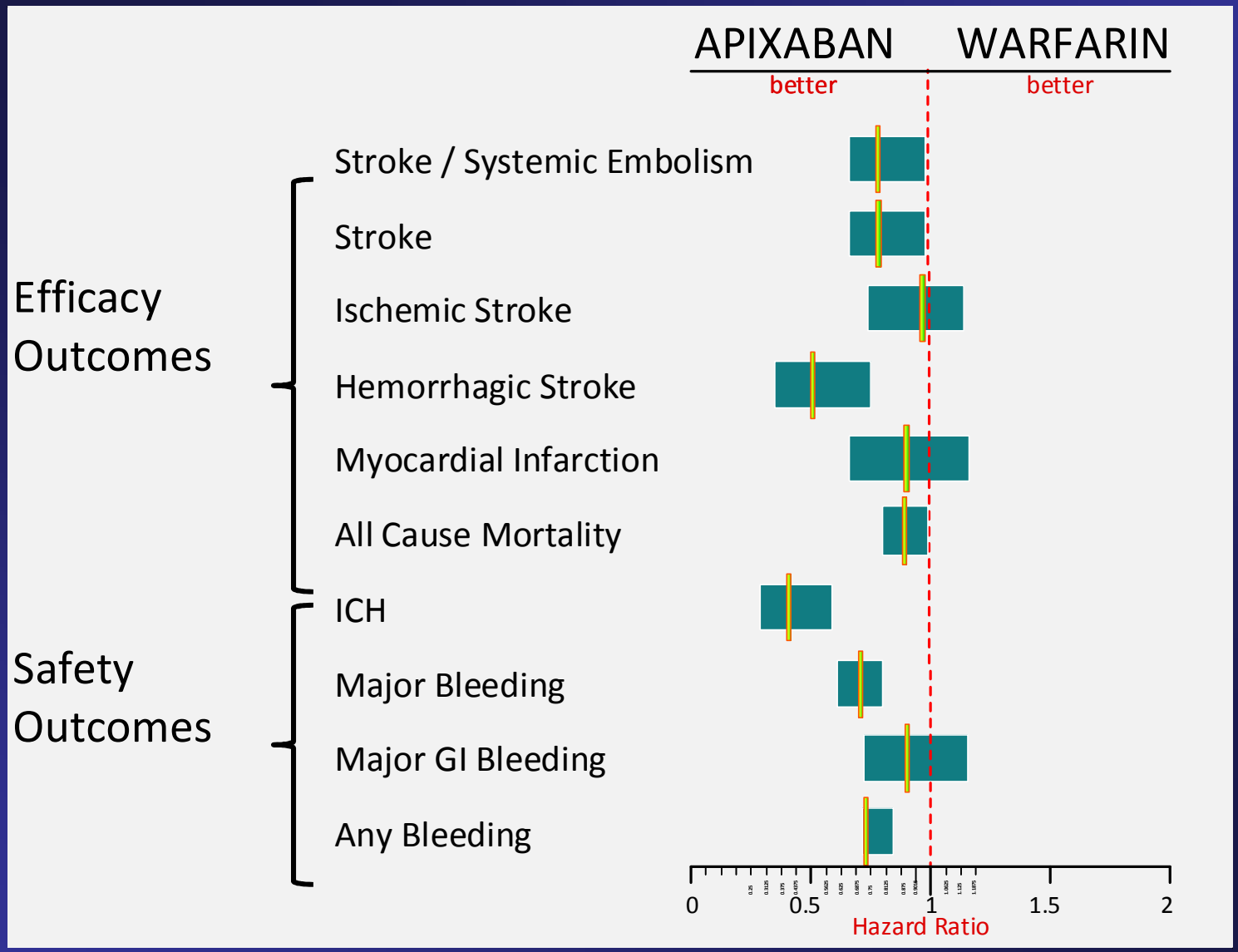


Any death (3.52 v 3.94%/yr), stroke, systemic embolism or major bleeding:

Apixaban 1009 patients, 6.13% per year
Warfarin 1168 patients, 7.20% per year
HR 0.85 (95% CI, 0.78–0.9); P (superiority)<0.001

