Novel Anticoagulants in Stroke Prevention in Patients with Atrial Fibrillation
The Past, the Present and the Future

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Conflict of Interest Statement

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- MindFrame
- Fresenius
- CoAxia
- Abbott
- Novartis
- Schering
- Janssen-Cilag
- Sanofi
- MSD
- Astra-Zeneca
- GlaxoSmithKline
- **Pfizer**

- Paion
- Solvay
- Schering Plough
- Medtronic
- Lundbeck
- Syngis
- Tacrelis
- **Boehringer Ingelheim**
- D-Pharm
- **BMS**
- **Bayer**
- Wyeth
- Knoll
- Servier
- EV3
- **J & J**

Goals for anticoagulation therapy in AF

Prevent ischaemic stroke

Minimize haemorrhagic stroke (minimize risk of ICH)

Role of the Neurologist

- The neurologist will see the consequences of
  - Non-treatment
  - Undertreatment (aspirin)
  - Poor treatment (INR < 2.0)

  As ischemic stroke on his stroke unit

- The neurologist will see the consequences of
  - Overtreatment (INR > 4.5)

  As intracranial hemorrhage on the critical care unit

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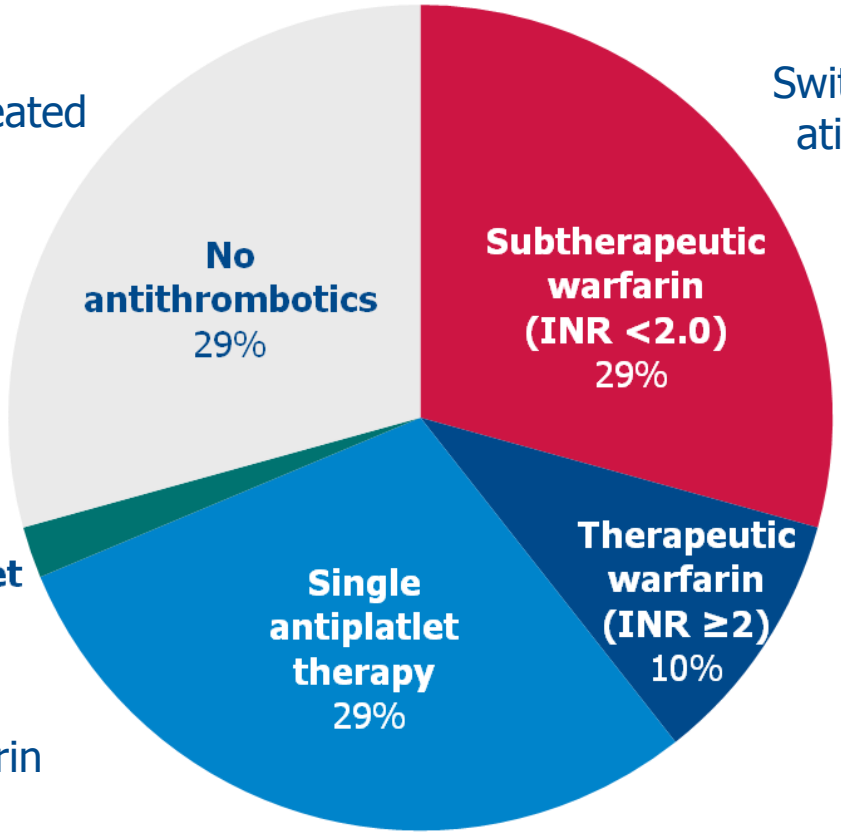
Most ischaemic strokes occur in patients who are suboptimally anticoagulated

Pre-admission medications in high-risk* AF patients admitted for first ischaemic stroke

Get untreated patients treated

Switch poorly controlled atients on warfarin to NOACs



Switch patients from aspirin

Data from a prospective stroke registry of 597 patients with AF at high risk of stroke (*1 high-risk factor or ≥1 moderate-risk factor according to American College of Chest Physicians guidelines)

Gladstone DJ et al. Stroke 2009;40:235–40

Limitations of traditional antithrombotics prevent effective stroke prevention

- Aspirin: insufficient protection in high-risk patients[1]
  - Limited stroke risk reduction (relative risk reduction 19%)[1]

- Vitamin-K-antagonists (e.g. warfarin):
  - Narrow therapeutic range,
  - Food/drug interactions,
  - Slow onset/offset of action,
  - Regular coagulation monitoring[2,3]
  - High risk of bleeding[4]

VKA = Vitamin K antagonist

1. Hart RG et al. Ann Intern Med 2007;146:857–67; **2.** Turpie AG. Eur Heart J 2008;29:155–65;
3. Khoo CW et al. Int J Clin Pract 2009;63:630–41; **4.** Albers GW et al. Chest 2001;119:194S–206S

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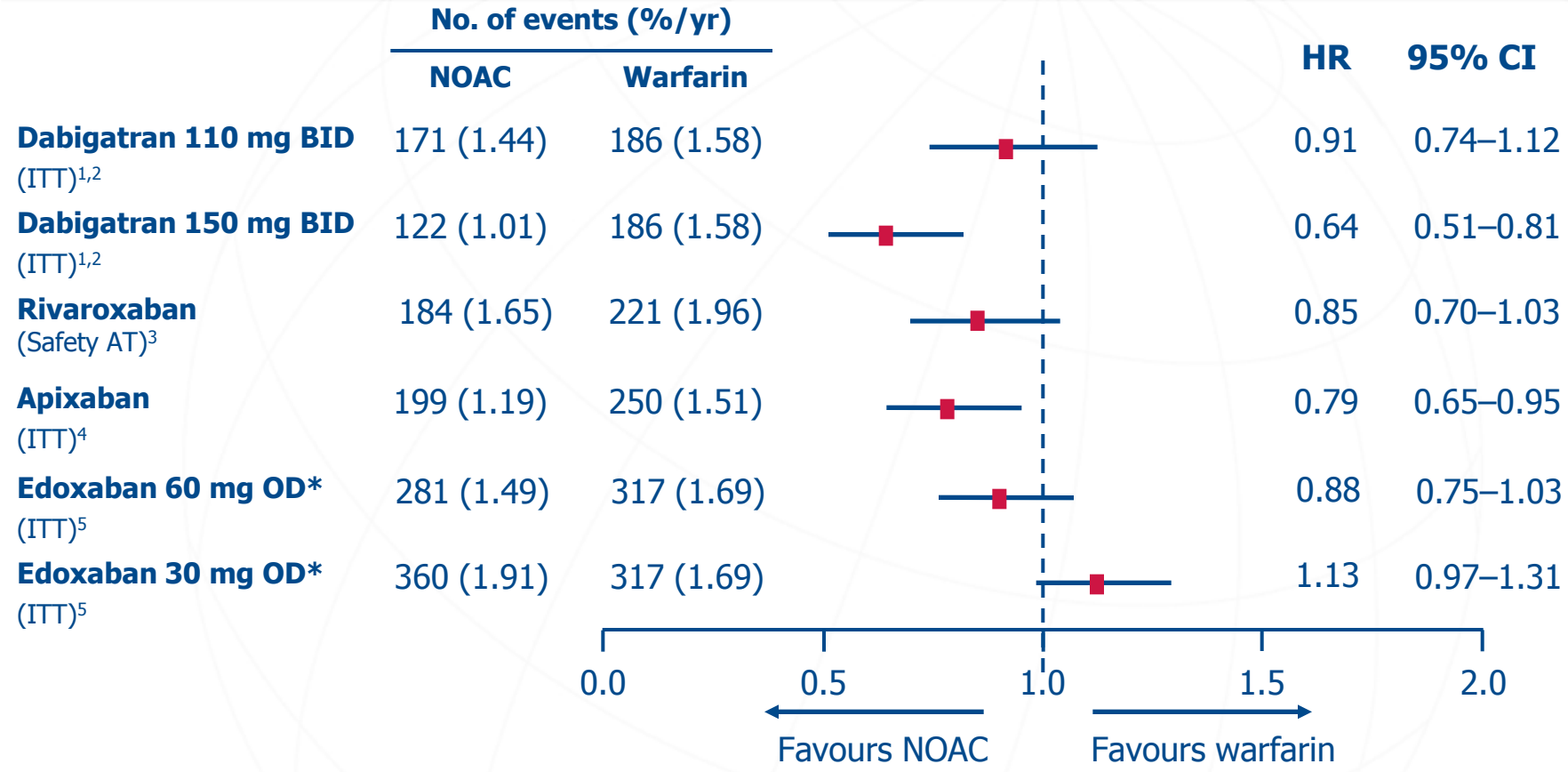
Stroke



Not head-to-head comparison – no clinical conclusions can be drawn – adapted from references 1–5

