Dabigatran: which indications should we re-ly on ?

- A Capucci FESC, FACC, FHRS
- Clinica di Cardiologia
- Universita' Politecnica delle Marche
- Ancona-Italy

AF Is Associated With Increased Thromboembolic Risk

- Major cause of stroke in elderly[1]
- 5-fold ↑ in risk of stroke[1,2]
- 15% of strokes in US are attributable to AF[3]
- Stroke severity (and mortality) is worse with AF than without AF[4]
- Incidence of all-cause stroke in patients with AF: 5%[1]
- Stroke risk persists even in asymptomatic AF[5]

1. Fuster V, et al. *J Am Coll Cardiol.* 2001;38(4):1231-1266.
2. Benjamin EJ, et al. *Circulation*. 1998;98(10):946-952.
3. Atrial Fibrillation Investigators. *Arch Intern Med*. 1994;154(13):1449-1457.
4. Dulli DA, et al. *Neuroepidemiology.* 2003;22(2):118-123.
5. Page RL, et al. *Circulation.* 2003;107(8):1141-1145.

Risk factors for ischemic stroke, TIA and systemic embolism

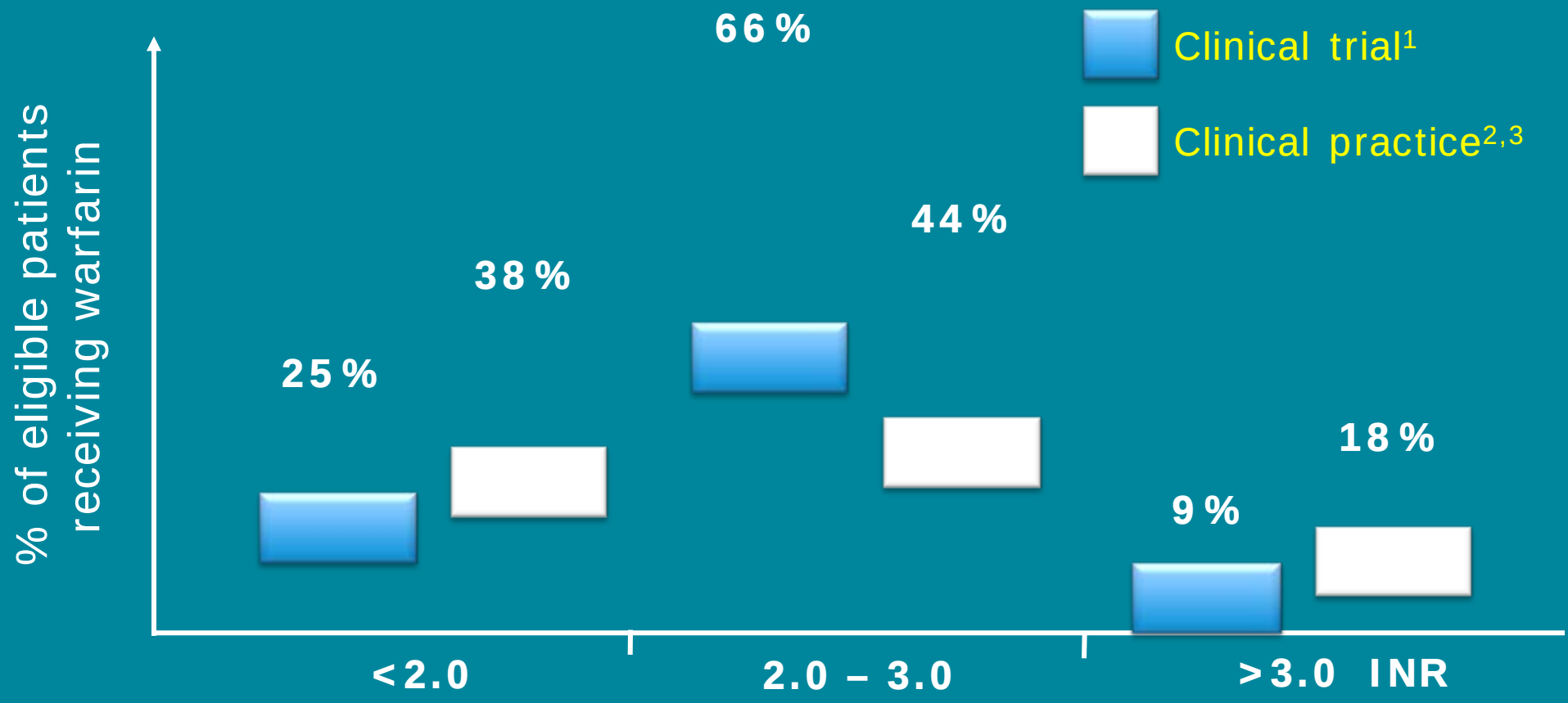
	Multivariate hazard ratios (95% CI)
Age (years) <65 65–74 ≥75	 1.0 (Reference) 2.97 (2.54–3.48) 5.28 (4.57–6.09)
Female sex	1.17 (1.11–1.22)
Previous ischaemic stroke	2.81 (2.68–2.95)
Intracranial bleeding	1.49 (1.33–1.67)
Vascular disease (any) • Myocardial infarction • Previous CABG • Peripheral artery disease	1.14 (1.06–1.23) 1.09 (1.03–1.15) 1.19 (1.06–1.33) 1.22 (1.12–1.32)
Hypertension	1.17 (1.11–1.22)
Heart failure (history)	0.98 (0.93–1.03)
Diabetes mellitus	1.19 (1.13–1.26)
Thyroid disease Thyrotoxicosis	1.00 (0.92–1.09) 1.03 (0.83–1.28)

Contraindications of Oral Anticoagulants

- GI haemorrhage
- Uncontrolled arterial hypertension
- Pregnancy
- Alcoholism
- Severe hepatic insufficiency
- Vascular malformations that can lead to risk of haemorrhage
- Coagulopathies
- Recent surgical interventions – eyes or CNS
- Previous severe haemorrhage during anticoagulation therapy
- Severe neoplastic disease

INR control: clinical trials vs. clinical practice

INR* control in clinical trial versus clinical practice (TTR**)