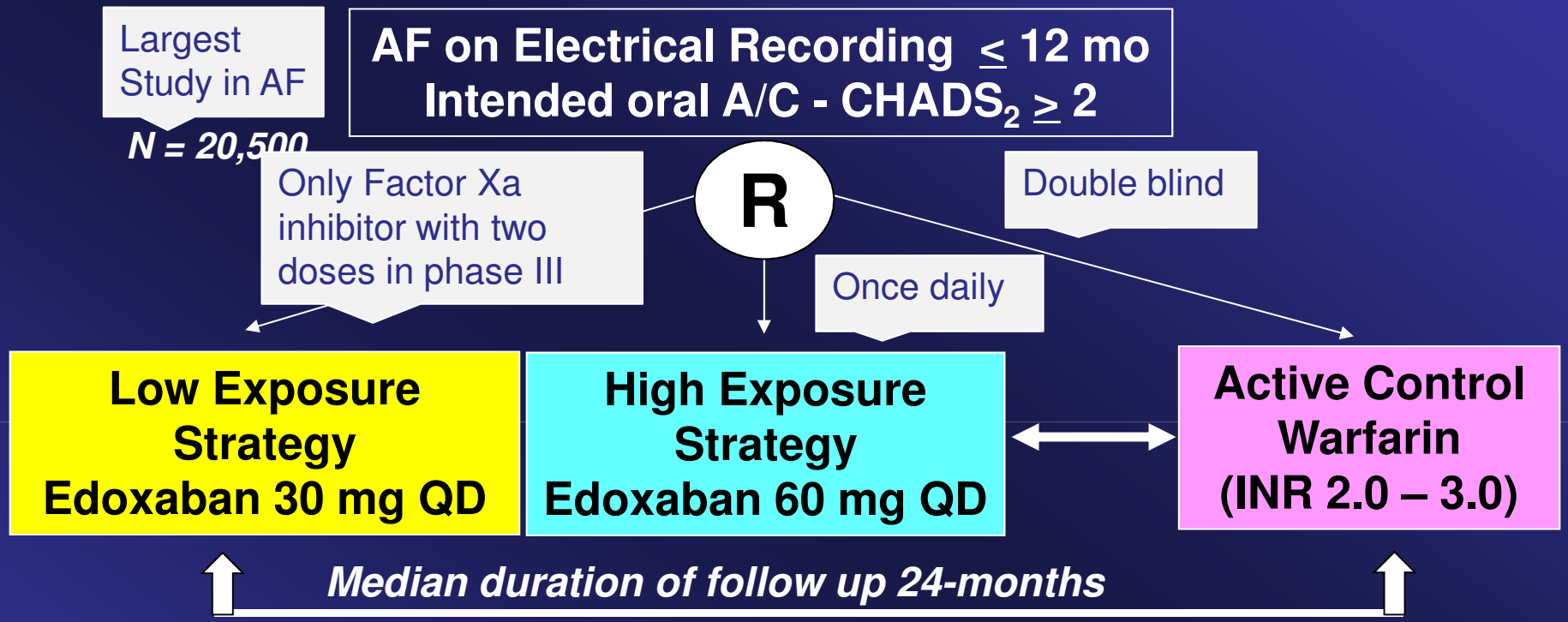
Granger et al. NEJM 2011;365:981-92

ARISTOTLE



Granger et al. NEJM 2011;365:981-92

ENGAGE AF TIMI 48 design



Primary Objective: Edoxaban Non inferior to Warfarin (HR boundary1.38)

1º EP = Stroke or systemic embolic event - 2º EP = Stroke or SEE or All-Cause Death
Safety EPs = modified ISTH Major Bleeding, Hepatic Function