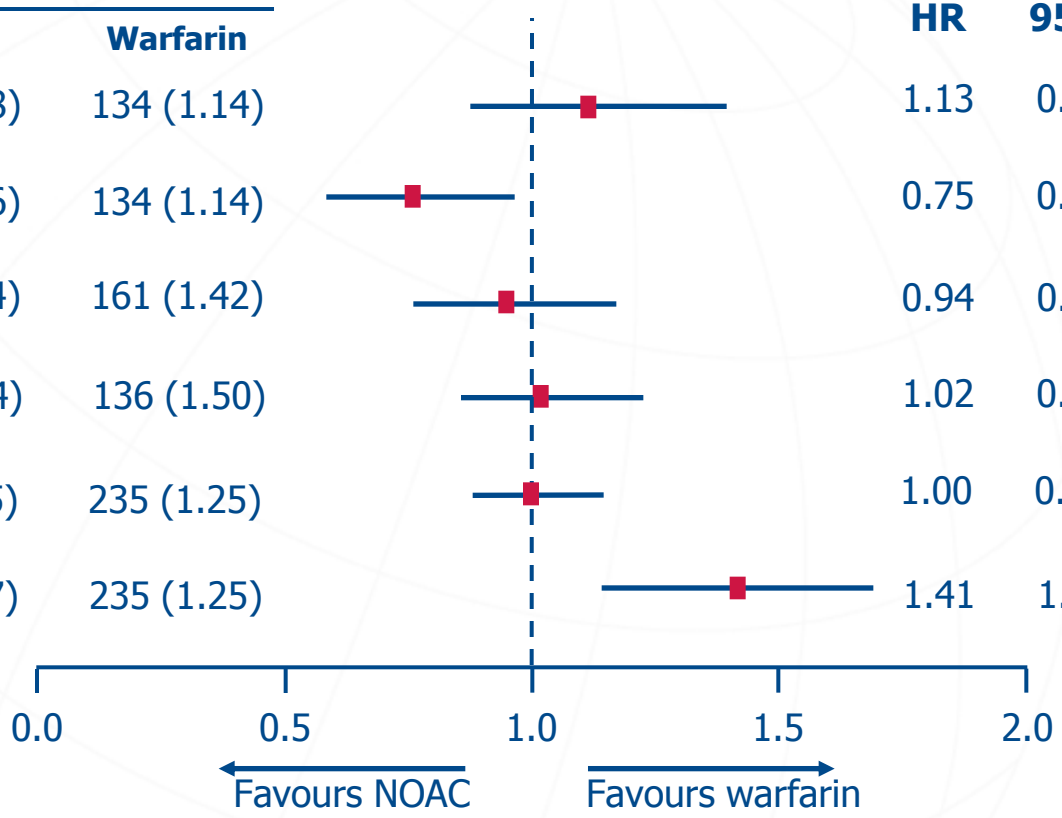
*Edoxaban dose halved (from 60 mg to 30 mg OD in high dose group; from 30 mg to 15 mg OD in low dose group) if CrCl 30–50 mL/min, weight <60kg, or concomitant verapamil, quinidine or dronedarone

AT = as treated; BID = twice daily; CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat

1. Connolly SJ et al. N Engl J Med 2009;361:1139–51; **2.** Connolly SJ et al. N Engl J Med 2010;363:1875–6;
3. Patel MR et al. N Engl J Med 2011;365:883–91; **4.** Granger C et al. N Engl J Med 2011;365:981–92;
5. Giugliano RP et al. N Engl J Med 2013; doi:10.1056/NEJMoa1310907

Ischaemic stroke

	No. of events (%/yr)		HR	95% CI
	NOAC	Warfarin		
Dabigatran 110 mg BID (ITT)[1–3]	152 (1.28)	134 (1.14)	1.13	0.89–1.42
Dabigatran 150 mg BID (ITT)[1–3]	103 (0.86)	134 (1.14)	0.75	0.58–0.97
Rivaroxaban (Safety AT)[4]	149 (1.34)	161 (1.42)	0.94	0.75–1.17
Apixaban* (ITT)[5]	140 (1.54)	136 (1.50)	1.02	0.81–1.29
Edoxaban 60 mg OD** (ITT)[6]	236 (1.25)	235 (1.25)	1.00	0.83–1.19
Edoxaban 30 mg OD** (ITT)[6]	333 (1.77)	235 (1.25)	1.41	1.19–1.67



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*Revised data; re-categorized following original publication

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AT = as treated; BID = twice daily; HR = hazard ratio; ITT = intention-to-treat; NOAC = novel oral anticoagulant

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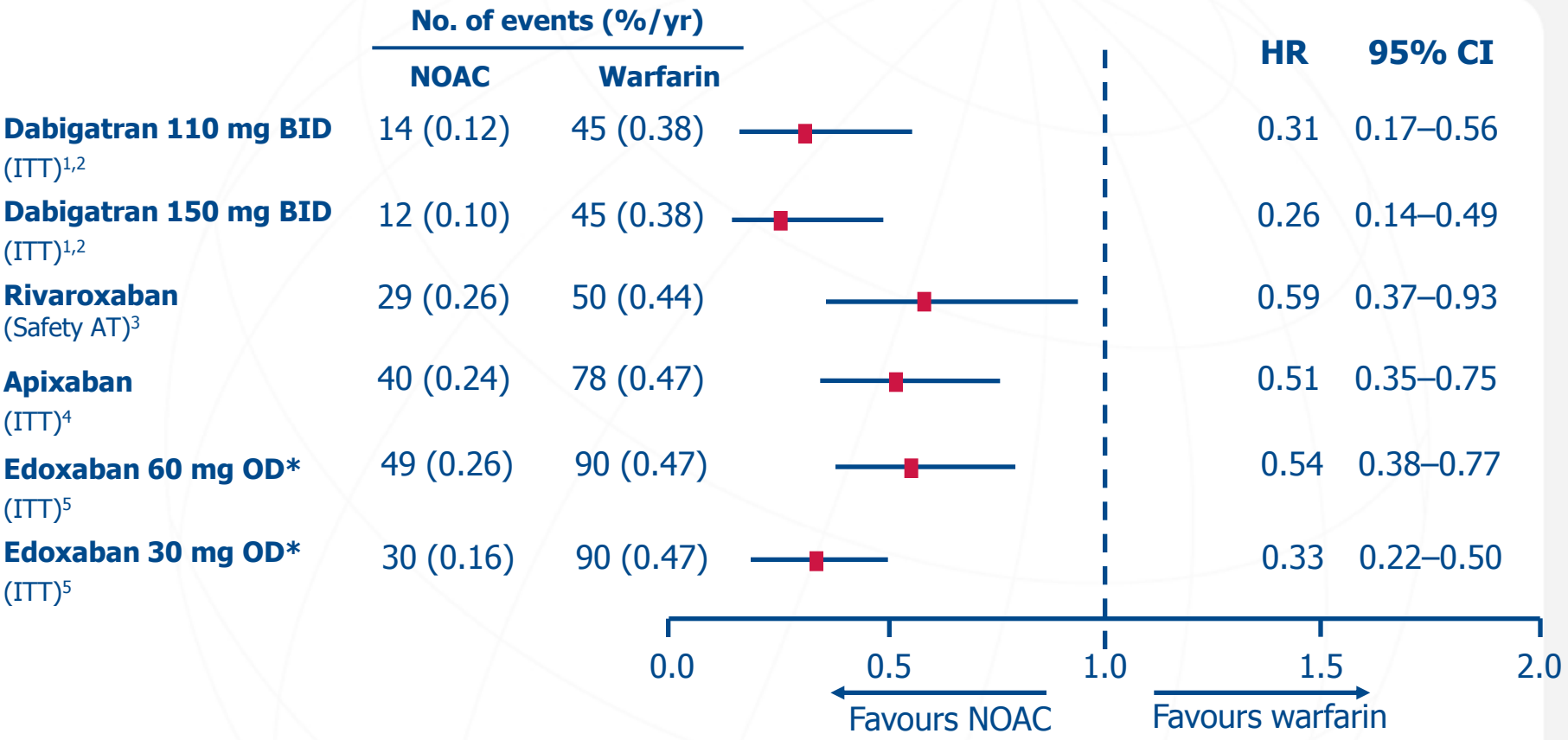
3. Boehringer Ingelheim. Pradaxa SmPC, 2013; **4.** Patel MR et al. N Engl J Med 2011;365:883–91;
5. Lopes R et al. Lancet 2012; 380:1749–58; **6.** Giugliano RP et al. N Engl J Med 2013; doi:10.1056/NEJMoa1310907

Haemorrhagic stroke



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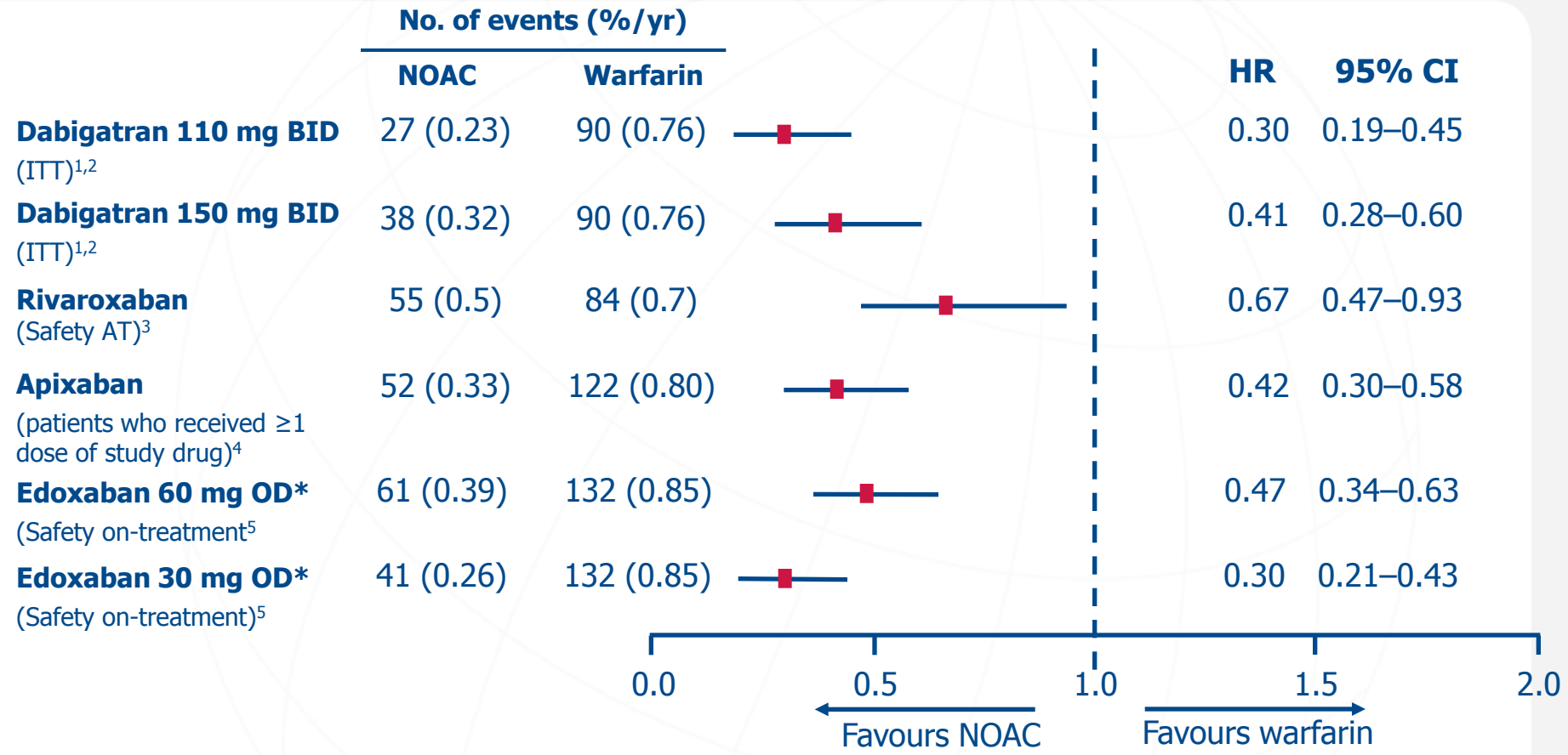
Intracranial bleeding