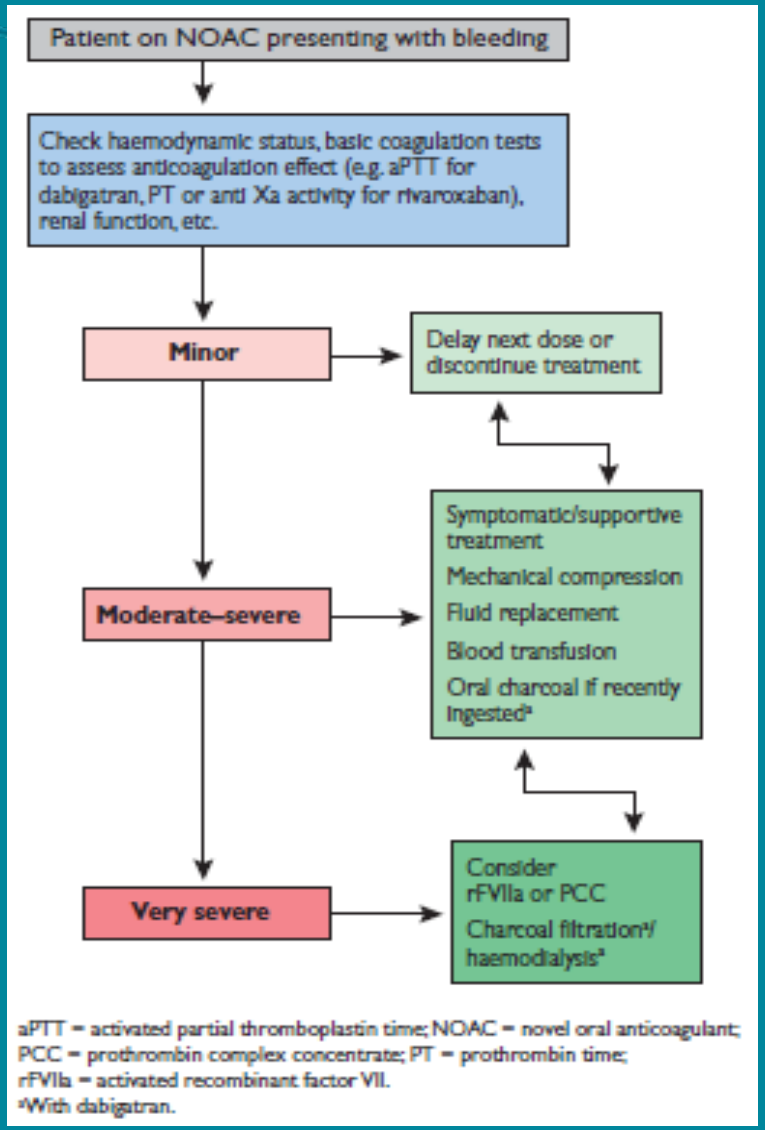


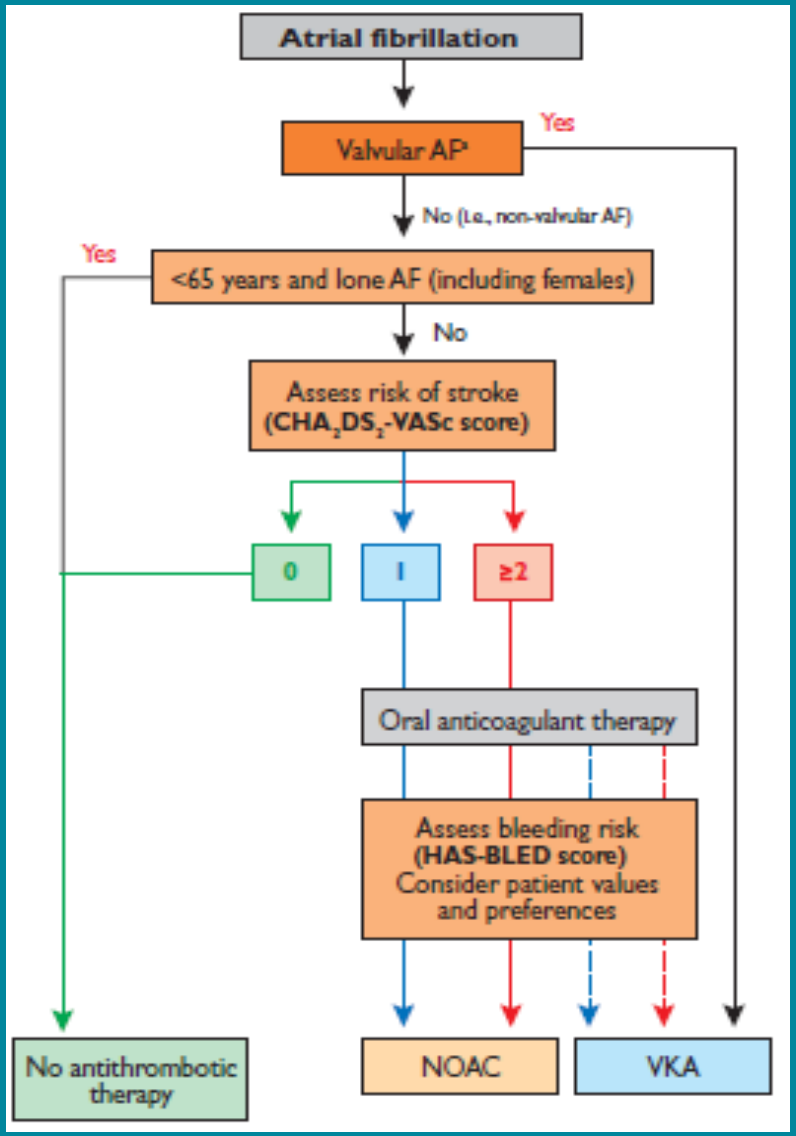
*INR = International normalized ratio

** TTR = Time in Therapeutic Range

1. Kalra L, et al. *BMJ* 2000;320:1236-1239 * Pooled data: up to 83% to 71% in individualized trials; 2. Samsa GP, et al. Arch Int Med 2000
3. Matchar DB, et al. *Am J Med* 2002; 113:42-51.

Choice of anticoagulant and bleeding management





2012 ACCP guidelines for antithrombotic therapy in AF: recommendations for dabigatran

- Dabigatran 150 mg BID preferable to dose-adjusted VKA* for:
  - patients at intermediate or high risk of stroke ($CHADS_2 \geq 1$)
  - secondary prevention of cardioembolic stroke

- Dabigatran as an alternative to dose-adjusted VKA or LMWH in patients undergoing elective cardioversion

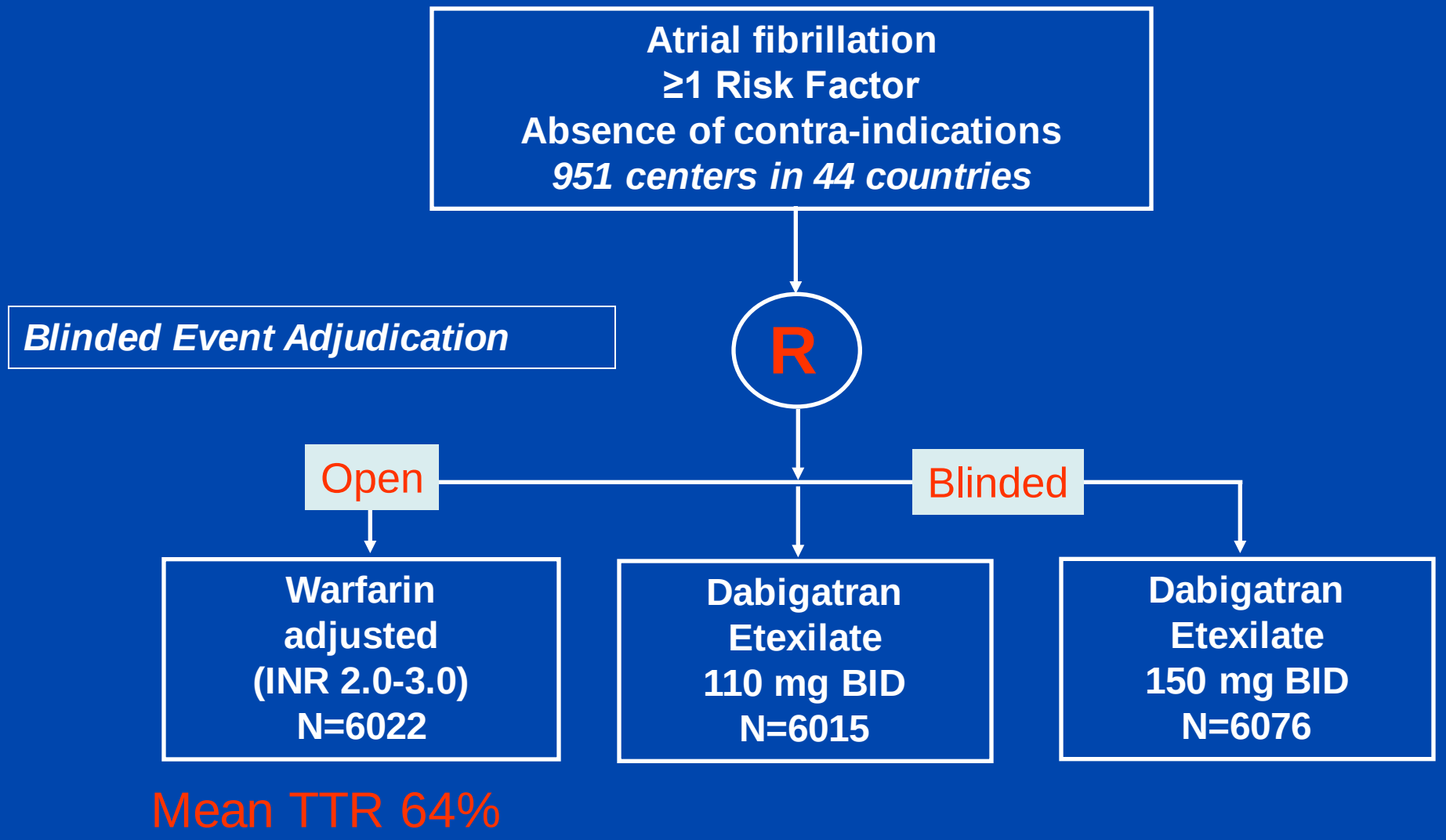
*Target range for international normalized ratio: 2.0–3.0

LMWH = low-molecular-weight heparin; VKA = vitamin K antagonist

You JY et al. Chest 2012;141;e531S–e575S

RE-LY: A Non-inferiority Trial

RELY®
Study of stroke prevention in atrial fibrillation



Wallentin L., et al. *Lancet* 2010; in press.

Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation

RE-LY®: trial conduct

- 99.9% complete follow-up
  - 20 patients of 18 113 lost to follow-up
- Percent time in therapeutic range
  - 64%: all warfarin-treated patients
  - 67%: warfarin-experienced
  - 61%: warfarin-naïve

Connolly SJ et al. N Engl J Med 2009;361:1139–51; Ezekowitz MD. ESC 2009; oral presentation #5019

