Rivaroxaban

Practical Experience in the Cardiology Setting

Bernhard Meier, Bern

Bayer Satellite Symposium
Cardiology Update
Davos
February 11, 2013

Overview of phase III clinical trials of new oral anticoagulants

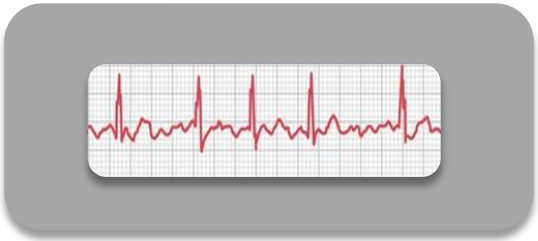
	Prevention DVT	Treatment DVT	AF	ACS
Apixaban (Eliquis®) Pfizer/BMS	Orthopedic **ADVANCE-1** **ADVANCE-2** **ADVANCE-3** Medical ADOPT (NCT00457002) Long term secondary prevention AMPLIFY-Ext NCT00633893)	AMPLIFY (NCT00643201)	**AVERROES** **ARISTOTLE**	(APPRAISE) **APPRAISE-2**
Dabigatran Etexilate (Pradaxa®) Boehringer Ingelheim	Orthopedic **RE-NOVATE** **RE-MODEL** **RE-MOBILIZE** Long term secondary prevention RE-MEDY (NCT00329238)	**RE-COVER** **RE-COVER II** (NCT00680186) RE-SONATE	**Re-LY** RELY-ABLE (NCT00808067)	**RE-DEEM**
Rivaroxaban (Xarelto®) Bayer	Orthopedic **RECORD I** **RECORD II** **RECORD III** **RECORD IV** Medical **MAGELLAN** Long term secondary prevention **EINSTEIN-Ext**	**EINSTEIN-DVT** **EINSTEIN-PE**	**ROCKET-AF** **J-ROCKET-AF**	**ATLAS-TIMI 46** **ATLAS-TIMI 51**

Adopted and updated (Dec 2011) according to
Steffel J., Braunwald E. European Heart Journal, 2011
Primary endpoint **acchieved** or **failed**

Atrial Fibrillation

Most frequent arrhythmia

Currently > 6 Mio affected in Europe



1-2 % of adult population

Increasing incidence and prevalence

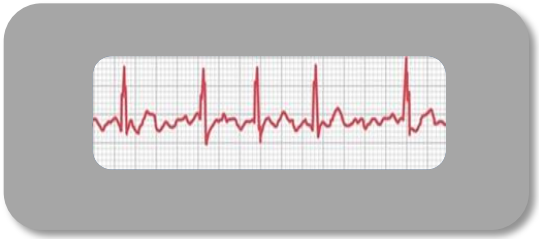
Age-dependent risk

- 60,000 patients
- 270,000 by 2050

Modified from Camm AJ et al. EHJ 2010; 31: 2369–2429

Atrial Fibrillation: Consequences

- 5x higher risk for stroke
- Increased risk for cardiac insufficiency
- Reduced quality of life