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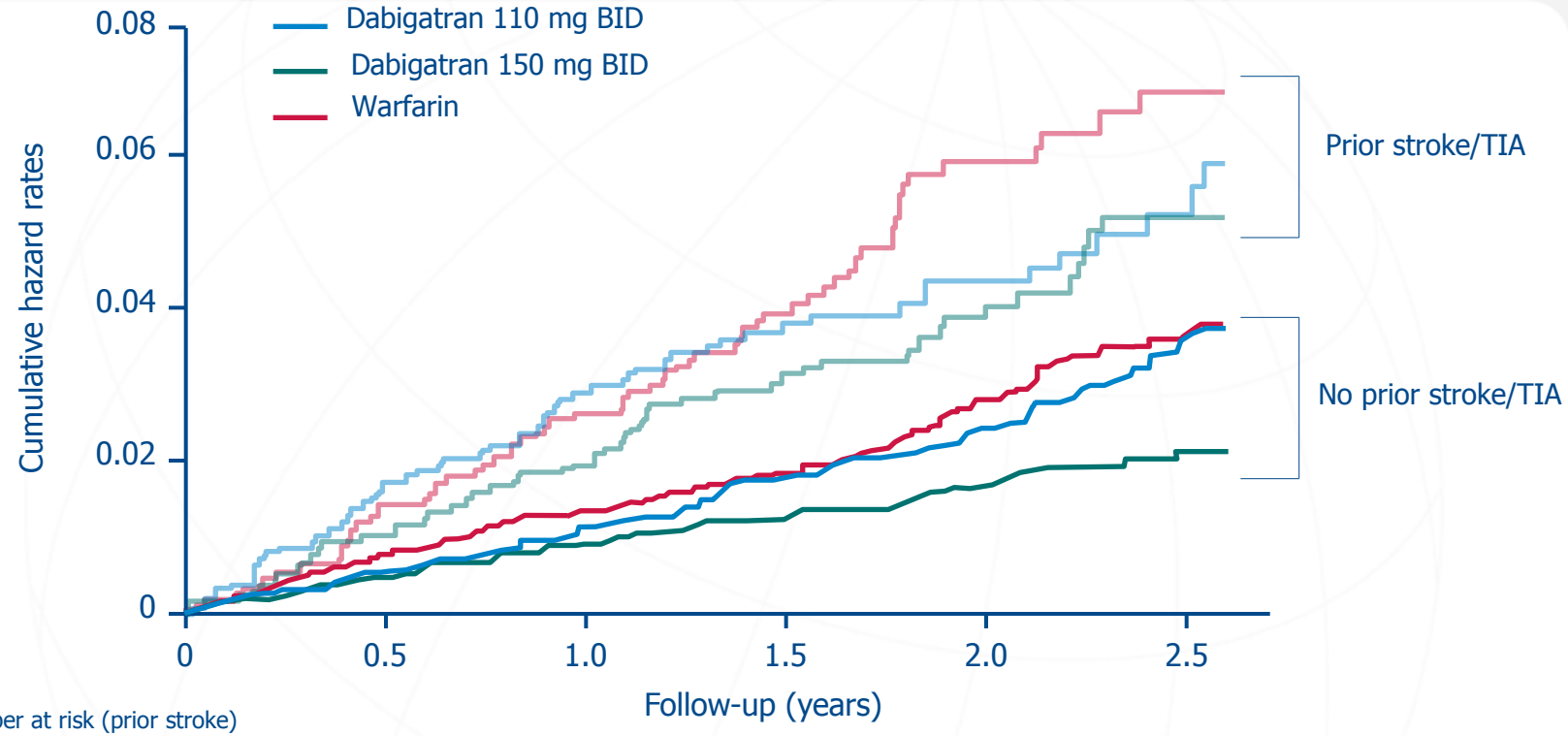
RE-LY® prior stroke subgroup analysis: time to stroke or systemic embolism in patients with/without previous stroke or TIA



Number at risk (prior stroke)						
Dabigatran 110 mg	1195	1159	1131	908	573	289
Dabigatran 150 mg	1233	1200	1163	938	517	321
Warfarin	1195	1159	1125	895	565	251
Number at risk (no prior stroke)						
Dabigatran 110 mg	4819	4702	4578	3684	2371	1096
Dabigatran 150 mg	4843	4739	4616	3744	2427	1108
Warfarin	4827	4703	4593	3698	2325	1061

BID = twice daily; TIA = transient ischaemic attack

Adapted from Diener HC et al. Lancet Neurol 2010;9:1157–63 and data on file.

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association | American Stroke Association

Nonvitamin-K-Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation and Previous Stroke or Transient Ischemic Attack : A Systematic Review and Meta-Analysis of Randomized Controlled Trials

George Ntaios, Vasileios Papavasileiou, Hans-Christoph Diener, Konstantinos Makaritsis and Patrik Michel

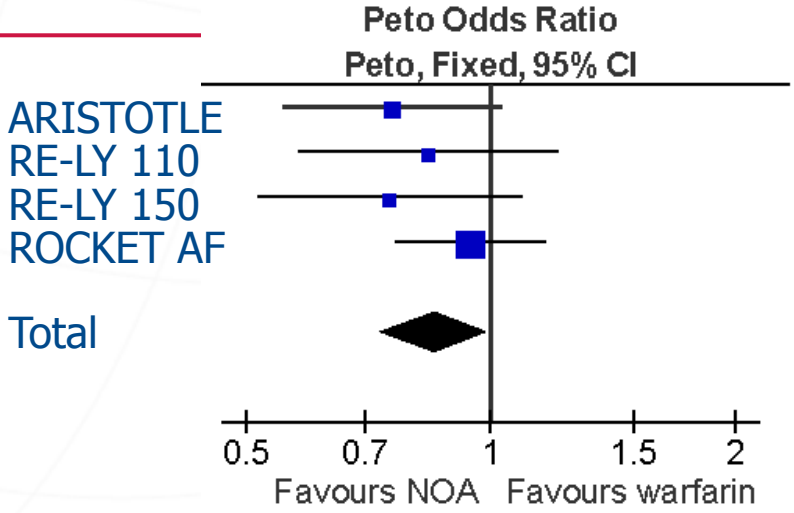
Stroke. published online November 13, 2012;

Ntaios G et al. Stroke 2012 Nov 13 [Epub ahead of print]

Effects of novel oral anticoagulants vs warfarin on stroke or systemic embolism in patients with AF and previous stroke or TIA (1)

Stroke or Systemic Embolism	NOACs		Warfarin			Peto Odds Ratio
Study or subgroup	*Events*	*Total*	*Events*	*Total*	*Weight*	*Peto, Fixed (95% CI)*
ARISTOTLE	73	1694	98	1742	22.1%	0.76 (0.56–1.03)
RE-LY 110	55	1195	65	1195	15.5%	0.84 (0.58–1.21)
RE-LY 150	51	1233	65	1195	15.0%	0.75 (0.52–1.09)
ROCKET AF	179	3754	187	3714	47.4%	0.94 (0.77–1.17)
Total (95% CI)		7876		7846	100%	0.85 (0.74–0.99)
Total events	358		415			

Heterogeneity: χ^2=1.93, df=3 (P=0.59); I^2=0%
Test for overall effect: Z=2.15 (P=0.03)



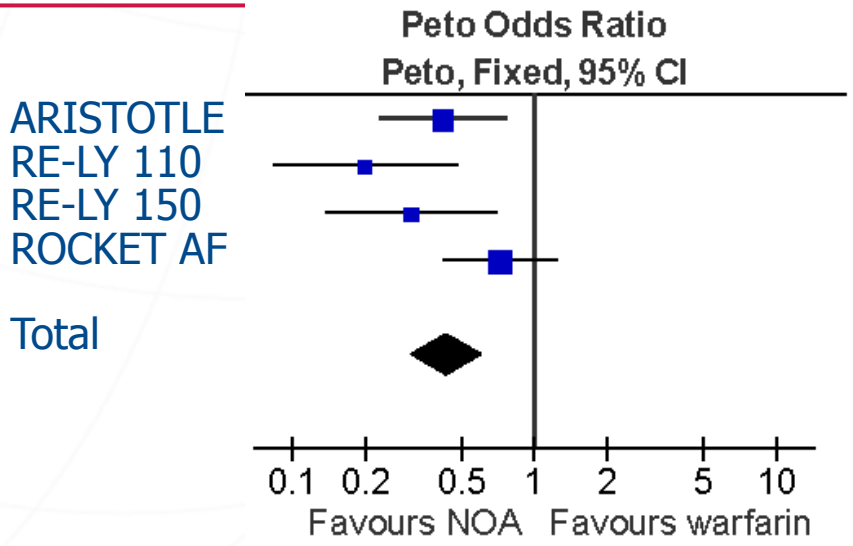
This study was not designed to compare NOACs against one another. Comparison between NOACs is not valid because of population differences among the studies. No head-to-head data are available

AF = atrial fibrillation; TIA = transient ischemic attack; NOAC = novel oral anticoagulant.