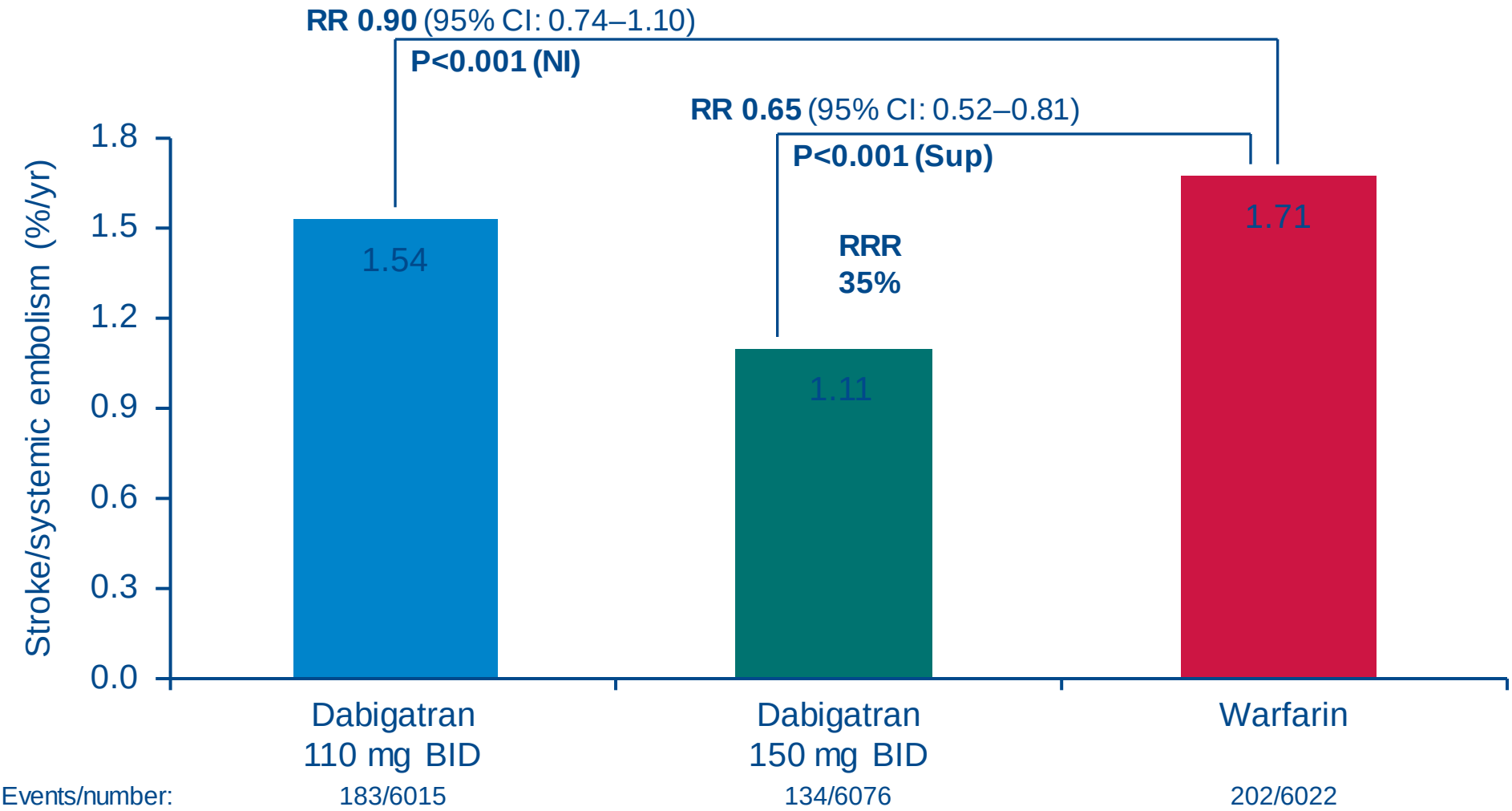
Baseline characteristics

Characteristic	Dabigatran 110 mg BID	Dabigatran 150 mg BID	Warfarin
Randomized, n	6015	6076	6022
Mean age, yrs	71.4	71.5	71.6
Male, %	64.3	63.2	63.3
$CHADS_2$ 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

ASA = acetylsalicylic acid (Aspirin); BID = twice daily; CHF = congestive heart failure; MI = myocardial infarction; TIA = transient ischaemic attack

Connolly SJ et al. N Engl J Med 2009;361:1139–51

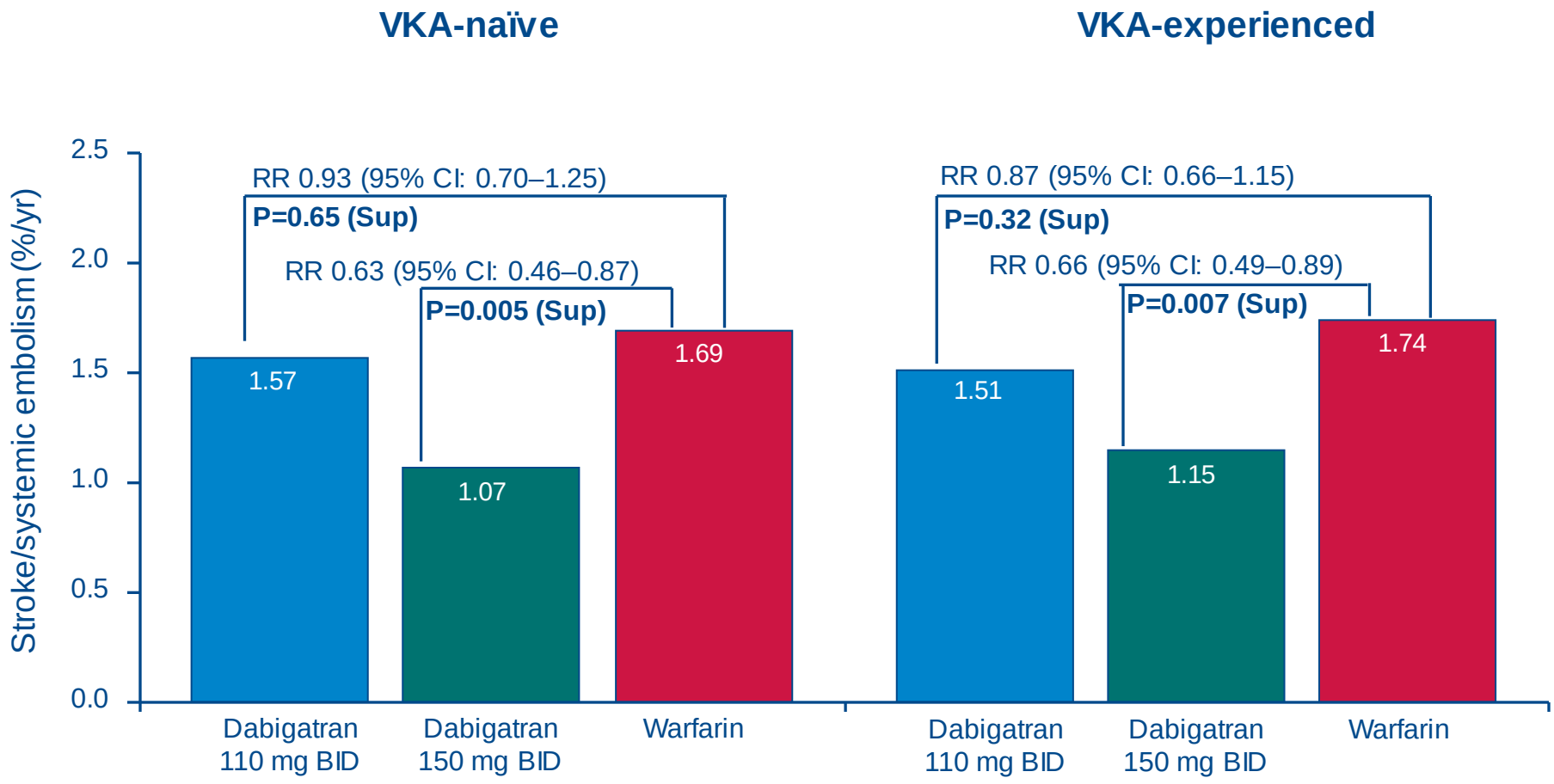
Incidence of stroke or systemic embolism



BID = twice daily; NI = non-inferiority; RR = relative risk; RRR = relative risk reduction; Sup = superiority

Connolly SJ et al. N Engl J Med 2010;363:1875–6

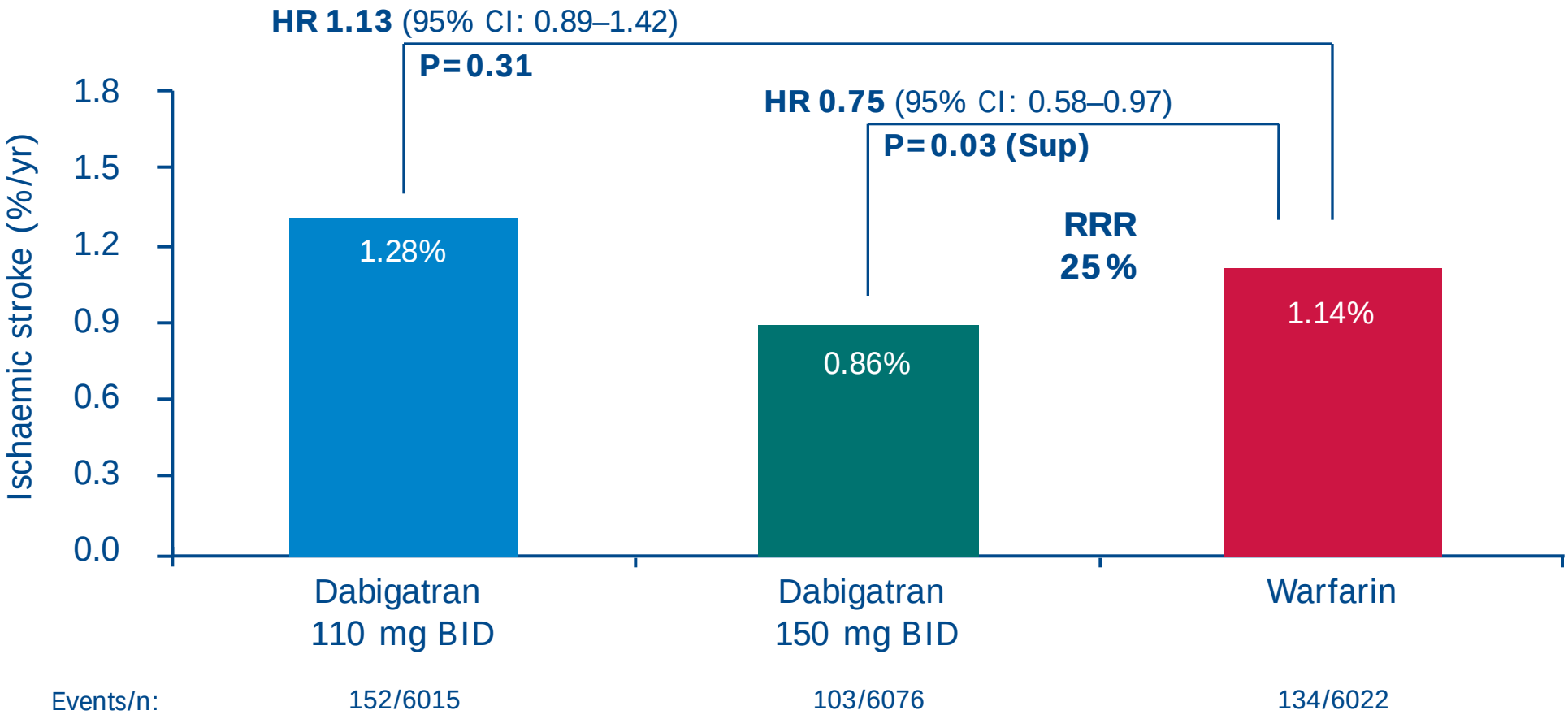
VKA-naïve vs VKA-experienced subgroup analysis: stroke or systemic embolism