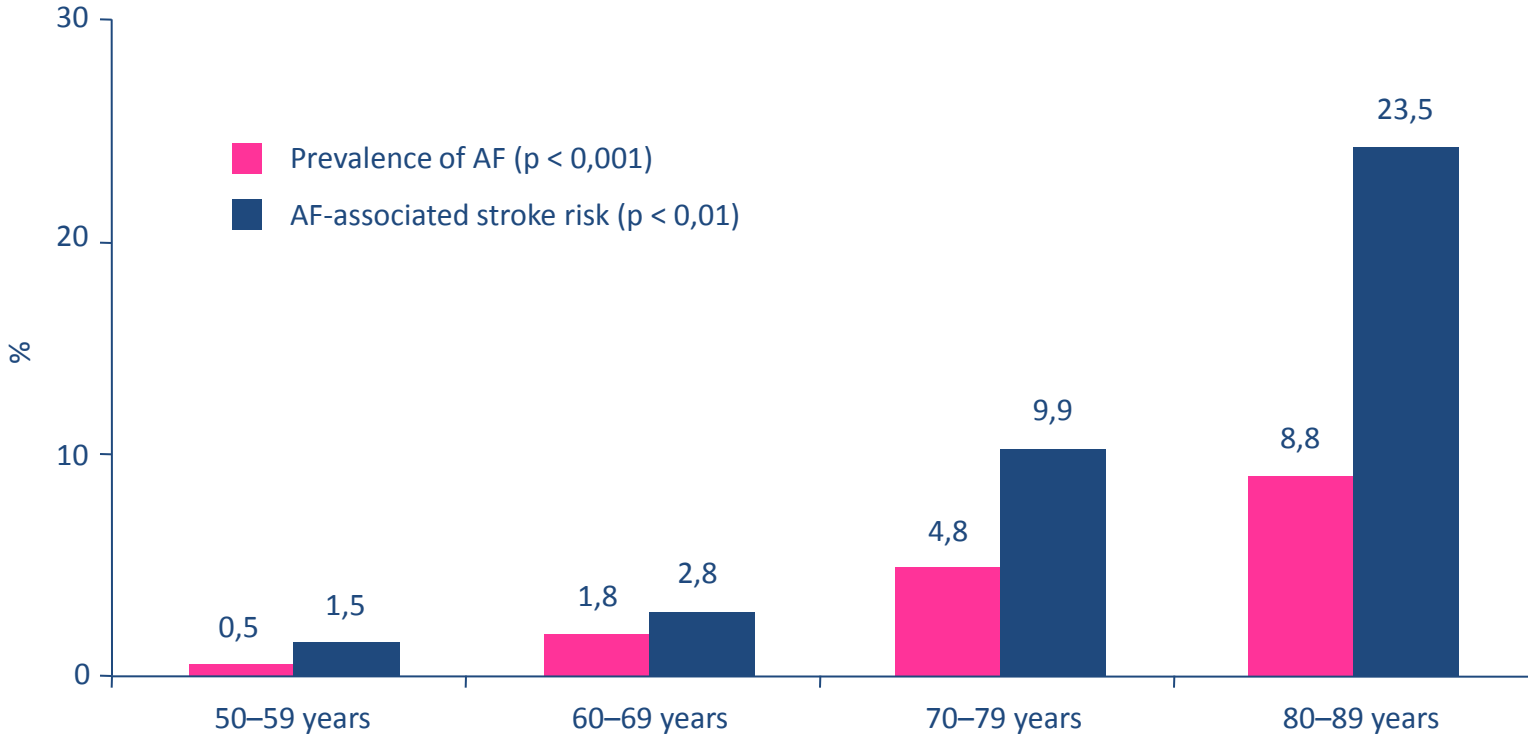


- Doubled mortality rate
- High follow-up costs
- Increased hospitalisation rate

Modified from Camm AJ et al. EHJ 2010; 31: 2369–2429

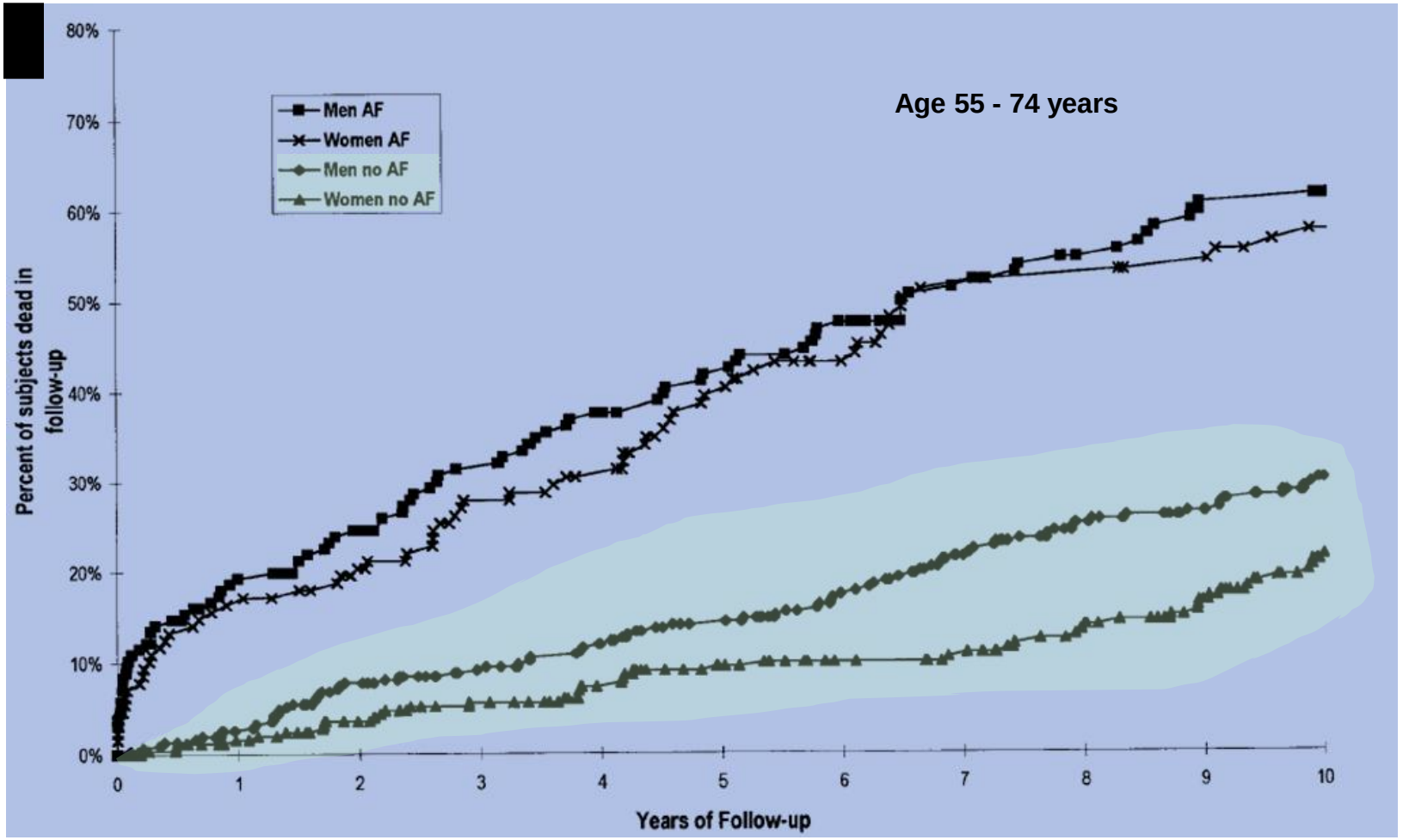
Stroke prevalence in AF patients in dependence of age

Framingham Heart Study (n = 5,070)