Ntaios G et al. Stroke 2012 Nov 13 [Epub ahead of print]

Effects of novel oral anticoagulants vs warfarin on haemorrhagic stroke in patients with AF and previous stroke or TIA (2)

Haemorrhagic stroke	NOACs		Warfarin			Peto Odds Ratio
Study or subgroup	*Events*	*Total*	*Events*	*Total*	*Weight*	*Peto, Fixed (95% CI)*
ARISTOTLE	12	1694	31	1742	31.1%	0.42 (0.23–0.77)
RE-LY 110	2	1195	18	1195	14.5%	0.20 (0.08–0.48)
RE-LY 150	5	1233	18	1195	16.7%	0.31 (0.14–0.70)
ROCKET AF	22	3754	30	3714	37.8%	0.73 (0.32–0.62)
Total (95% CI)		7876		7846	100%	0.44 (0.32– 0.62)
Total events	41		97			
Heterogeneity: χ^2=7.07, df=3 (P=0.07); I^2=58%						
Test for overall effect: Z=4.79 (P<0.00001)						



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AF = atrial fibrillation; TIA = transient ischemic attack; NOAC = novel oral anticoagulant.

Ntaios G et al. Stroke 2012 Nov 13 [Epub ahead of print]

NOACs: Special Problems

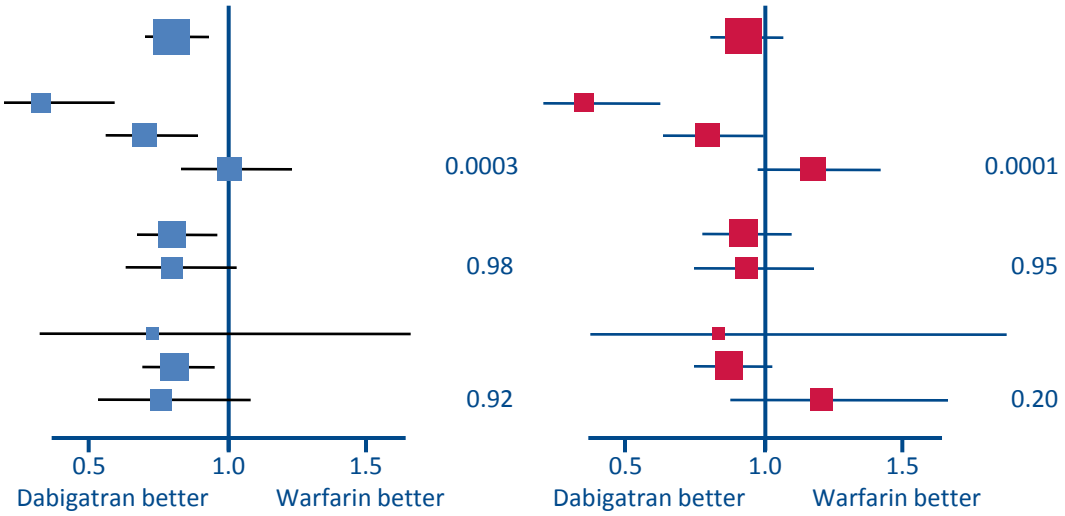
- Patients > 80 years
- CrCl 30-50 l/min
- Prior GI bleed
- Prior intracerebral bleed
- Gait apraxia and falls
- Cognitive impairment
- Start after TIA or stroke
- Afib and carotid stenosis
- Afib and stable coronary heart disease
- Afib and DVT prevention

Outline

- **Patients > 80 years**
- CrCl 30-50 l/min
- Prior GI bleed
- Prior intracerebral bleed
- Gait apraxia and falls
- Cognitive impairment
- Start after TIA or stroke
- Afib and carotid stenosis
- Afib and stable coronary heart disease
- Afib and DVT prevention

Age and bleeding subgroup analysis in the RE-LY trial: major bleeding in key subgroups

		Rate (% per year)						
		Dabigatran				Dabigatran 110 mg vs. warfarin	P value for interaction	Dabigatran 150 mg vs. warfarin	P value for interaction
	n	110 mg	150 mg	Warfarin				
Overall	18 113	2.87	3.31	3.57				
Age <65 yrs	2971	0.82	0.89	2.43				
Age 65–74 yrs	7884	2.29	2.60	3.25				
Age ≥75 yrs	7258	4.43	5.10	4.37			0.0003		0.0001
Male	11 514	2.92	3.37	3.63					
Female	6598	2.79	3.23	3.46			0.98		0.95
Weight <50 kg	376	4.30	4.92	5.95					
Weight 50–99 kg	14 629	2.91	3.13	3.57					
Weight ≥100 kg	3099	2.56	4.02	3.34			0.92		0.20



- Both doses of dabigatran compared with warfarin were associated with an increasing relative risk of major bleeding with increasing age categories
- No significant interactions between sex or body weight

Eikelboom JW et al. Circulation 2011;123:2362–72

Conclusion 1

- In patients with age >75 years and increased risk of bleeding the 2 x 110 mg dose of dabigatran should be used
- In the ROCKET-AF and ARISTOTLE trials elderly patients had higher absolute rates of stroke and systemic embolism and higher absolute rates of major bleeding
- The overall relative effects of rivaroxaban or apixaban vs. warfarin were consistent among elderly (and younger) patients for both efficacy and safety

Outline

- Patients > 80 years
- **CrCl 30-50 l/min**
- Prior GI bleed
- Prior intracerebral bleed
- Gait apraxia and falls
- Cognitive impairment
- Start after TIA or stroke
- Afib and carotid stenosis
- Afib and stable coronary heart disease
- Afib and DVT prevention

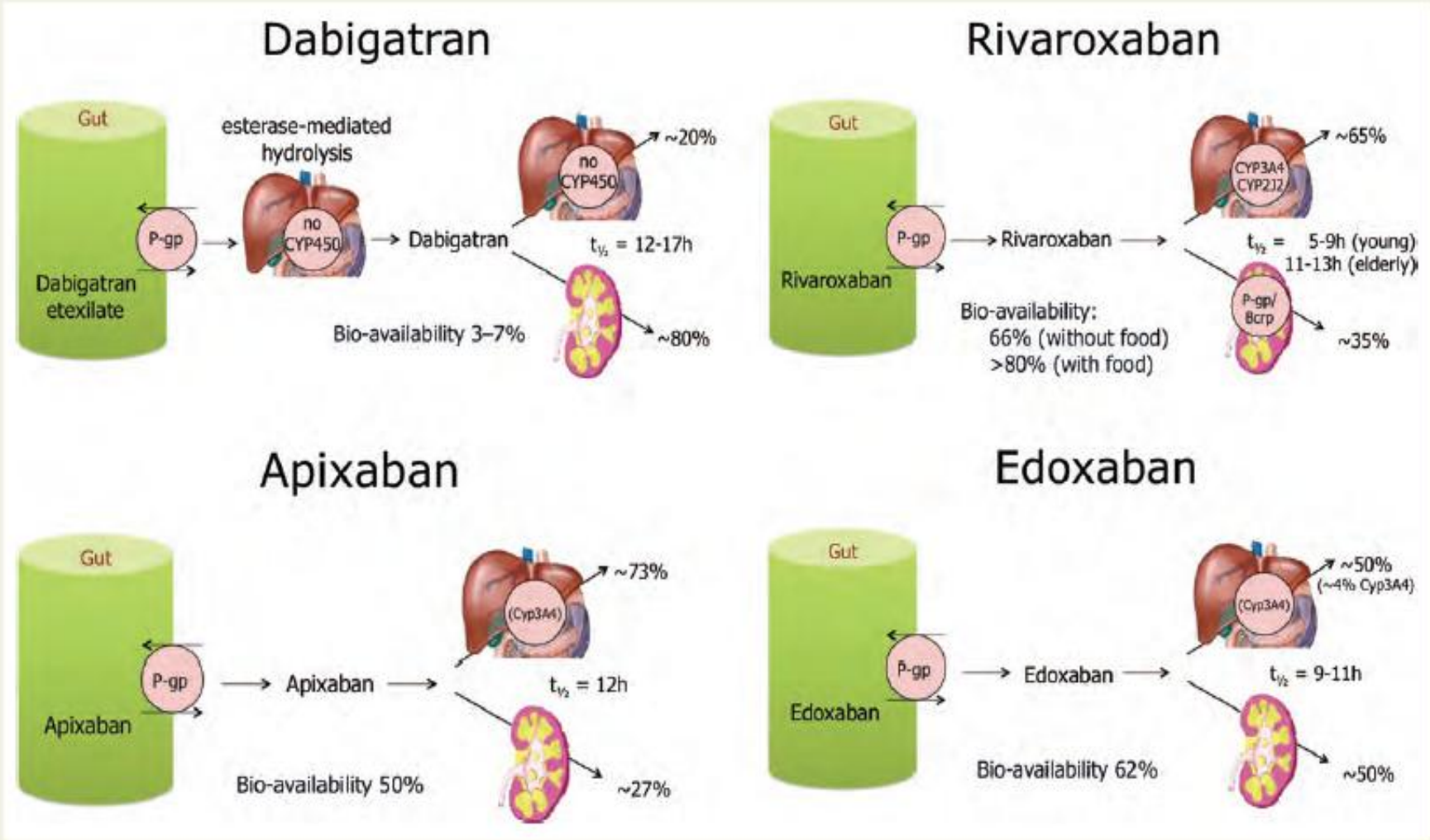
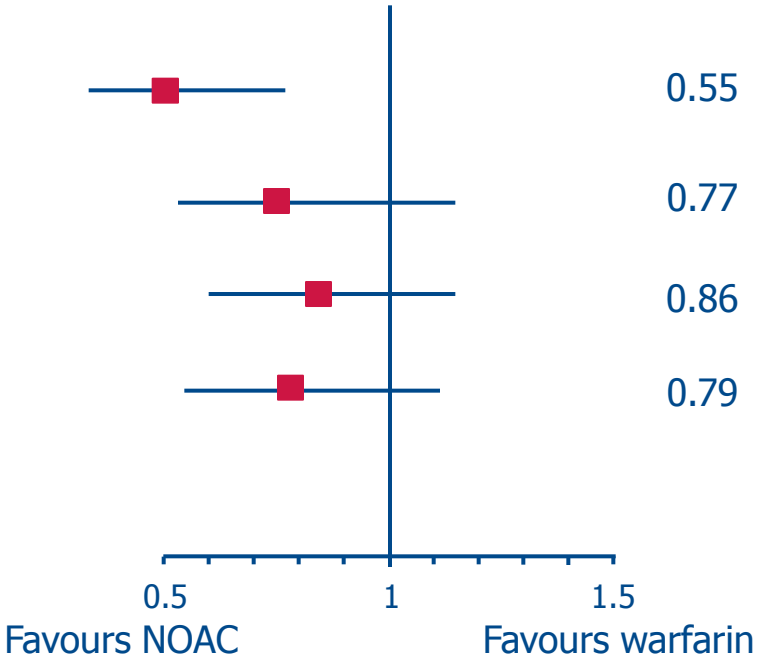


Figure 5 Absorption and metabolism of the different new anticoagulant drugs. There are interaction possibilities at the level of absorption or first transformation, and at the level of metabolisation and excretion. The brackets around (Cyp3A4) in the apixaban graph indicate a minor contribution of this pathway to hepatic clearance, the majority of the drug being excreted as unchanged parent. See also *Table 4* for the size of the interactions based on these schemes.