BID = twice daily; RR = relative risk; Sup = superiority; VKA = vitamin K antagonist

Ezekowitz M et al. Circulation 2010;122:2246–53

Ischaemic stroke



BID = twice daily; hr = hazard ratio; RRR = relative risk reduction; Sup = superiority

Pradaxa®: EU SmPC 2012

Stroke or systemic embolism according to cTTR

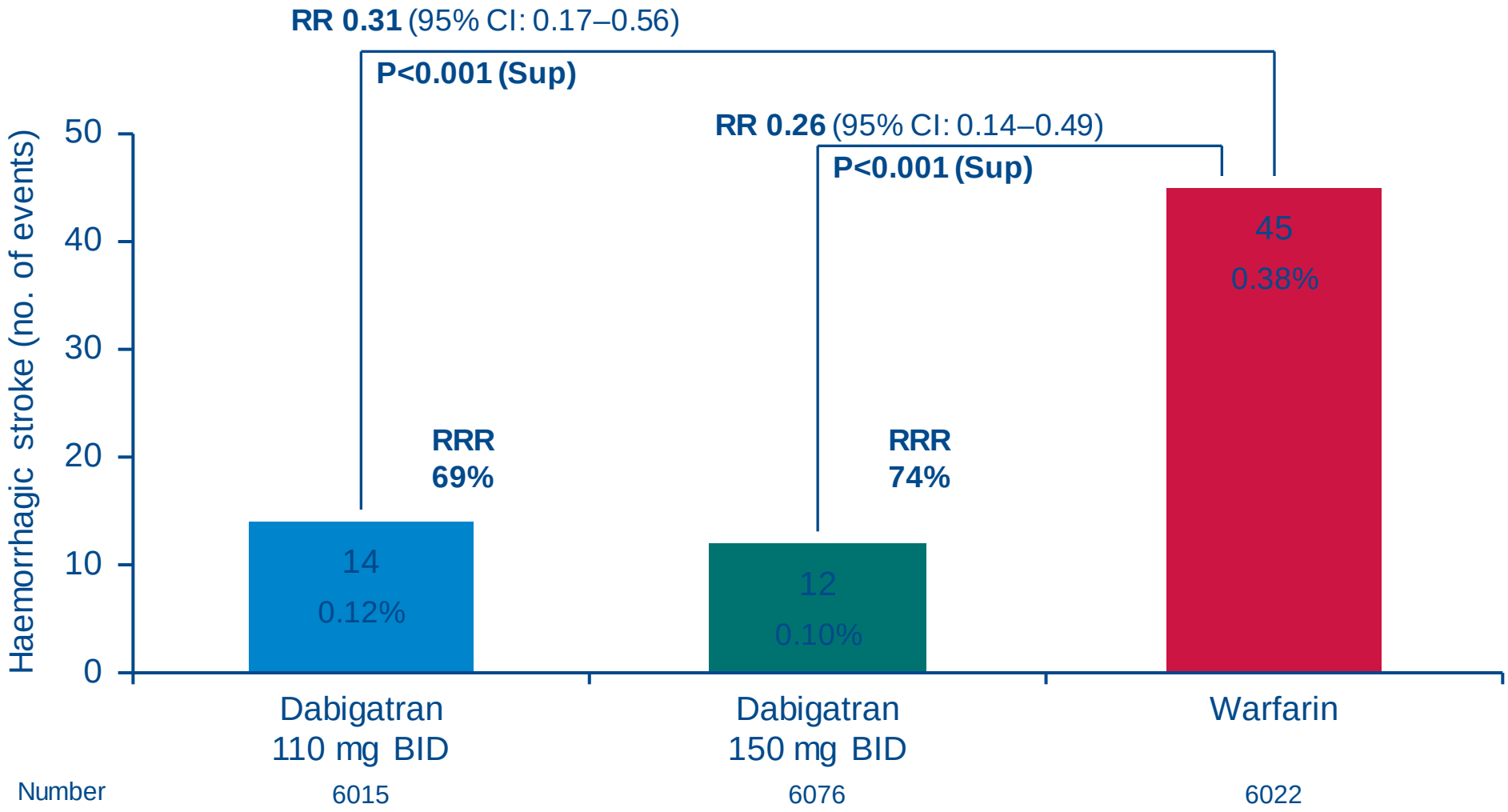
cTTR	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	Dabigatran 110 mg vs warfarin		Dabigatran 150 mg vs warfarin	
	Rate per 100-person yrs	Rate per 100-person yrs	Rate per 100-person yrs	HR (95% CI)	P* (interaction)	HR (95% CI)	P* (interaction)
<57.1%	1.91	1.10	1.92	1.00 (0.68–1.45)	–	0.57 (0.37–0.88)	–
57.1–65.5%	1.67	1.04	2.06	0.81 (0.56–1.17)	–	0.50 (0.33-0.77)	–
65.5–72.6%	1.34	1.04	1.51	0.89 (0.58–1.36)	–	0.69 (0.44–1.09)	–
>72.6%	1.23	1.27	1.34	0.92 (0.59–1.45)	0.89	0.95 (0.61–1.48)	0.20

*Interaction P evaluated by a multivariate approach with centre-based TTR as a continuous variable

TTR = time in therapeutic range; cTTR = centre mean TTR; HR = hazard ratio

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

Haemorrhagic stroke



BID = twice daily; RR = relative risk; RRR = relative risk reduction; Sup = superiority

Connolly SJ et al. N Engl J Med 2009;361:1139–51; Connolly SJ et al. N Engl J Med 2010;363:1875–6

Intracranial Bleeding

RELY®
Study of stroke prevention in atrial fibrillation

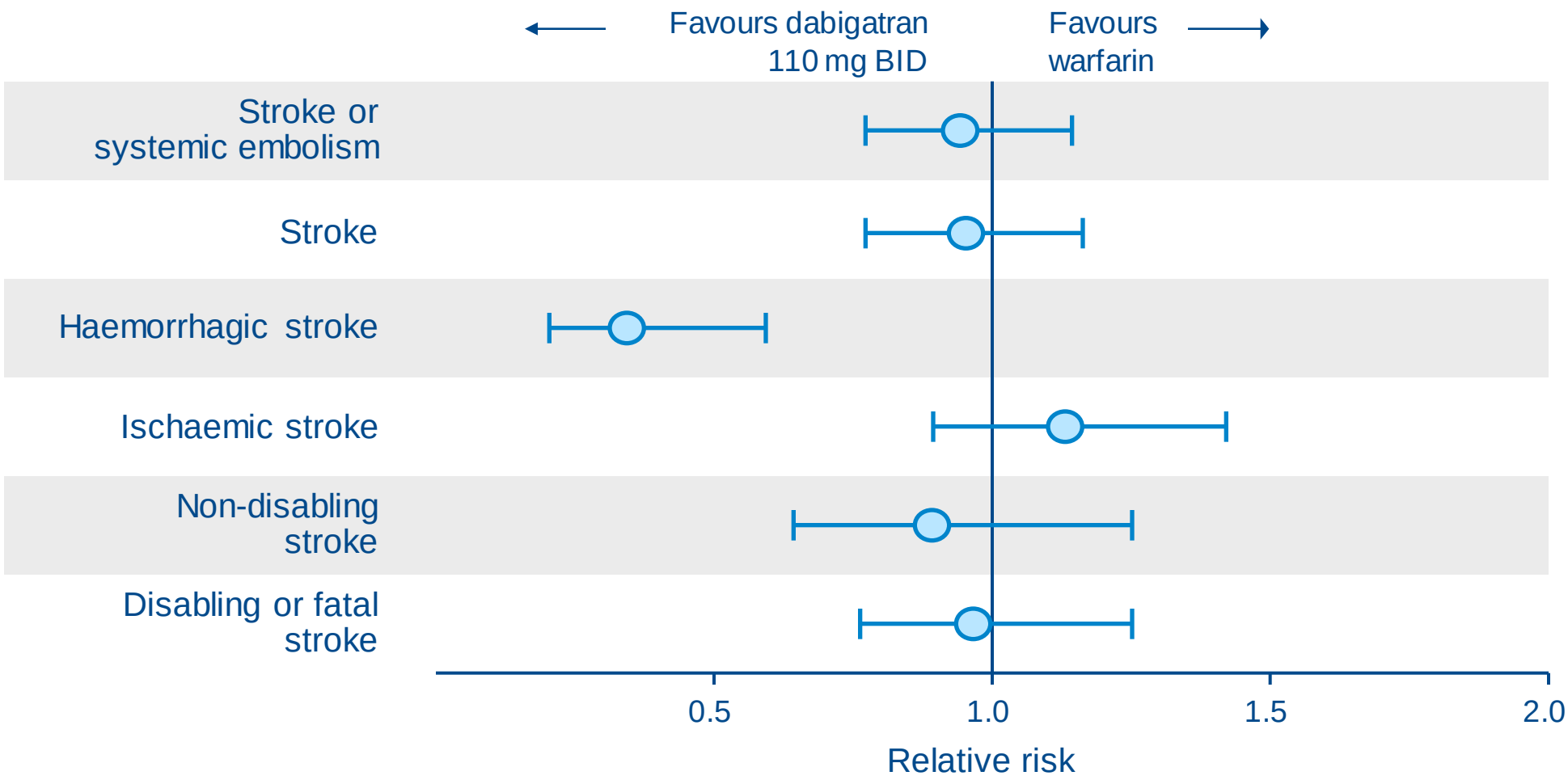
	D 110mg	D 150mg	Warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
Center TTR	Annual rate	Annual rate	Annual rate	RR 95% CI	P	RR 95% CI	P
All patients	0.23%	0.32%	0.76%	0.30 0.19-0.45	<0.001	0.41 0.28-0.60	<0.001
< 57.1%	0.28%	0.34%	0.64%	0.43 0.19-1.00		0.53 0.25-1.15	
57.1% – 65.5%	0.30%	0.42%	0.93%	0.31 0.15-0.66		0.45 0.24-0.88	
65.5% – 72.6%	0.13%	0.24%	0.67%	0.20 0.07-0.58		0.35 0.15-0.82	
> 72.6%	0.21%	0.30%	0.77%	0.27 0.11-0.66		0.39 0.18-0.84	
Int P*					0.71		0.89

***Interaction p evaluated by a multivariable approach with center based TTR as a continuous variable.**

Wallentin L., et al. *Lancet* 2010; in press.

Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation

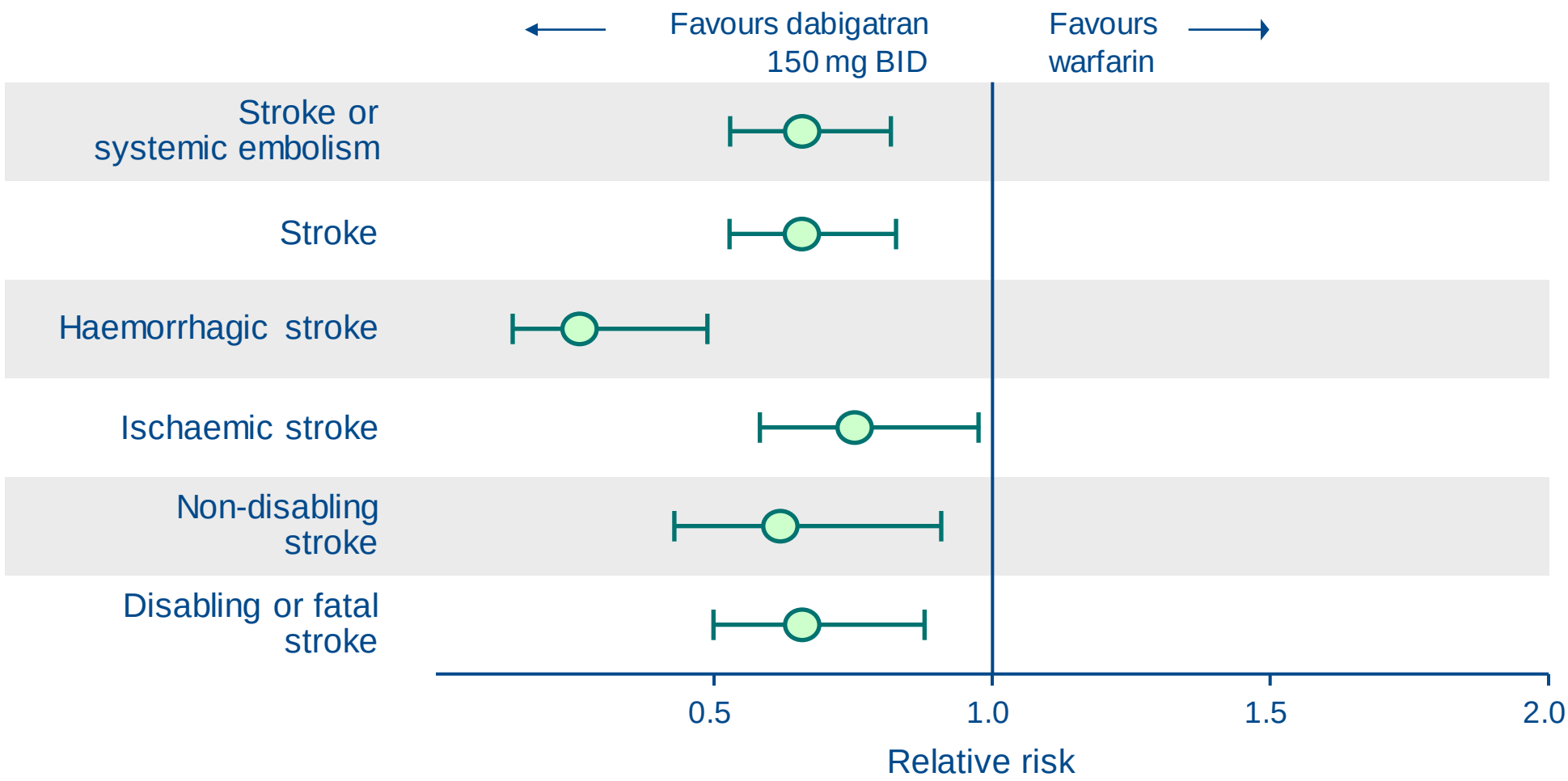
Dabigatran etexilate 110 mg BID compared with warfarin for stroke prevention in AF



Error bars = 95% CI; BID = twice daily

Connolly SJ et al. N Engl J Med 2009;361:1139–51; Connolly SJ et al. N Engl J Med 2010;363:1875–6;
Pradaxa®: EU SmPC 2011

Dabigatran etexilate 150 mg BID compared with warfarin for stroke prevention in AF



Error bars = 95% CI; BID = twice daily

Connolly SJ et al. N Engl J Med 2009;361:1139–51; Connolly SJ et al. N Engl J Med 2010;363:1875–6;
Pradaxa®: EU SmPC 2011

Total death

RELY®
Study of stroke prevention in atrial fibrillation

	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
Center TTR	Annual rate	Annual rate	Annual rate	RR 95% CI	P	RR 95% CI	P
All patients	3.75%	3.64%	4.13%	0.91 0.80-1.03	0.13	0.88 0.77-1.00	0.051
< 57.1%	4.17 %	3.85%	5.72%	0.73 0.58-0.92		0.67 0.53-0.85	
57.1% – 65.5%	3.97%	3.75%	4.09%	0.97 0.75-1.24		0.92 0.71-1.18	
65.5% – 72.6%	3.19%	3.64%	3.70%	0.86 0.65-1.13		0.98 0.75-1.28	
> 72.6%	3.60%	3.30%	3.04%	1.18 0.89-1.57		1.08 0.81-1.44	
Int P*					0.066		0.052

***Interaction p evaluated by a multivariable approach with center based TTR as a continuous variable.**

Wallentin L., et al. *Lancet* 2010; in press.

Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation

2012 ACCP guidelines for antithrombotic therapy in patients with AF (I)

Patient features	Recommended antithrombotic therapy
Low risk of stroke (e.g. $CHADS_2$ = 0)	**None** (rather than antithrombotic therapy)
Intermediate risk of stroke (e.g. $CHADS_2$ = 1)	Oral anticoagulation (rather than no therapy, Aspirin, or Aspirin + clopidogrel)) ✓ **Dabigatran 150 mg BID** (rather than dose-adjusted VKA*)
High risk of stroke (e.g. $CHADS_2$ = 2)	Oral anticoagulation (rather than no therapy, Aspirin, or Aspirin + clopidogrel) ✓ **Dabigatran 150 mg BID** (rather than dose-adjusted VKA*)
Previous stroke/TIA	Oral anticoagulation (rather than no therapy, Aspirin, or Aspirin + clopidogrel) ✓ **Dabigatran 150 mg BID** (rather than dose-adjusted VKA*)

BID = twice daily; TIA = transient ischaemic attack;
VKA = vitamin K antagonist *Target range for international normalized ratio: 2.0–3.0

You JY et al. Chest 2012;141;e531S–e575S

2012 ACCP guidelines for antithrombotic therapy in patients with AF (II)

Patient features	Recommended antithrombotic therapy
Atrial flutter	Same risk-based recommendations as for AF
Mitral stenosis	Oral anticoagulation (rather than no therapy, Aspirin, or Aspirin + clopidogrel) ✓**Dose-adjusted VKA***
Stable CAD	Oral anticoagulation (rather than dose-adjusted VKA + Aspirin) ✓**Dose-adjusted VKA***
Intracoronary stent	• If high risk of stroke ($CHADS_2 \geq 2$): – **Triple therapy (VKA, Aspirin, clopidogrel)** during month after bare-metal stent **OR** 3–6 months after drug-eluting stent (rather than dual AP therapy) – **Dose-adjusted VKA* + single AP therapy** after initial period of triple therapy (rather than VKA alone) – Antithrombotic therapy as for stable CAD, after 12 months • If low/intermediate risk of stroke ($CHADS_2 \leq 1$): – **Dual AP therapy** for 12 months after stent placement (rather than triple therapy) – Antithrombotic therapy as for stable CAD ,after 12 months

*Target range for international normalized ratio: 2.0–3.0

AP = antiplatelet; CAD = coronary artery disease; VKA = vitamin K antagonist

You JY et al. Chest 2012;141;e531S–e575S

Who is NOT a Candidate For NOAs ?