Ruff et al. AHJ 2010;160:635-41

NOACs vs Warfarin in NVAF: 2012 Summary

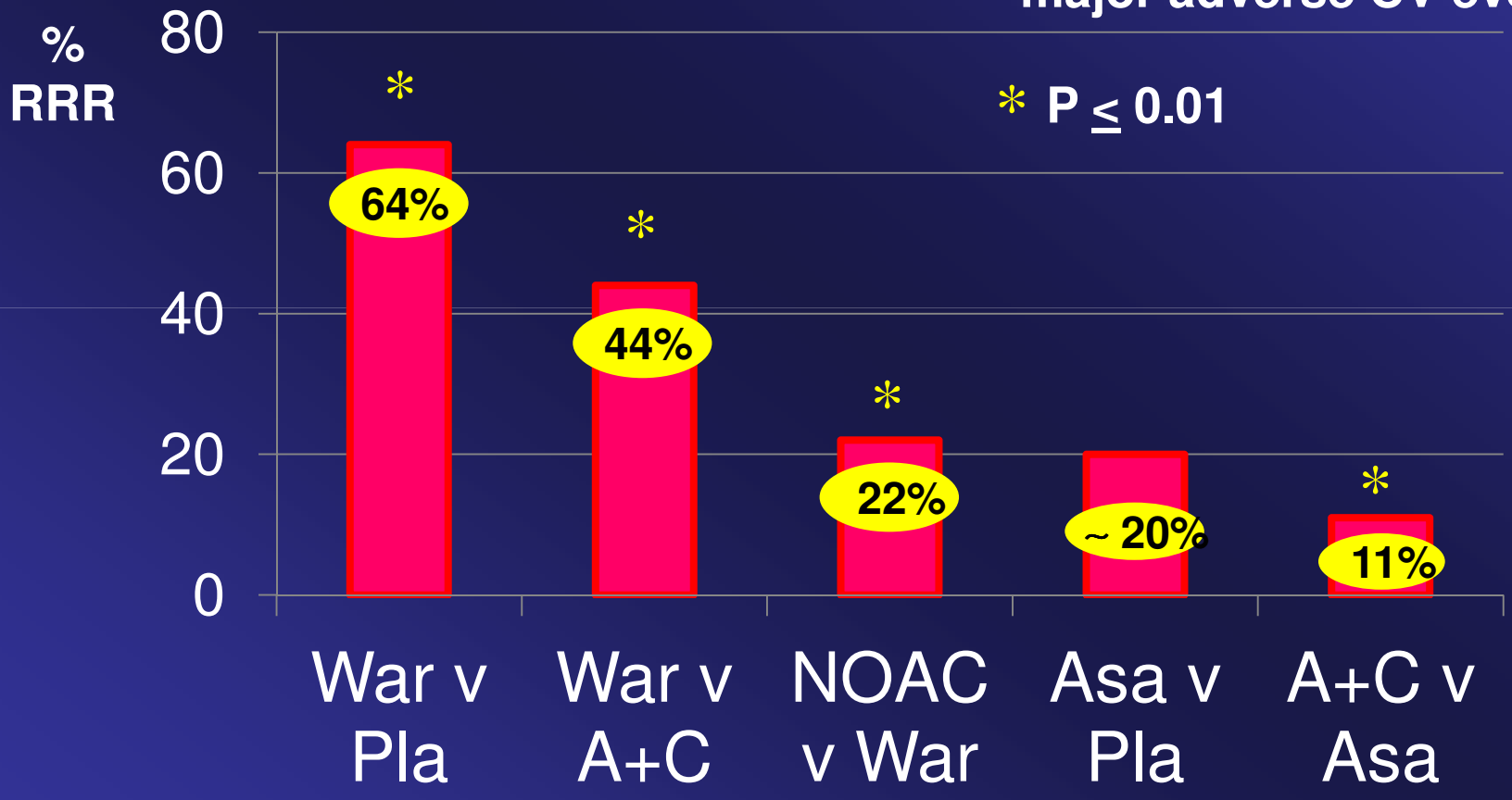
Effect on outcome event	D150	D110	Riva	Apix
Noninferiority stroke/syst embol	√	√	√	√
Superiority stroke or syst embol	√			√
↓ Hemorrhagic stroke	√	√	√	√
↓ Ischemic stroke	√			
↓ Mortality	(√)			√
↓ Major bleeding		√		√
↑ GI bleeding	√		√	
↑ MI	(√)	(√)		
Fewer discontinuations				√
Validation in 2nd RCT				√