Wolf PA et al. Stroke 1991; 22: 983–988.

Atrial Fibrillation and Mortality



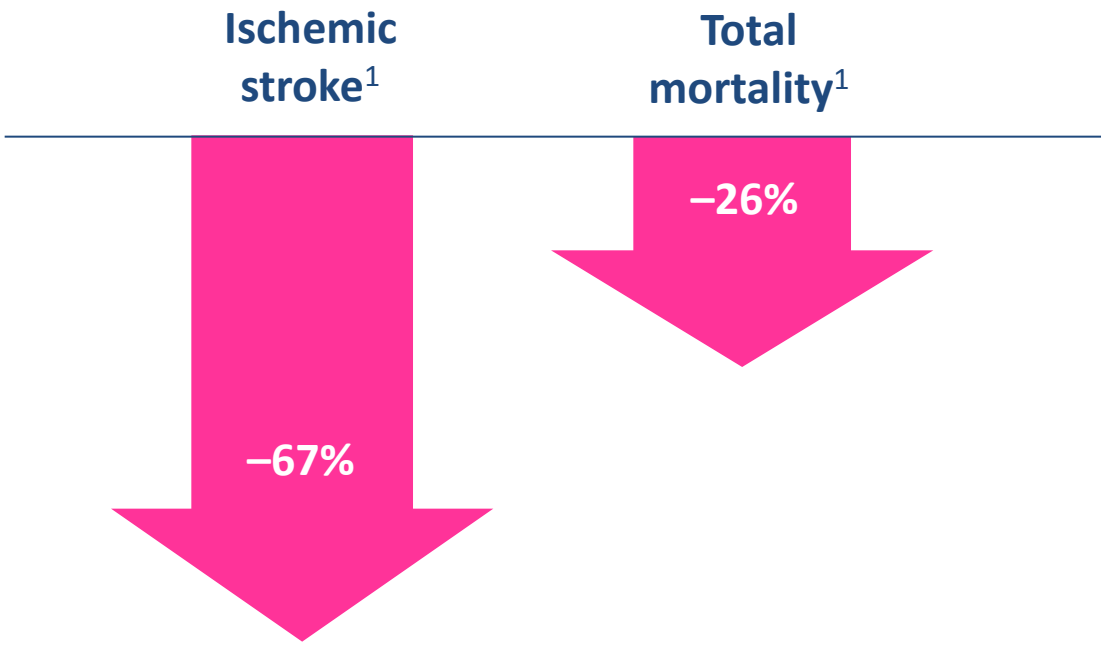
Benjamin et al, 1998

Risk Reduction with Anticoagulation

- Decrease in ischemic stroke and total mortality (Meta-analysis of 6 studies with 2'900 patients)[1]