- Mechanical valve
- Creat-Cl < 30 ml/min
- Severe hepatic dysfunction
- Non-compliant with W ?
- *Stable on W (???)*

Cardioversion – key points

- Available data suggest that cardioversion can be safely performed on dabigatran
- Coagulation with dabigatran is required for 3 weeks pre-cardioversion and for ≥4 weeks post-cardioversion
- Event rates were not different between conventional and TEE guided cardioversion while patients were on dabigatran
- OAC should be continued long-term, whether with a VKA or with dabigatran
- No published data on cardioversion with rivaroxaban or apixaban are available

OAC = oral anticoagulation; TEE = transoesophageal echocardiography; VKA = vitamin K antagonist

Camm AJ et al. Eur Heart J doi:10.1093/eurheartj/ehs253

Cardioversion recommendations

Recommendation	Class	Level
For patients with AF of ≥48 hour duration, or when the duration of AF is unknown, OAC therapy (e.g. VKA with INR 2–3 or dabigatran) is recommended for ≥3 weeks prior to and for ≥4 weeks after cardioversion, regardless of the method (electrical or oral/i.v. pharmacological)	I	B
In patients with risk factors for stroke or AF recurrence, OAC therapy, whether with dose-adjusted VKA (INR 2–3) or a NOAC, should be continued lifelong irrespective of the apparent maintenance of sinus rhythm following cardioversion	I	B

INR = international normalized ratio; NOAC = novel oral anticoagulant; OAC = oral anticoagulation; VKA = vitamin K antagonist;
Camm AJ et al. Eur Heart J doi:10.1093/eurheartj/ehs253

2012 ACCP guidelines for antithrombotic therapy in patients undergoing cardioversion for AF

Patient features	Recommended antithrombotic therapy
AF of >48 hrs or unknown duration with elective cardioversion	Therapeutic anticoagulation (dose-adjusted VKA*, LMWH, or **dabigatran**) for ≥3 weeks before cardioversion **OR** TEE-guided approach with abbreviated anticoagulation ✓Therapeutic anticoagulation ≥4 weeks after successful cardioversion
AF of known duration ≤48 hrs with elective cardioversion	Immediate anticoagulation with IV UFH or LMWH, then therapeutic anticoagulation (dose-adjusted VKA*, LMWH, or **dabigatran**) ✓≥4 weeks after successful cardioversion
Urgent cardioversion for haemodynamically unstable AF	Parenteral anticoagulation as soon as possible, then therapeutic anticoagulation (dose-adjusted VKA*, LMWH, or **dabigatran**) ✓≥4 weeks after successful cardioversion
Cardioversion of atrial flutter	As for patients undergoing cardioversion for AF

- Long-term antithrombotic therapy should follow the risk-based recommendations for AF

*Target range for international normalized ratio: 2.0–3.0
IV = intravenous; LMWH = low-molecular-weight heparin; TEE = transoeosophageal echocardiography; UFH= unfractionated heparin; VKA = vitamin K antagonist

You JY et al. Chest 2012;141;e531S–e575S

Catheter ablation – peri-procedural dabigatran: Di Biase et al. methodology

- Multicentre, prospective, observational registry of AF patients undergoing ablation

- 145 consecutive patients on dabigatran 150 mg
  - Dabigatran discontinued on day of procedure
  - Restarted within 3 hours of haemostasis post-procedure

- Matched with 145 patients on warfarin
  - INR 2.0–3.0 at time of procedure
  - No treatment interruption

BID = twice daily; INR = international normalized ratio

Di Biaise Let al. Circulation 2011;124:A14277

Catheter ablation – peri-procedural dabigatran
Di Biase et al. results and conclusions

Complication	Dabigatran (n=145) %	Warfarin (n=145) %	P value
Major bleeding	6	1	0.019
Minor bleeding	8	8	0.350
Total bleeding	14	9	0.031
Embolic (CVA/TIA)	2	0	0.250
Composite	16	9	0.009

- Continuation of dabigatran associated with a small increase in peri-procedural complications
- Further studies required to optimize dabigatran use in patients undergoing catheter ablation

CVA = cerebral vascular accident; TIA = transient ischaemic attack

Di Biaise L et al. Circulation 2011;124:A14277

Catheter ablation – peri-procedural dabigatran Bassiouny et al. methodology

- Patients undergoing PVI

- 47 patients receiving dabigatran 150 mg
  - Dabigatran withheld 12–24 hours before the procedure
  - Restarted post-procedure (in catheter laboratory or on ward arrival)

- 54 patients receiving warfarin
  - INR ≥1.8
  - No treatment interruption

INR = international normalized ratio; PVI = pulmonary vein isolation

Bassiouny M et al. Circulation 2011;124:A13128

Catheter ablation – peri-procedural dabigatran: Bassiouny et al. results and conclusions

- Compared with warfarin group, patients in the dabigatran group had:
  - Significantly higher total heparin dose/kg during procedure
  - Significantly lower mean ACT during procedure

- No peri-procedural cerebrovascular events or major bleeding events in either group
  - Minor bleeding: n=1 with dabigatran; n=2 with warfarin
  - Gastrointestinal bleeding: n=2 with dabigatran

- Dabigatran appears to be a suitable alternative to warfarin for peri-procedural anticoagulation during PVI

ACT = activated clotting time; PVI = pulmonary vein isolation

Bassiouny M et al. Circulation 2011;124:A13128

Catheter ablation – post-procedure dabigatran: Winkle et al. results and conclusions

- No thromboembolic events or bleeding complications during 30 days' follow-up
- Beyond 30 days: no strokes or bleeding problems while on dabigatran or after dabigatran discontinuation
- Dabigatran well tolerated; discontinued in 3 patients:
  - severe dyspepsia, severe diarrhoea, diffuse rash
- Dabigatran appears to be an alternative to warfarin following ablation in AF patients

Winkle RA et al. J Cardiovasc Electrophysiol 2011:doi: 10.1111/j.1540-8167.2011.02175.x

Management Issues With NOAs

Periprocedural Management

Timing of Discontinuation of Dabigataran Prior to Procedure

Renal Function (ClCr ml/min)	Half-life Hours (range)	Moderate Bleeding Risk	High Bleeding Risk
> 50	15 (12-34)	1-2 days	2-3 days
31-50	18 (13-23)	3-4 days	4-5 days
≤ 30	27 (22-35)	4-5 days	>5 days

Adapted from:
Van Ryn J. Thromb Hamost 2010; 103: 1118-27
Pradaxa monograph 2010, Boeringer Ingelheim Ldt

Timing of Resumption of Dabigataran After Procedure

Renal Function (ClCr ml/min)	Moderate Bleeding Risk	High Bleeding Risk
> 50	24 hours	48 hours
31-50	24 hours	48 hours
≤ 30	consider Warfarin	consider Warfarin

Adapted from:
Van Ryn J. Thromb Hamost 2010; 103: 1118-27
Pradaxa monograph 2010, Boeringer Ingelheim Ldt

Status of New Anticoagulants

- 2011: Dabigatran e Rivaroxaban licensed for stroke prevention in AF

Indirect Comparisons of New Oral Anticoagulant Drugs for Efficacy and Safety When Used for Stroke Prevention in Atrial Fibrillation

Table 1 Summary of the Main Clinical Trials Involving Novel Anticoagulants for Stroke Prevention in Nonvalvular AF

	Dabigatran (RE-LY)	Rivaroxaban (ROCKET-AF)	Apixaban (ARISTOTLE)
Drug characteristics			
Mechanism	Oral direct thrombin inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor
Bioavailability, %	6	60–80	50
Time to peak levels, h	3	3	3
Half-life, h	12–17	5–9	9–14
Excretion	80% renal	2/3 liver, 1/3 renal	25% renal, 75% fecal
Dose	150 mg BID	20 mg OD	5 mg BID
Dose in renal impairment	110 mg BID	15 mg OD (if creatinine clearance 30–49 ml/min)	2.5 mg BID
Special considerations	Intestinal absorption is pH dependent and is reduced in patients taking proton pump inhibitors.	Higher levels expected in patients with renal or hepatic failure. Activity lower in fasted patients, so should be taken after food.	
Study characteristics			
Study design	Randomized open label	Multicenter, randomized, double-blind, double-dummy	Randomized control, double-blind, parallel arm
Number of patients	18,113	14,264	18,201
Follow-up period, months	24	40	40
Randomized groups	Dose-adjusted warfarin vs. blinded doses of dabigatran (150 mg BID, 110 mg BID)	Dose-adjusted warfarin vs. rivaroxaban 20 mg OD	Dose-adjusted warfarin vs. apixaban 5 mg BID

Indirect Comparisons of New Oral Anticoagulant Drugs for Efficacy and Safety When Used for Stroke Prevention in Atrial Fibrillation

Table 2 Risk Differences and Confidence Intervals, in Relation to Differences in the Study Populations at Baseline

Baseline Characteristics	RE-LY (N = 18,113)	ROCKET-AF (N = 14,264)	ARISTOTLE (N = 18,201)	RE-LY vs. ROCKET-AF	RE-LY vs. ARISTOTLE Percent Point (% Study 1; % Study 2)	ROCKET-AF vs. ARISTOTLE Percent Point (% Study 1; % Study 2)
Age, yrs*	71.5 ± 8.7	73 [65–78]	70 [63–76]	—	—	—
Female, %	36.4	39.7	35.2	−3.3 (−4.3; −2.2)	1.1 (0.2; 2.2)	4.5 (3.3; 5.5)
$CHADS_2$, mean	2.2	3.5	2.1	−1.26 (−1.28; −1.23)	0.1 (0.08; 0.12)	1.36 (1.34; 1.38)
$CHADS_2$ 3–6, %	32.5	87.0	30.2	−54.5 (−55.3; −53.6)	2.2 (1.3; 3.2)	56.7 (55.9; 57.6)
Paroxysmal AF, %	32.8	17.6	15.3	15.2 (14.3; 16.1)	17.5 (16.6; 18.4)	2.3 (1.5; 3.1)
Prior stroke, TIA, or systemic embolism, %	20.0	54.8	19.4	−34.8 (−35.8; −33.8)	0.6 (−0.03; 1.4)	35.3 (43.3; 36.3)
Heart failure, %	32.0	62.5	35.4	−30.5 (−31.5; −29.4)	−3.5 (−4.4; −2.5)	27.0 (26.0; 28.1)
Prior myocardial infarction, %	16.6	17.3	14.2	−0.7 (−1.5; 0.1)	2.4 (1.6; 3.1)	3.1 (2.3; 3.9)
Diabetes, %	23.3	40.0	25.0	−16.6 (−17.6; −15.6)	−1.7 (−2.6; −0.8)	14.9 (13.9;16.0)
Hypertension, %	78.9	90.5	87.5	−11.7 (−12.4; −10.9)	−8.6 (−9.4; −7.8)	3.1 (2.9; 3.7)
Medication						
Aspirin, %	39.8	36.5	30.9	3.3 (2.2; 4.3)	8.8 (7.8; 9.8)	5.5 (4.5; 6.6)
Vitamin K antagonist, %	49.6	62.4	57.2	−12.8 (−13.9; −11.7)	−7.5 (−8.5; −6.5)	5.3 (4.2; 6.3)