Data from Phase III trials in patients with moderate renal impairment (CrCl 30–49 mL/min)

Stroke and systemic embolism

	Study drug (%/yr)	Warfarin (%/yr)	HR
RE-LY®: Dabigatran 150 mg*[1,2]	1.52	2.78	0.55
RE-LY®: Dabigatran 110 mg*[1,2]	2.15	2.78	0.77
ROCKET AF: Rivaroxaban[3]	2.95	3.44	0.86
ARISTOTLE: Apixaban*[4]	2.11	2.67	0.79



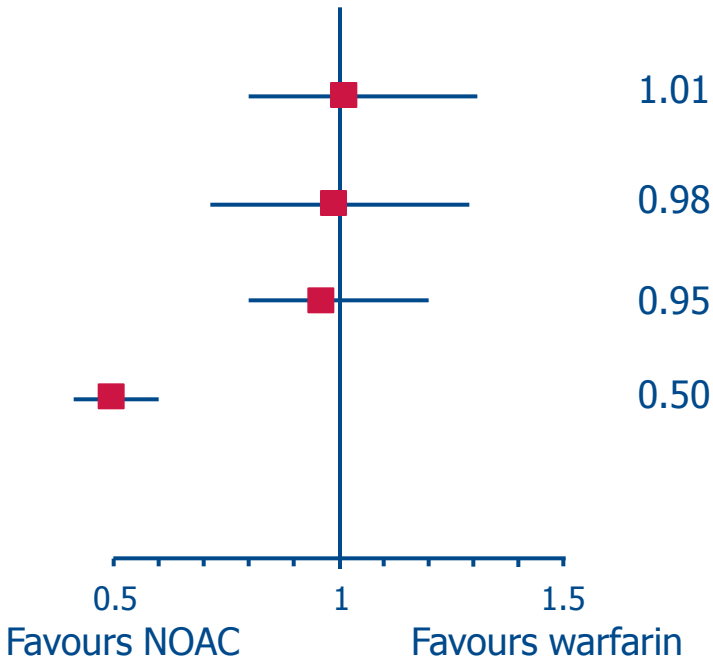
*Includes patients with CrCl <50; HR = hazard ratio; Error bars = 95% confidence intervals

1. Connolly S et al. NEJM 2009; 361:1139–51; **2**. Eikelboom J et al. Circulation 2011;123:2363–72; **3**. Fox et al. Eur Heart J 2011; 32:2387–94; **4**. Hohnloser S et al. Eur Heart J 2012; 33:2821–31

Data from Phase III trials in patients with moderate renal impairment (CrCl 30–49 mL/min)

Major bleeding

	Study drug (%/yr)	Warfarin (%/yr)	HR
RE-LY®: Dabigatran 150 mg*[1,2]	5.44	5.41	1.01
RE-LY®: Dabigatran 110 mg*[1,2]	5.29	5.41	0.98
ROCKET AF: Rivaroxaban[3]	4.49	4.70	0.95
ARISTOTLE: Apixaban*[4]	3.21	6.44	0.50



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Conclusion 2

- Efficacy of new anticoagulants seems to be preserved in the CrCl range of 30-50 ml/min
- Bleeding risk might be increased (but less so compared to warfarin)
- Patients at old age, with low body weight and co-morbidity need to be monitored on a regular basis and dose of NOAC might be reduced
- Acute infections leading to fluid loss are a risk factor for bleeding with NOACs

Outline

- Patients > 80 years
- CrCl 30-50 l/min
- **Prior GI bleed**
- Prior intracerebral bleed
- Gait apraxia and falls
- Cognitive impairment
- Start vafter TIA or stroke
- Afib and carotid stenosis
- Afib and stable coronary heart disease
- Afib and DVT prevention

Conclusion 3

- Detailed subgroup data not published for apixaban and rivaroxaban
- Prior GI bleed is not a contraindication for anticoagulation with NOACs when the source of bleeding has been identified
- In patients >75 years and a history of lower GI bleeding, the lower dose of dabigatran (2 x 110 mg) should be used

The NEW ENGLAND JOURNAL of MEDICINE

Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.*

Analysis	Dabigatran			Warfarin		
	No. of Patients	No. of Events	Incidence *no. of events/ 100,000 days at risk*	No. of Patients	No. of Events	Incidence *no. of events/ 100,000 days at risk*
Gastrointestinal hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,599	16	1.6	43,541	160	3.5
Sensitivity analysis without required diagnosis of atrial fibrillation	12,195	19	1.6	119,940	338	3.1
Intracranial hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,587	8	0.8	43,594	109	2.4
Sensitivity analysis without required diagnosis of atrial fibrillation	12,182	10	0.9	120,020	204	1.9

* Patients were included in the cohorts if, in the 183 days before the index dispensing of dabigatran or warfarin, they were enrolled in plans for drug and medical coverage and had been given a diagnosis of atrial fibrillation in any care setting. Patients were excluded from the cohorts if, in the 183 days before the index dispensing, they had a claim for an event of interest in an inpatient or emergency department setting or a claim for dispensing of dabigatran or warfarin. Events were assessed during drug exposure, from inpatient or emergency department settings only.

Outline

- Patients > 80 years
- CrCl 30-50 l/min
- Prior GI bleed
- **Prior intracerebral bleed**
- Gait apraxia and falls
- Cognitive impairment
- Start vafter TIA or stroke
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- Afib and DVT prevention

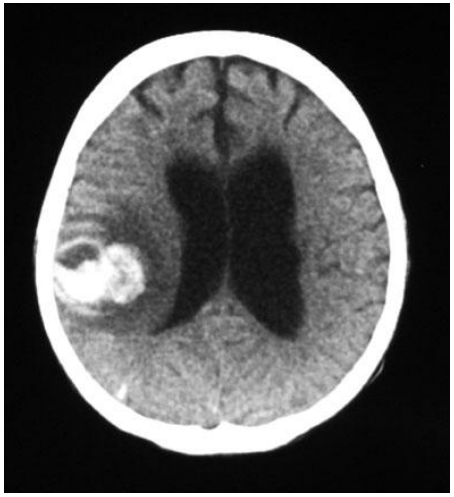
Afib and Intracerebral Bleed

- Patients with prior intracerebral bleeds were excluded from the trials with NOACs
- Treatment with NOACs depends on the aetiology of the bleed
- Conditions that can be treated or controlled (e.g. hypertension) are no contraindication
- Sustained high bleeding risk (imaging information suggesting amyloid angiopathy) is a clear contraindication

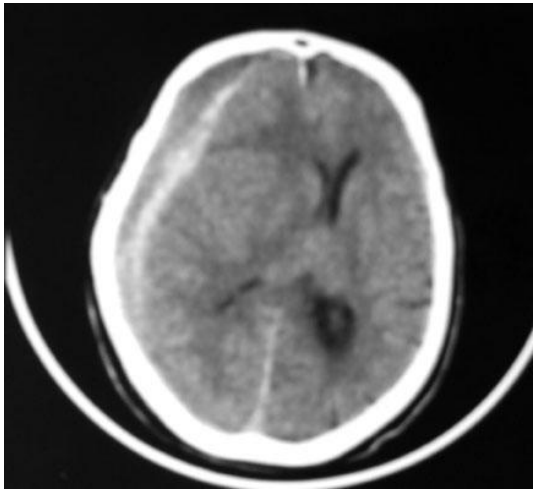
Types of Intracranial Haemorrhage

Intracranial Hemorrhages in RE-LY
n=154

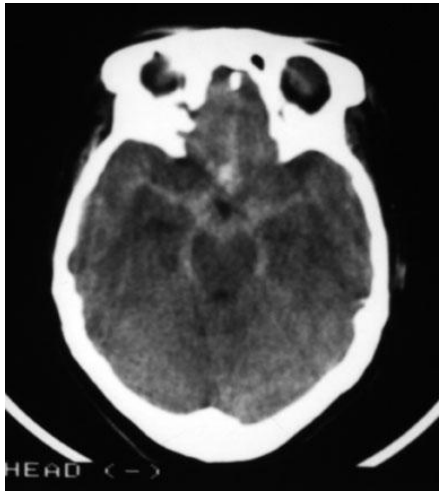
Intracerebral
46%



Subdural
45%

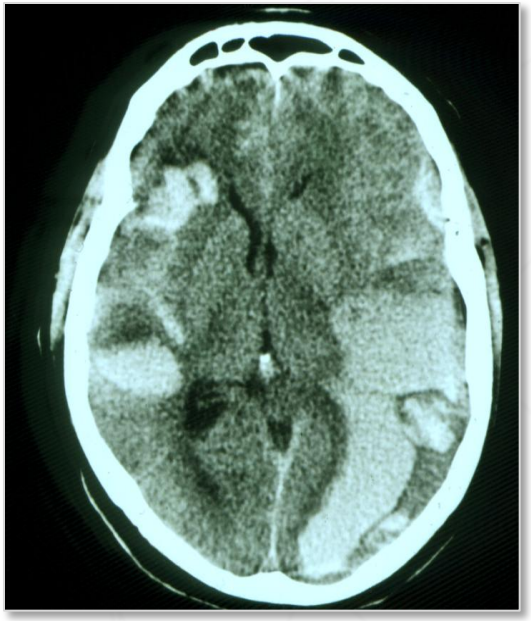


Subarachnoid
8%

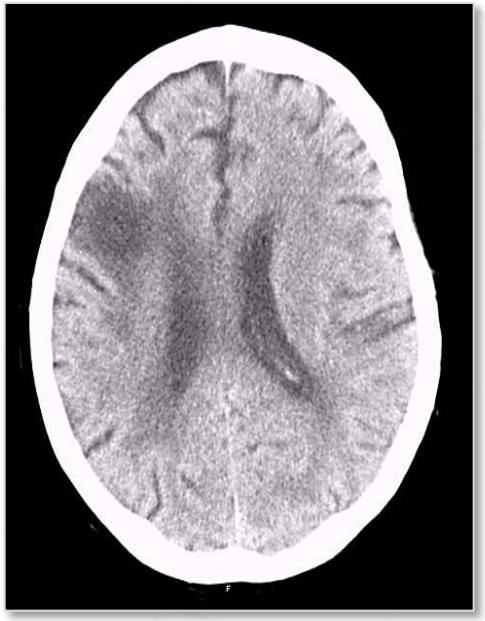


Connolly S, et al. *N Engl J Med*. 2009;361:1139-1151.