RRR*:

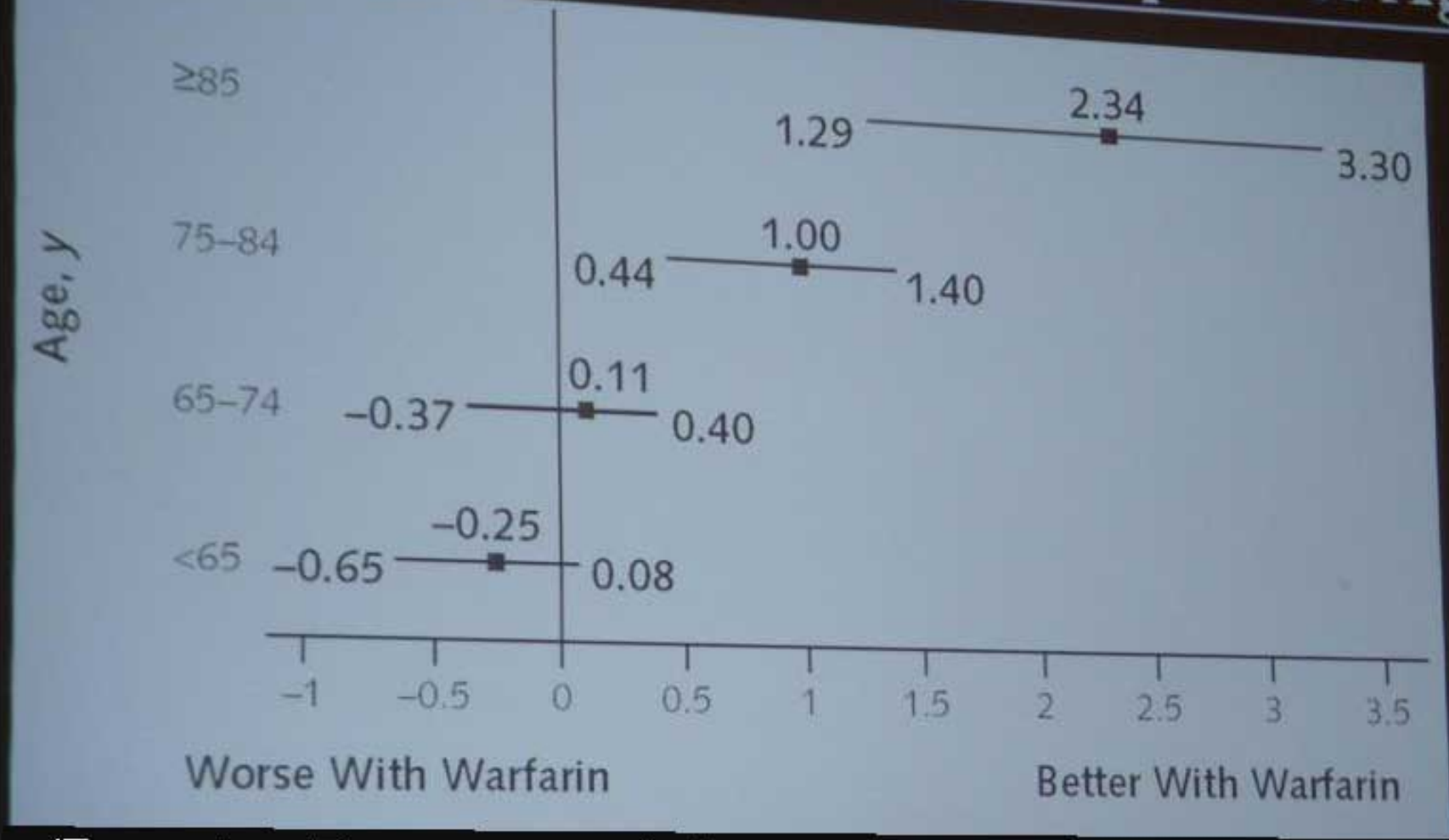
Warfarin vs. Placebo or vs. no treatment