Indirect Comparisons of New Oral Anticoagulant Drugs for Efficacy and Safety When Used for Stroke Prevention in Atrial Fibrillation

Table 3 Weighted Average Effects of New OAC Versus Warfarin

	Any NOAC (Dabigatran 110 mg BID, Apixaban, Rivaroxaban) vs. Warfarin				Any NOAC (Dabigatran 150 mg BID, Apixaban, Rivaroxaban) vs. Warfarin			
	Weighted Average Effect HR	95% CI Lower	95% CI Upper	p Value	Weighted Average Effect HR	95% CI Lower	95% CI Upper	p Value
Stroke or systemic embolism	0.856	0.772	0.948	0.003	0.793	0.714	0.881	0.000
Stroke	0.847	0.756	0.949	0.004	0.769	0.684	0.864	0.000
Ischemic or uncertain type of stroke	0.983	0.866	1.116	0.788	0.878	0.771	1.000	0.051
Hemorrhagic stroke	0.485	0.373	0.632	0.000	0.474	0.363	0.619	0.000
Death from any cause	0.890	0.825	0.961	0.003	0.880	0.815	0.950	0.001
Myocardial infarction	0.953	0.810	1.120	0.557	0.949	0.807	1.116	0.525
ISTH major bleeding	0.831	0.765	0.902	0.000	0.875	0.806	0.950	0.001
Intracranial bleeding	0.465	0.378	0.572	0.000	0.490	0.400	0.601	0.000

Lip et al. JACC Vol. 60, No. 8, 2012
New Oral Anticoagulant Drugs in AF August 21, 2012:738–46

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

The concerns over the small increase in MI with dabigatran have prompted a detailed analysis where there was no excess of new angina hospitalizations or revascularization with dabigatran-treated patients, with a vascular mortality and a net clinical benefit in favour of dabigatran. A meta-analysis of seven dabigatran studies (AF, venous thromboembolism, etc.) in over 30 000 patients showed a significant 33% increase in MI, but an 11% reduction in all-cause mortality, when dabigatran was compared to warfarin. However, this may reflect a better protective effect of warfarin against MI.

FDA approved 150 mg and 75 mg (renal impairment)
EMA approved both 150 mg and 110 mg

EUROPEAN SOCIETY OF CARDIOLOGY®

Management Issues With NOAs

Monitoring

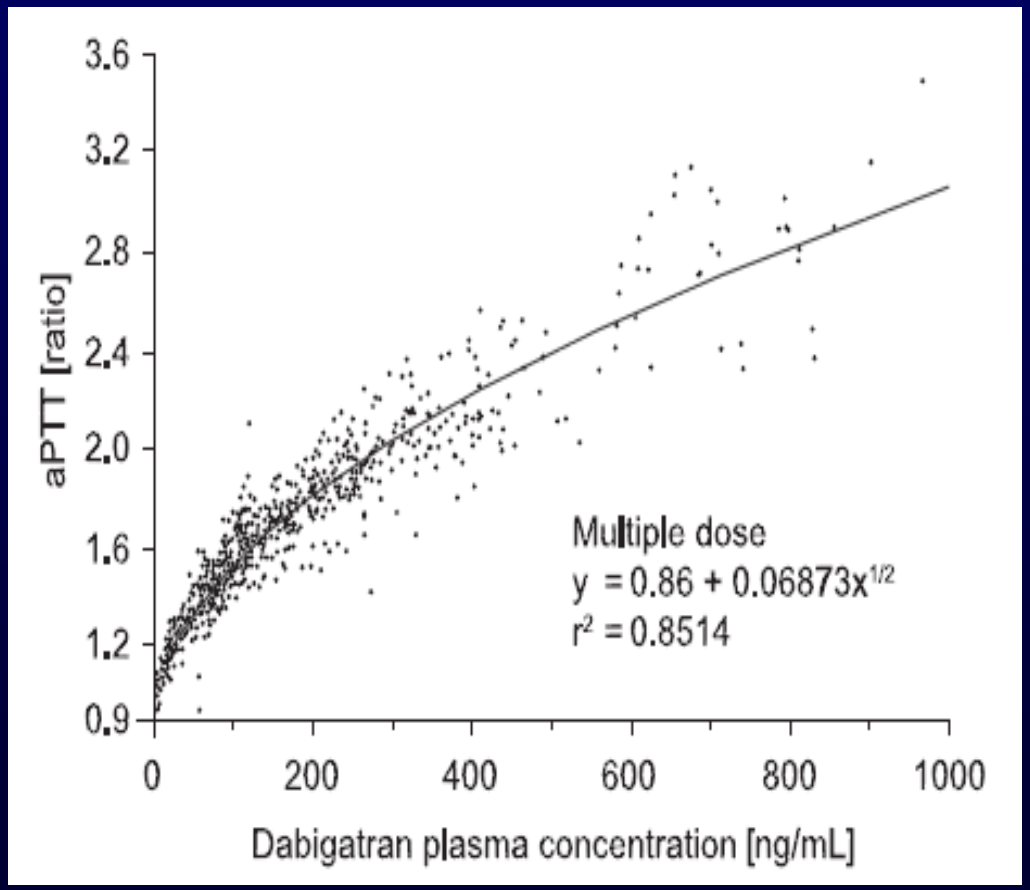
NOAs

Why Monitor ?

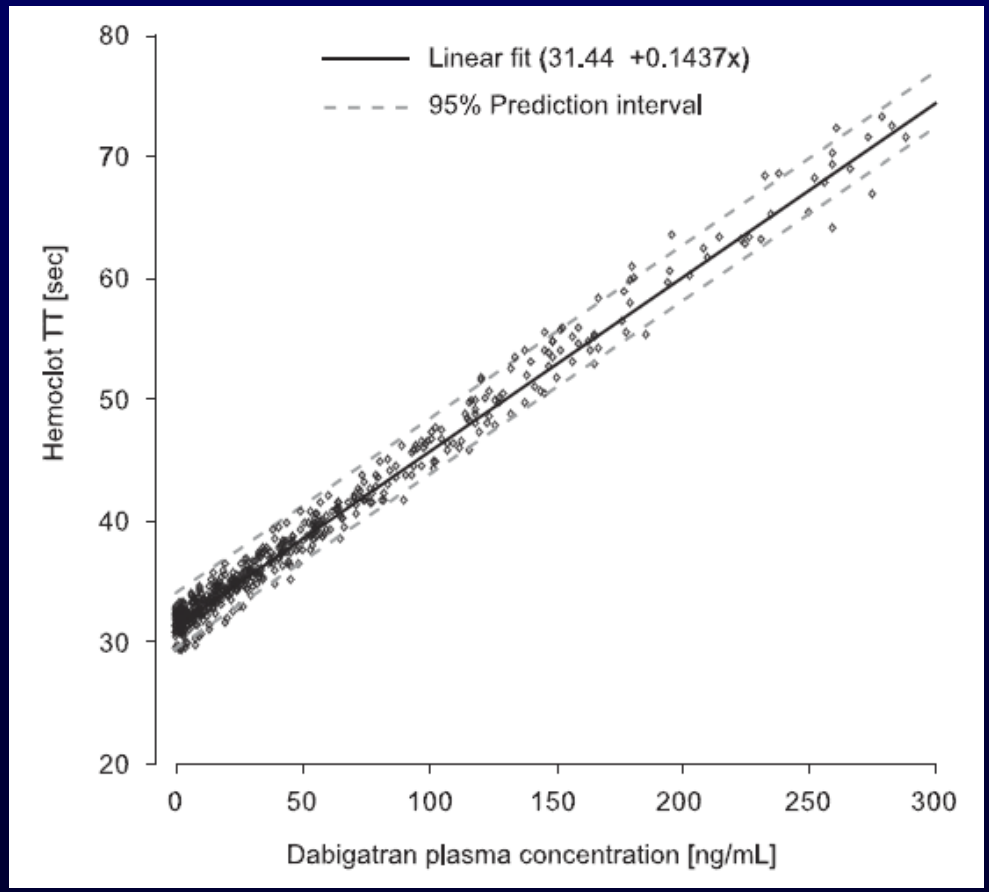
- Assess adherence
- Confirm dosing adequacy
- Detect accumulation / overdose
- Plan timing of urgent surgery
- Identification of bleeding mech
- Pts reassurance