Mortality index after hemorrhagic stroke/ICH and ischaemic stroke: data from the RE-LY study



ICH



Ischaemic stroke

In comparison: mortality after a major bleed*
6.8%

	Mortality
Warfarin	**36%** (32/90)
Dabigatran 150 mg BID	**35%** (13/37)
Dabigatran 110 mg BID	**41%** (12/27)

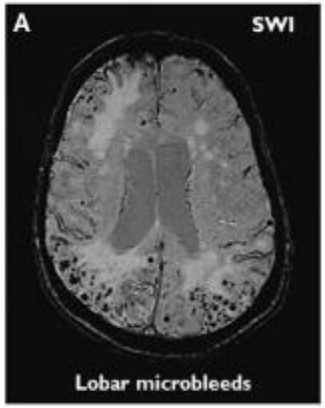
Mortality
20%

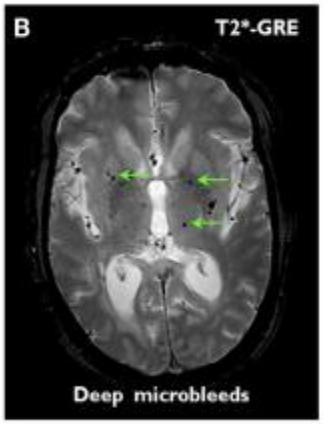
*RE-LY study. Boehringer Ingelheim, data on file

BID = twice daily; ICH = intracranial haemorrhage

Gladstone DJ et al. Stroke 2009;40:235–40; Hart RG et al. Stroke 2012;43:1511–17

Cererbral microbleeds





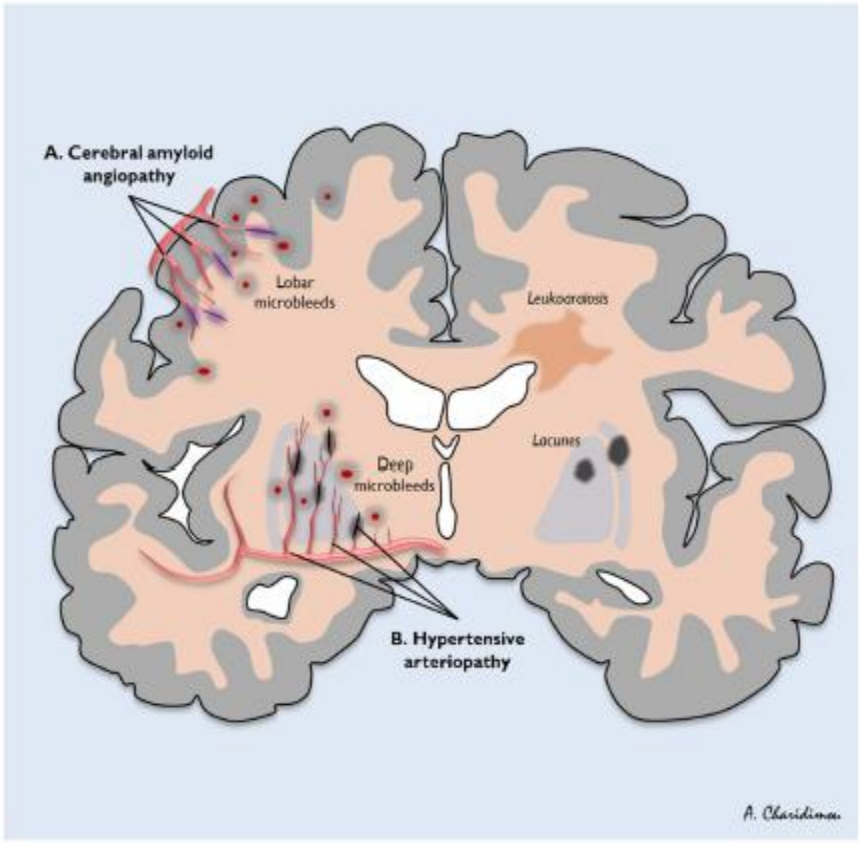
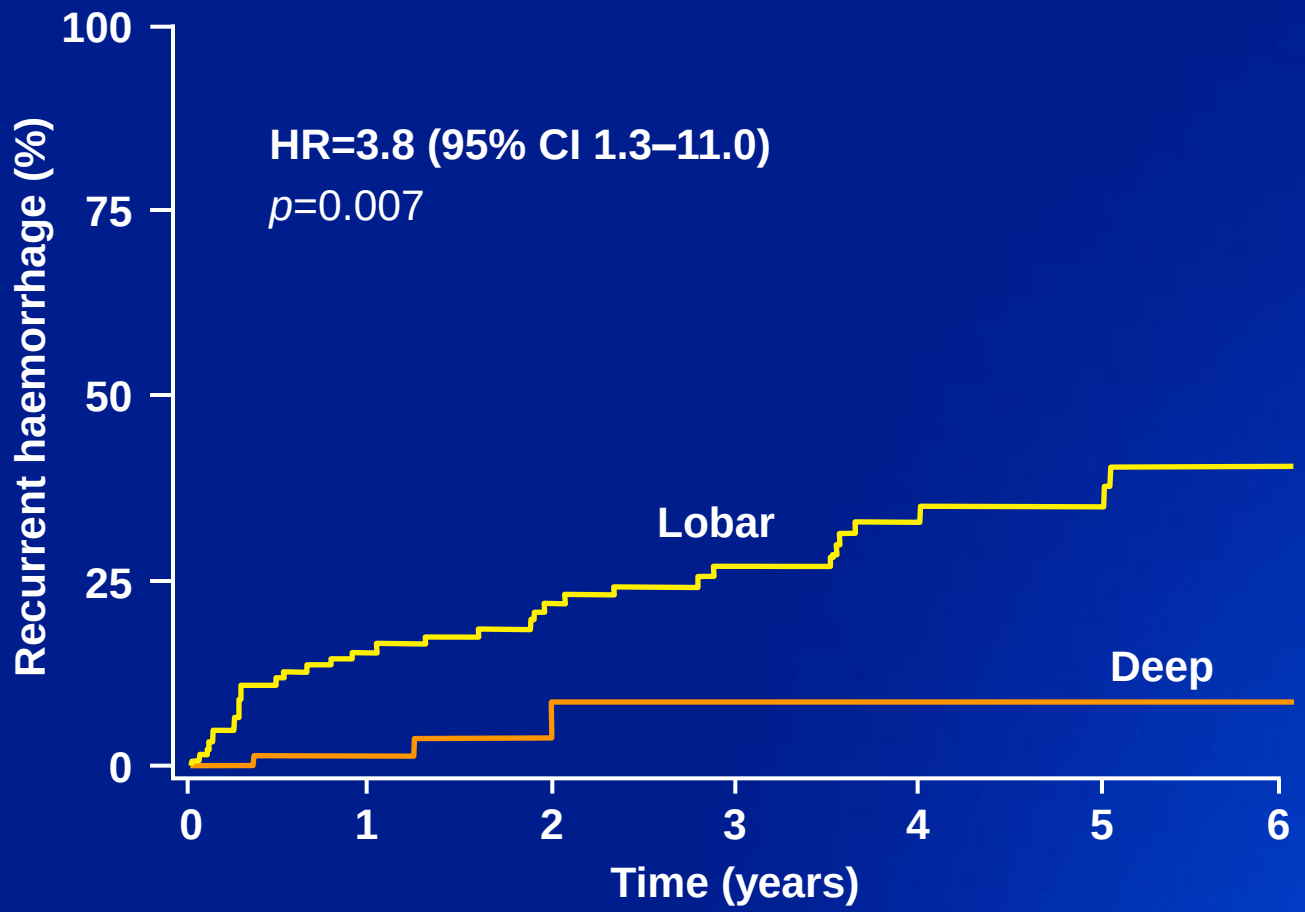


FIGURE 3 | The distribution of sporadic small vessel disease in the brain and the topography of cerebral microbleeds (CMBs). (A) Cerebral amyloid angiopathy (CAA) preferentially affects the small arteries and arterioles of the cerebral cortex and gray–white matter junction by the deposition of amyloid-β in the vessel walls (purple); **(B)** hypertensive arteriopathy typically affects small deep arterial perforators (black). CMBs are a marker for the severity and type of small vessel disease; their anatomic distribution is meant to reflect the underlying pathological vessel damage. Hence, CMBs (dark, rounded lesions) located in cortical-subcortical regions are presumably caused by CAA **(A)**, whereas CMBs located in deep brain regions mainly result from hypertensive arteriopathy **(B)**. **(A)** is an axial susceptibility-weighted imaging (SWI) which is currently the most sensitive means to image CMBs. **(B)** is an axial T2*-weighted gradient-recalled echo (T2*-GRE) MRI.