Connolly et al. NEJM 2009;361:1139-51 - Patel et al. NEJM 2011;365:883-91 - Granger et al. NEJM 2011;365:981-92

Antithrombotic therapy in NVAF update

% Relative risk reduction of Stroke or MACE* in NVAF

* major adverse CV event



Hart. J Thromb Tlysis 2008;25:26-32 – ACTIVE W. Lancet 2006;367:1903-12
ACTIVE A. NEJM 2009;360:2067-78 – Miller et al. AJC 2012;Apr 24

CONCLUSIONS

NOACs vs coumadin, in patients with nonvalvular atrial fibrillation, can prolong life and improve its quality through stroke prevention, are generally safer and more convenient, and are projected to be cost-effective

Conclusions

A new era of anticoagulation for pateints with NVAF

- All 3 new OACs are non inferior to warfarin in reducing the risk of stroke and systemic embolization
- All three agents reduce the risk of life-threatening bleeding and intracranial hemorrhage

Differences and Future Challenges:

- Dabigatran has a 2-dose approach to the treatment of patients with AF; at a dose of 150 mg it was associated with a reduction in ischemic stroke.
- Rivaroxaban is a once a day drug associated with a lower rate of fatal bleeding
- Apixaban was associated with a reduction in all-cause mortality

Other established thromboembolic risk factors

On TEE, the presence of

- LA thrombus (RR 2.5; P=0.04),
- complex aortic plaques (RR 2.1; P<0.001),
- spontaneous echo-contrast (RR 3.7; P<0.001), and
- low LAA velocities (≤20 cm/s; RR 1.7; P<0.01)

are independent predictors of stroke and thromboembolism

Hughes M & Lip GY. Thromb Haemost 2008;99:295–304
Stroke in AF working group. Neurology 2007;69:546–554

Stroke risk by CHADS2 or CHADS-VASc

Table IV. Stroke risk according to $CHADS_2$ score (1).

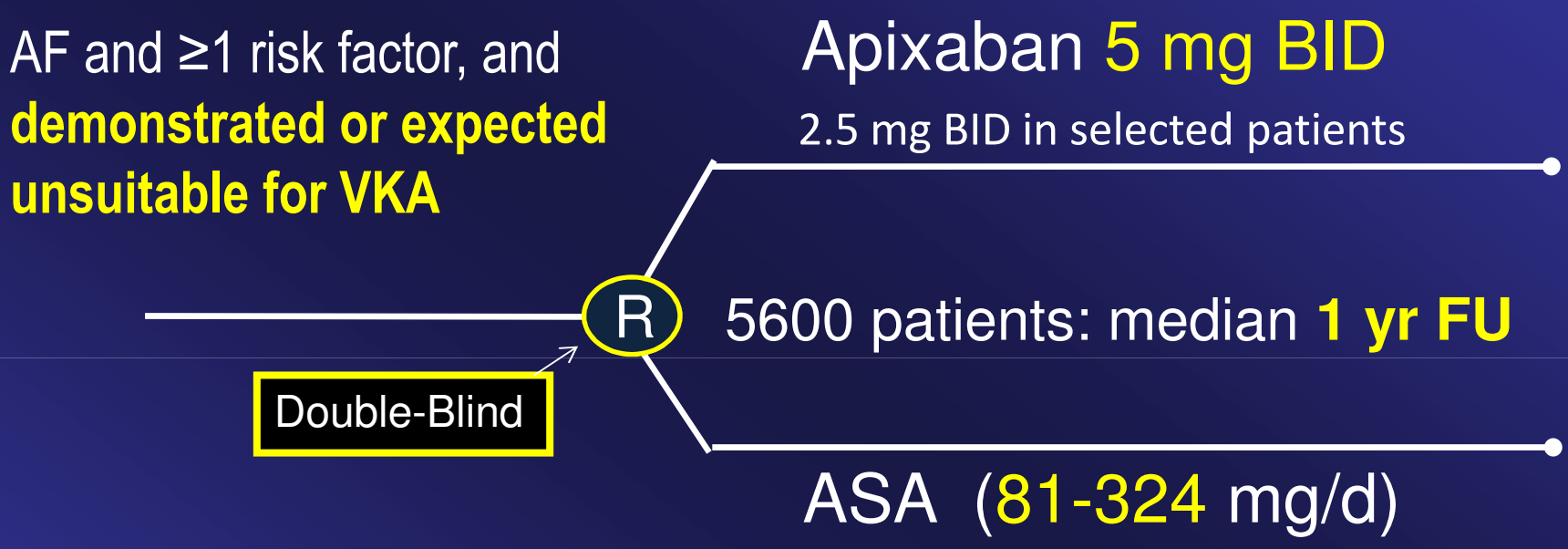
Score	Annual risk (%)
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2