Dabigatran Monitoring

aPTT



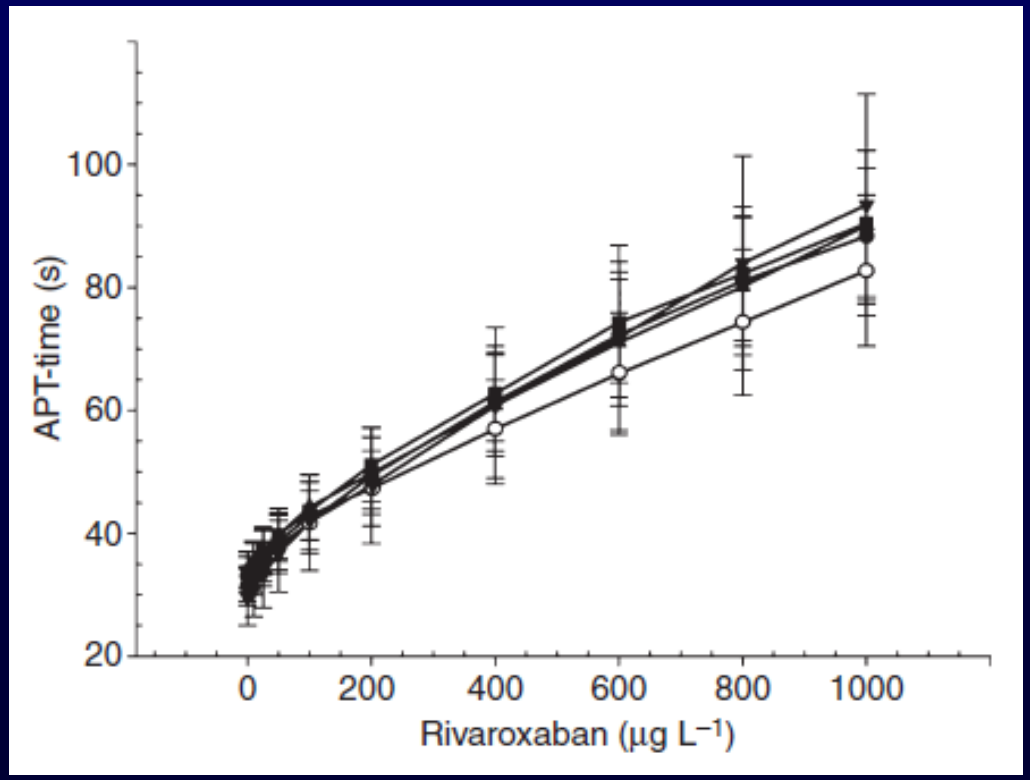
Hemoclot Test



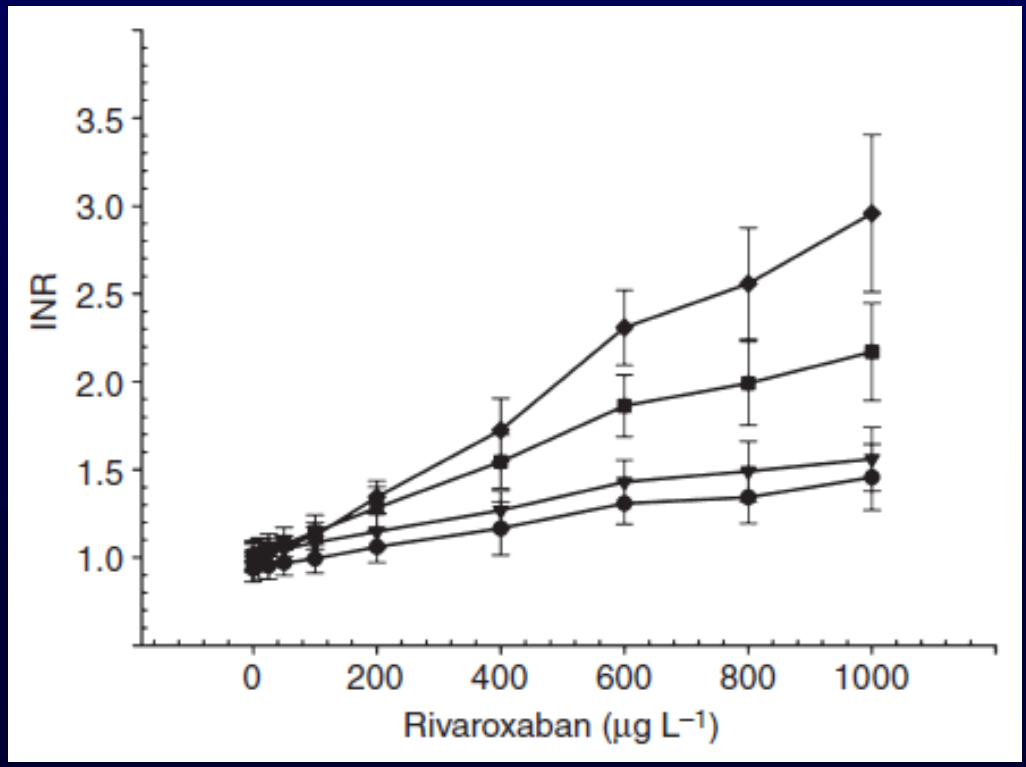
Van Ryn J. Thromb Hamost 2010; 103: 1118-27

Rivaroxaban Monitoring

aPTT



PT



Hillarp A. J Thromb Haemost 2011; 9: 133-9

Management Issues With NOAs

Reversal

NOAs
Management of Bleeding

- Hold drug(s)
- Resuscitation
  (i.v. access, fluid administartion,
  blood product transfusion)
- Maintain diuresis to clear drug
- Mechanical compression and
  surgical methods to stop bleeding

NOAs
if Bleeding Continues …

- Consider general hemostatic measures
  - antifibrinolytic drugs
  - PCC (non-activated or activated)
  - recombinant VIIa

- Hemodialysis or hemofiltration

Beriplex P/N Reverses Bleeding in an Acute Renal Injury Model after Dabigatran Overdose in Rabbits

Figure 1: Blood Loss (mL) over 30 min

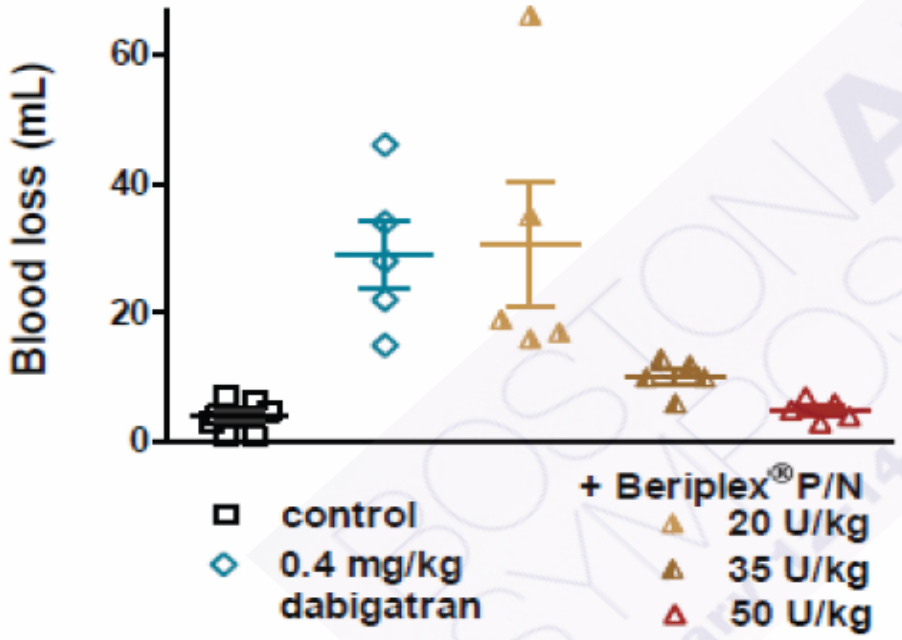
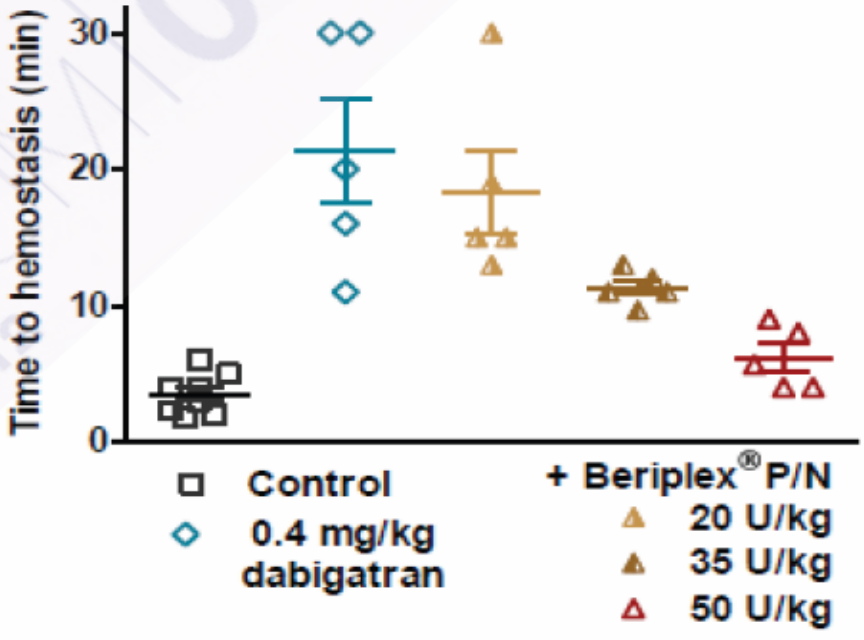


Figure 2: Time to Hemostasis (minutes up to 30 min)



Data are shown as mean ± SD, n = 5, except control n = 8.

Pragst et al, ISTH 2011

Conclusion

- Dabigatran and NOAs are poised to replace warfarin, but only for the right patients
- Optimal use of NOAs depends on the drug knowledge together with understanding of monitoring, peri-procedural management and reversal.

	Dabigatran	Rivaroxaban	Apixaban
DVT orto	RENOVATE REMODEL RENOVATE II REMOBILIZE	RECORD 1 RECORD 2 RECORD 3 RECORD 4	ADVANCE 1 ADVANCE 2 ADVANCE 3
AF	RE-LY	ROCKET-AF	AVERROES ARISTOTLE
Acute DVT e PE	RE-COVER RECOVER II	EINSTEIN DVT	AMPLIFY
Secondary prev TVP	REMEDY RESONATE	EINSTEIN EXT	AMPLIFY EXT
Medical ill pat.	/	MAGELLAN	ADOPT
ACS	REDEEM (fase II)	ATLAS ACS 2 TIMI 51 (Fase III)(Pubblicato NEJM, 2011)	APPRAISE (Fase III) (Interrotto)