Risk for recurrent ICH varies with location



Viswanathan *et al*, 2006

Conclusion 4

- In cases of high risk of ischemic stroke (CHADS2) and moderate risk of cerebral bleeding NOACs are clearly preferred over warfarin
- Re-initiation of oral anticoagulation after 4-8 weeks
- Safety data from prospective registries needed

Outline

- Patients > 80 years
- CrCl 30-50 l/min
- Prior GI bleed
- Prior intracerebral bleed
- **Gait apraxia and falls**
- Cognitive impairment
- Start after TIA or stroke
- Afib and carotid stenosis
- Afib and stable coronary heart disease
- Afib and DVT prevention

Afib Gait Apraxia and Falls

- Need to teach cardiologists to refer these patients for evaluation to a neur[illegible]st
- Parkinsons's dise[illegible]ure hydr[illegible] c[illegible]
- A[illegible] [illegible]disease with gait ap[illegible] cognitive impairment is a contraindication

RISK OF FALLS?
Number needed to fall/J: 295
high risk of falls = high risk of ischemia
Arch Intern Med 1999;159:677; Am J Med 2005;118:612

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Afib and Cognitive Impairment

- Cognitive impairment is not a contraindication for anticoagulation as long as compliance is controlled by a caregiver
- Severe small vessel disease is a contraindication
- New oral anticoagulants are easier to handle than vitamin-K antagonists (no INR control required)

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When to Start a NOAC After an Acute Stroke?

*'As a rule of thumb the **1-3-6-12 day** with re-institution of anticoagulation in patients with a transient ischaemic attack (TIA) after 1 day, with small, non-disabling infarct after 3 days, with a moderate stroke after 6 days, while large infarcts involving large parts of the arterial territory will be treated not before 2 (or even 3) weeks.'* EHRA PRACTICAL GUIDE

Patients with a very recent stroke were excluded from the AF trials as follows:

RE-LY:	Stroke within 14 days or severe stroke within 6 months of screening
ROCKET-AF:	Severe, disabling stroke (modified Rankin score of 4 to 5, inclusive within 3 months or any stroke within 30 days before the randomization visit
ARISTOTLE:	Recent stroke (within 7 d)
ENGAGE:	Stroke within 30 days

Heidbuchel European Heart Journal doi:10.1093/eurheartj/eht134
Patel N EJM 2011 Sep 8;365(10):883-91
Connolly et al. NEJM. 2009 Sep 17;361(12):1139-51
Granger et al. NEJM. 2011 Sep 15;365(11):981-92

Start after TIA or Stroke

- Patients who had a TIA or stroke could not be randomised in the first 7-14 days after the event

Stroke Severity	Restart
TIA	as soon as imaging has excluded a cerebral haemorrhage
Mild Stroke	**3-5 days after symptom onset**
Moderate Stroke	**5-7 days after stroke onset**
Severe Stroke	**2 weeks after stroke onset**

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- Afib and stable coronary heart disease
- Afib and DVT prevention

Afib and Carotid stenosis

- Patients with Afib and symptomatic carotid stenosis should be operated and not stented to avoid triple therapy (anticoagulation + aspirin + clopidogrel)

Concomitant Aspirin + clopidogrel subgroup analysis: major bleeding

	Dabigatran 110 mg BID	Dabigatran 150 mg BID	Warfarin
Aspirin + clopidogrel			
Annual rate (%)	4.72	4.66	5.21
RR (95% CI) vs. warfarin	0.77 (0.50–1.21)	0.81 (0.52–1.26)	
No Aspirin + clopidogrel			
Annual rate (%)	2.77	3.24	3.48
RR (95% CI) vs. warfarin	0.81 (0.61–0.94)	0.95 (0.82–1.10)	
P value for interaction	0.8727	0.5167	

- A separate analysis found that concomitant use of antiplatelet therapy increases the risk of major bleeding, with similar effects seen for dabigatran 110 mg BID, 150 mg BID or warfarin

BID = twice daily

Eikelboom JW et al. Circulation 2011;123:2363–72

Outline

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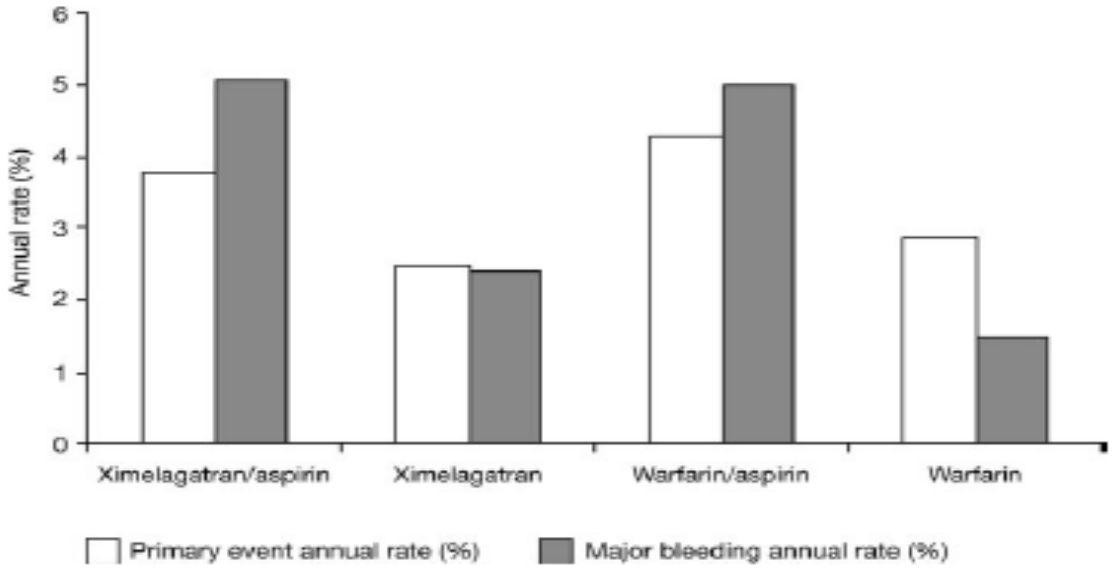
- **Afib and stable coronary heart disease**
- Afib and DVT prevention

Afib and Stable Coronary Heart Disease

- Patients with stable coronary heart disease do not benefit from the combination of warfarin and aspirin
- The bleeding risk is increased with the combination of aspirin and anticoagulation



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- Afib and stable coronary heart disease
- **Afib and DVT prevention**

Afib, Acute Stroke and DVT

- All new anticoagulants are effective in the prevention of deep vein thrombosis
- In patients at risk of DVT after an acute stroke DVT prevention with LMWH should be terminated 24 hours after the initiation of therapy with a new anticoagulant

Summary

- Patients > 80 years
- CrCl 30-50 l/min
- Prior GI bleed
- Prior intracerebral bleed
- Gait apraxia and falls
- Cognitive impairment
- Start after TIA or stroke
- Afib and carotid stenosis
- Afib and stable coronary heart disease
- Afib and DVT prevention
- Thrombolysis

Novel Anticoagulants in Stroke Prevention in Patients with Atrial Fibrillation
The Past, the Present and **the Future**

Hans-Christoph Diener

Department of Neurology and Stroke Center

University Hospital Essen

Germany

Rationale for anti-dabigatran Fab approach

Safe restoration of coagulation:

- Binds dabigatran with high affinity
- No homology of dabigatran to endogenous receptors/ligands
  - ➢ Off-target binding is not expected
- No activated coagulation expected since Fab targets only dabigatran
  - Shorter half life than full mAb (hrs vs days for a full mAb)

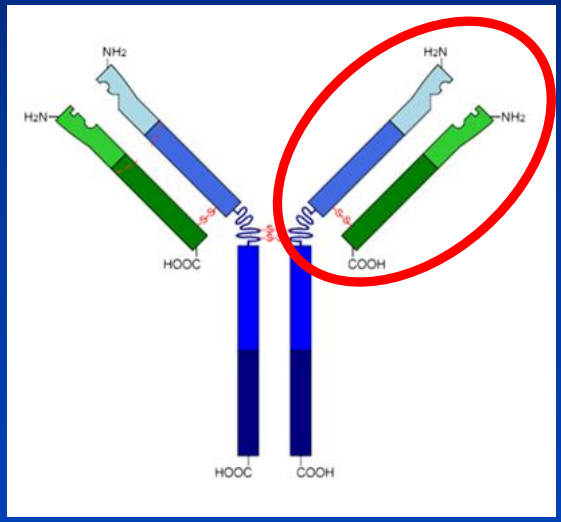
Easy and rapid administration:

- Administration route is intravenous, immediate onset of action

Low risk of adverse reactions:

- Humanized antibody fragment (Fab)
- No Fc receptor binding

Fab = **F**ragment **a**ntigen **b**inding



Fc = fragment crystallizable; mAb = monoclonal antibody

A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa

Genmin Lu[1], Francis R DeGuzman[2], Stanley J Hollenbach[2], Mark J Karbarz[1], Keith Abe[2], Gail Lee[2], Peng Luan[1], Athiwat Hutchaleelaha[3], Mayuko Inagaki[3], Pamela B Conley[1], David R Phillips[1] & Uma Sinha[1]