$CHADS_2$ risk criteria	Score
Congestive heart failure	1
Hypertension	1
Age >75 years	1
Diabetes mellitus	1
(Prior) stroke or TIA	2

CHA_2DS_2-VASc score	Patients (n=7329)	Adjusted stroke rate (%/year)[b]
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

2010 ESC AF Guidelines

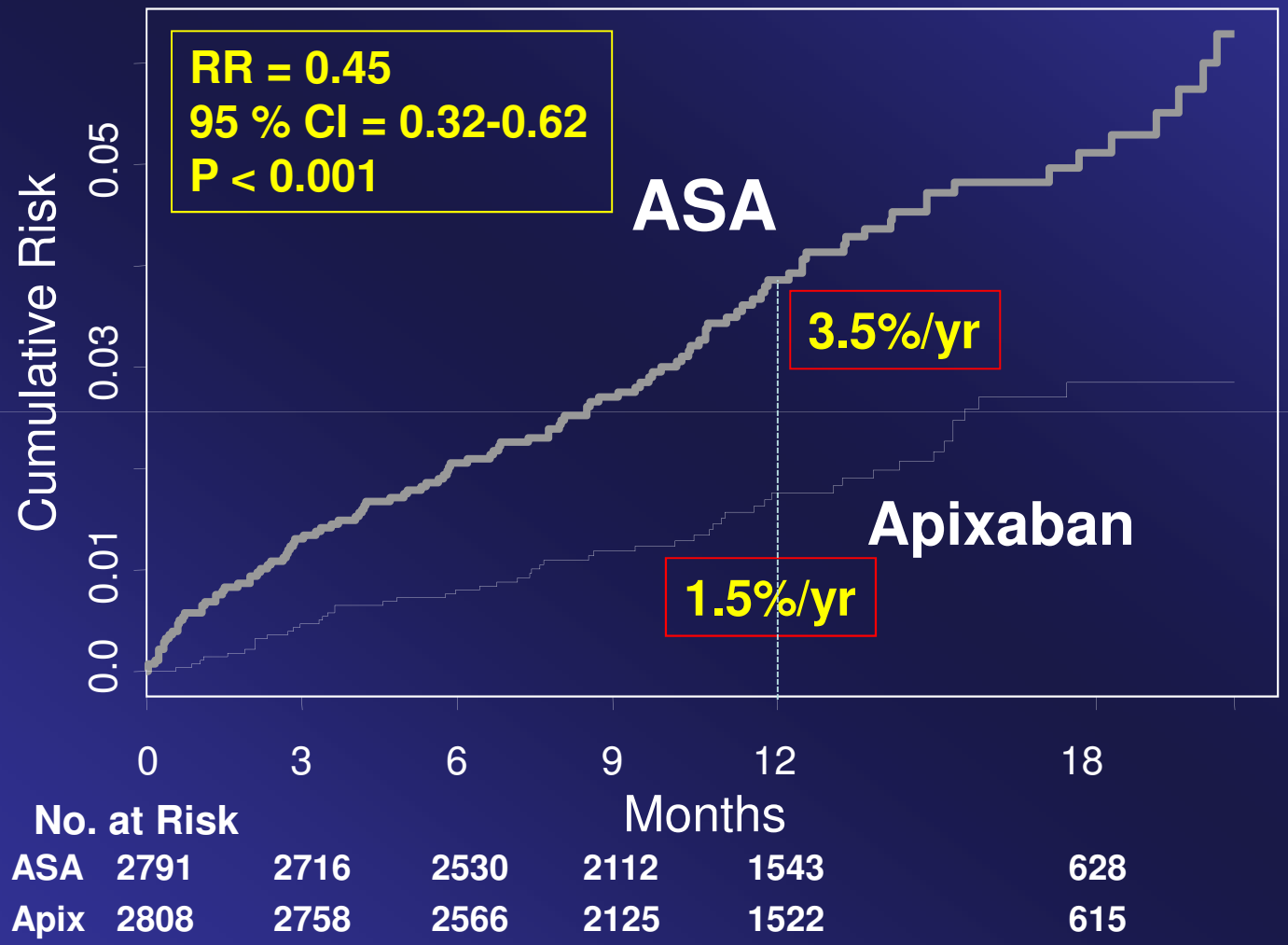
AVERROES design



Primary outcome: stroke or systemic embolism

Connolly S et al. N Engl J Med 2011;364:806-17

AVERROES stroke/systemic embolism



Connolly S et al. N Engl J Med 2011;364:806-17

AVERROES major bleeding

	0	3	6	9	12	18	Months
ASA	2791	2738	2572	2152	1510	642	No. at Risk
Apix	2808	2759	2567	2123	1521	622	

Connolly S et al. N Engl J Med 2011;364:806-17

Warfarin vs ASA in Elderly AF

Warfarin vs aspirin for stroke prevention in an elderly (≥75y) community with AF (the Birmingham AF Treatment of the Aged study, **BAFTA**): a randomised controlled trial

Mant J et al. Lancet 2007; 370: 493-503

Mean follow-up: 2.7 yrs

BAFTA: stroke, ICH, arterial embolism

	Warfarin (n=488)		Aspirin (n=485)		Warfarin vs aspirin	
	n	Risk per year	n	Risk per year	RR (95% CI)	p
Stroke	21	1·6%	44	3·4%	0·46 (0·26–0·79)	0·003
By severity						
Fatal	13	1·0%	21	1·6%	0·59 (0·27–1·24)	0·14
Disabling non-fatal	8	0·6%	23	1·8%	0·33 (0·13–0·77)	0·005
Type of stroke*						
Ischaemic	10	0·8%	32	2·5%	0·30 (0·13–0·63)	0·0004
Haemorrhagic	6	0·5%	5	0·4%	1·15 (0·29–4·77)	0·83
Unknown	5	0·4%	7	0·5%	0·69 (0·17–2·51)	0·53
Other intracranial haemorrhage†	2	0·2%	1	0·1%	1·92 (0·10–113·3)	0·65
Systemic embolism‡	1	0·1%	3	0·2%	0·32 (0·01–3·99)	0·36
Total number of events	24	1·8%	48	3·8%	0·48 (0·28–0·80)	0·0027

Mant J et al. Lancet 2007; 370: 493-503

Drug Interactions of NOAC

	Dabigatran	Rivaroxa	Apixaban	Edoxaban
Potential metabolic drug interactions	Verapamil - reduce dose Dronedarone - avoid Potent inducers of P-gp** - avoid	Potent inhibitors of CYP3A4 and P-gp* - avoid Potent inducers of CYP3A4*** and P-gp - use with caution	Potent inhibitors of CYP3A4 and P-gp* - avoid Potent inducers of CYP3A4*** and P-gp - use with caution	Potent inhibitors of P-gp* - reduce dose Potent inducers of P-gp** - avoid