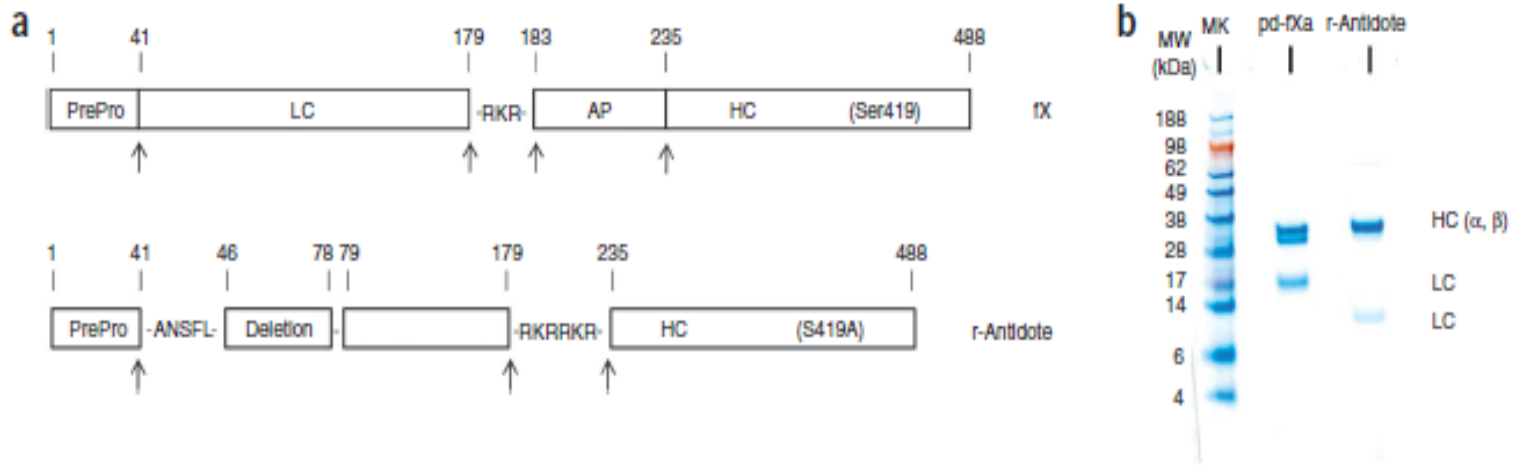
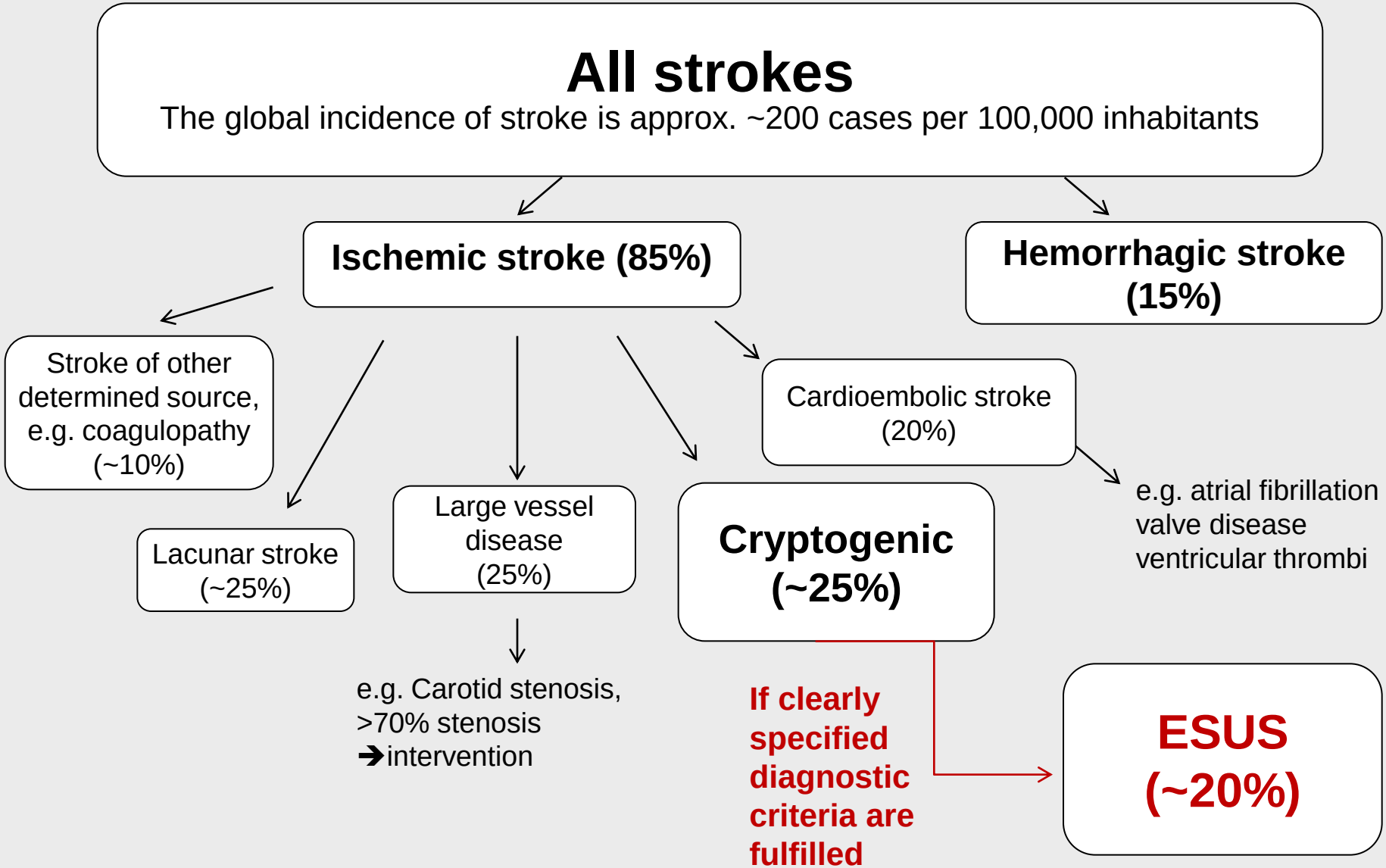


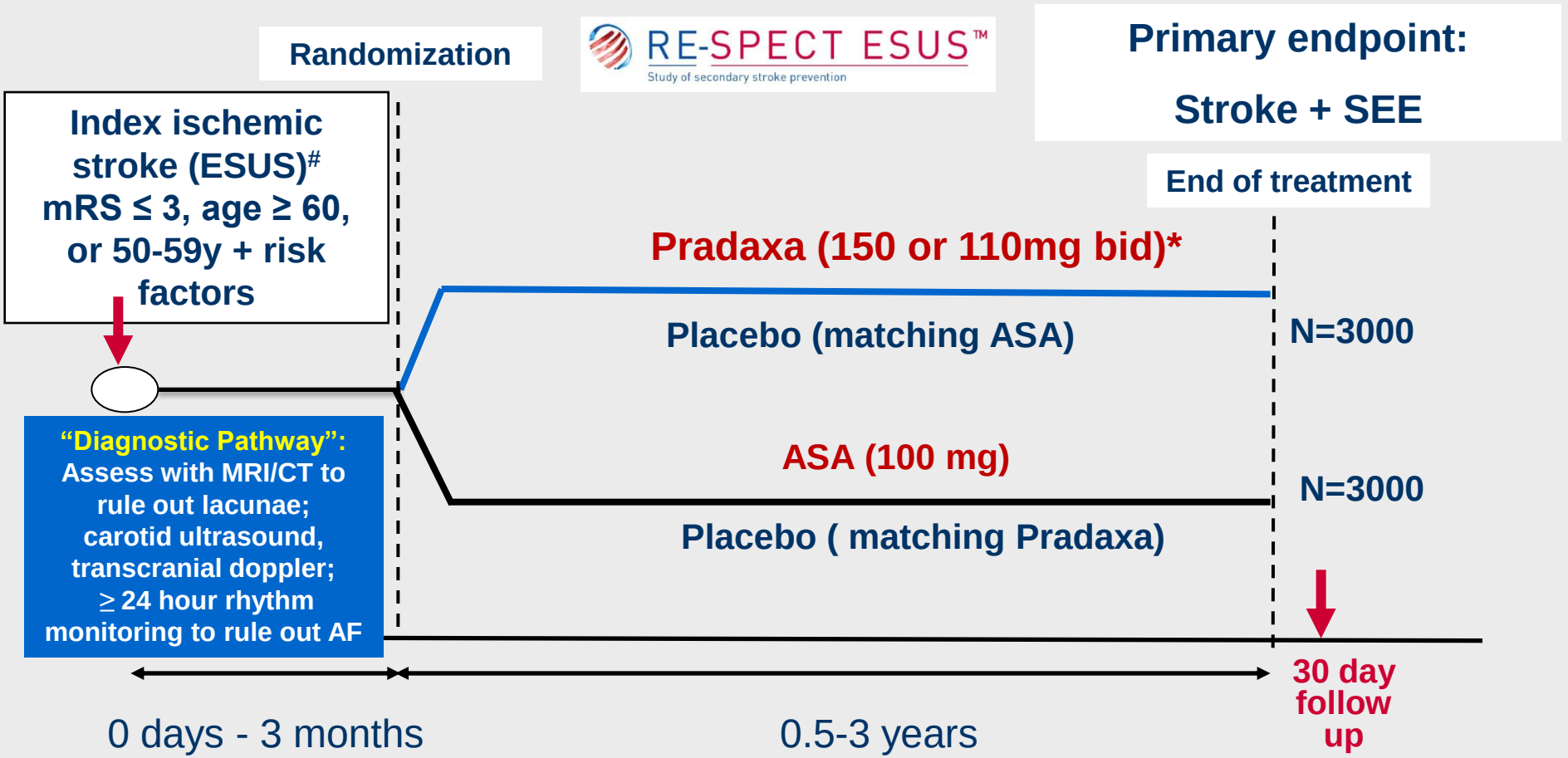
Figure 1 Design of r-Antidote and protein expression in CHO cells. (**a**) Schematic illustration of the domain structure of full-length human fX and r-Antidote (PRT064445) precursors. Using fX as a template, modifications were made in three regions to generate r-Antidote: deletion of a 34-residue fragment (residues 46–78) that contains the 11 GLA residues; replacement of the activation peptide (AP) with ArgLysArg (RKR) to form the RKRRKR linker that connects the light chain (LC) to the heavy chain (HC); and mutation of the active-site serine to alanine (S419A). Arrows indicate potential cleavage sites. (**b**) Reduced SDS-PAGE of purified r-Antidote showing bands of expected molecular weight (MW) for the light (~11 kDa) and heavy (~28 kDa) chains. The double bands of the heavy chain of plasma-derived fXa (pd-fXa) and r-Antidote correspond to the α- and β-isoforms. MK, molecular weight marker.

What is Embolic Stroke of Undetermined Source ?

RE-SPECT ESUS™
Study of secondary stroke prevention



Double blind randomized controlled clinical trial comparing safety and efficacy of dabigatran to ASA for secondary prevention of ESUS



***All patients will receive Dabigatran 150mg bid, unless they are ≥ 75 years of age or have a CrCL < 50ml/min, who will receive 110mg bid**

 # Includes "TIA" *with pathological imaging evidence* according to the 2013 updated stroke definitions

Thank you for your attention