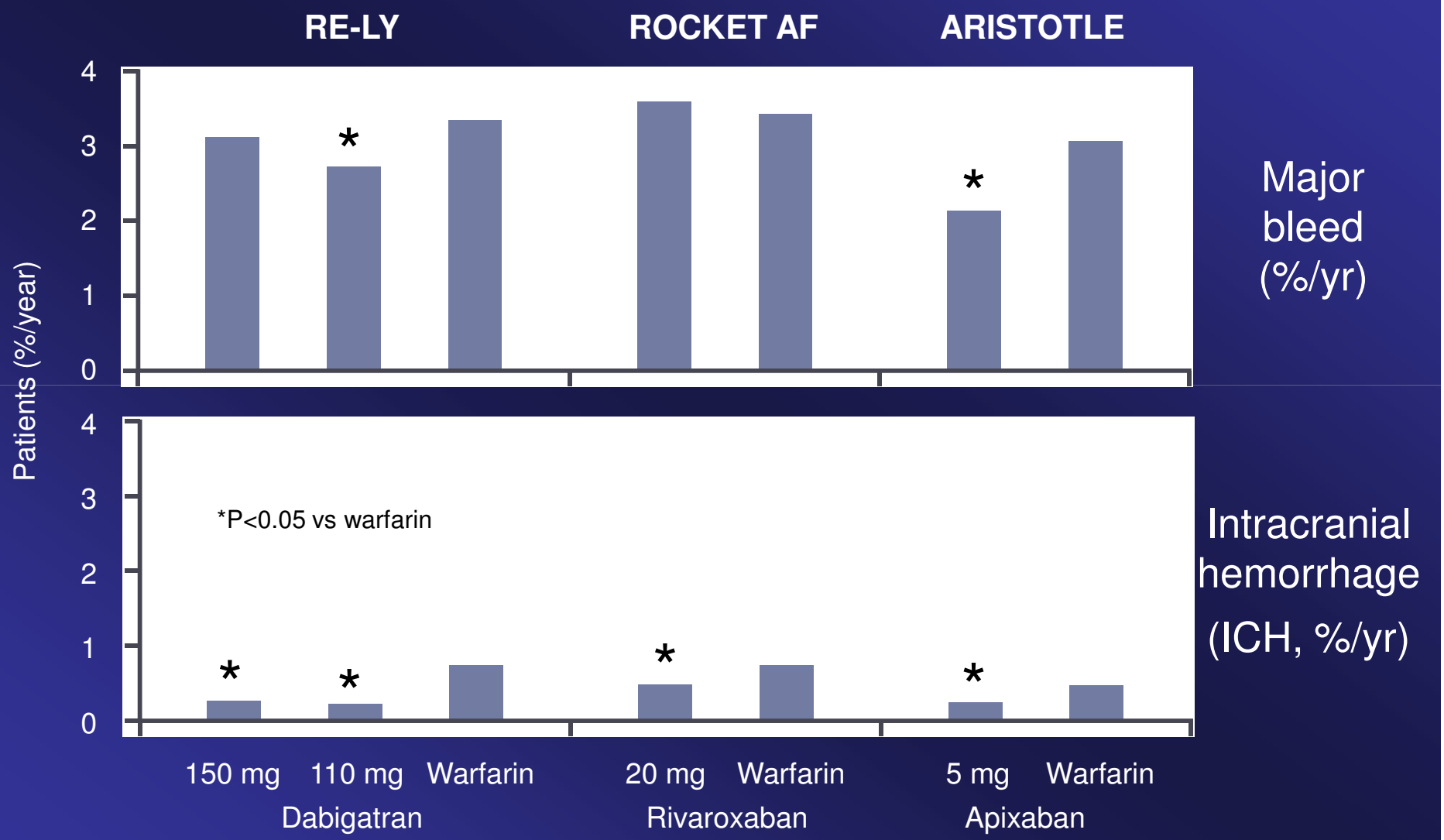
* Potent inhibitors of CYP3A4 include antifungals (e.g., ketoconazole, itraconazole, voriconazole, posaconazole), chloramphenicol, clarithromycin, and protease inhibitors (e.g., ritonavir, atanazavir). P-gp inhibitors include verapamil, amiodarone, quinidine and clarithromycin. ← > AUC

**P-gp inducers include rifampicin, St. John's wort (Hypericum perforatum), carbamazepine, or phenytoin. ←

*** Potent CYP3A4 inducers include phenytoin, carbamazepine, phenobarbital or St. John's Wort. ← < AUC

De Caterina R et al. JACC 2012

Fewer ICH with NOACs vs warfarin



Connolly et al. NEJM 2009;361:1139-51 - Patel et al. NEJM 2011;365:883-91 - Granger et al. NEJM 2011;365:981-92