- 2/3 of non-valvular AF-related ischemic strokes are avoidable with oral anticoagulation

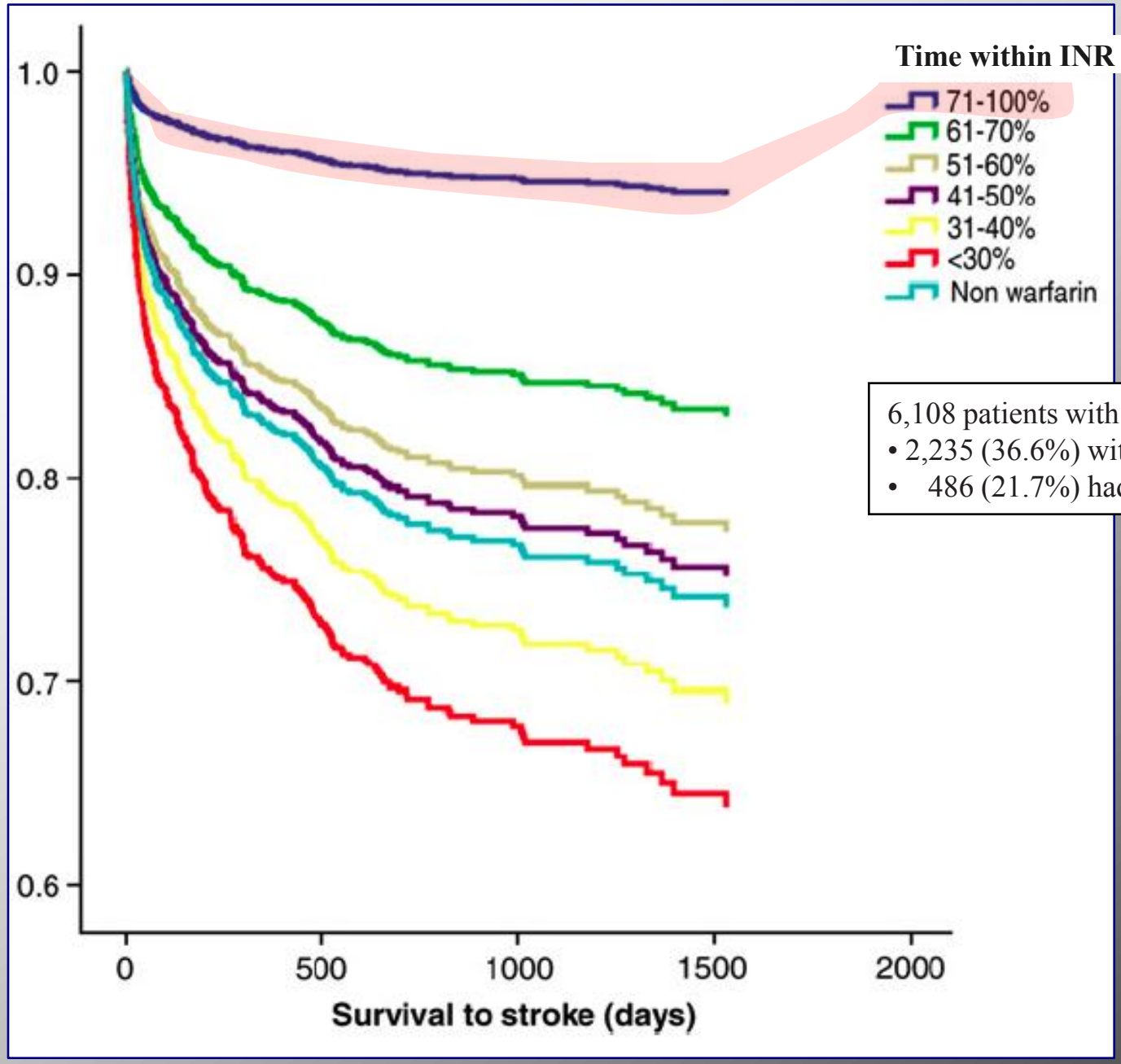
*Relativ Risk Reduction
AF: Atrial Fibrillation
1. Modified from Hart RG et al. Ann Intern Med. 2007;146:857-867

Warfarin Net Clinical Benefit: Impact of Age



Events Prevented Per 100 Patient-Years

Atrial Fibrillation and INR: Stroke

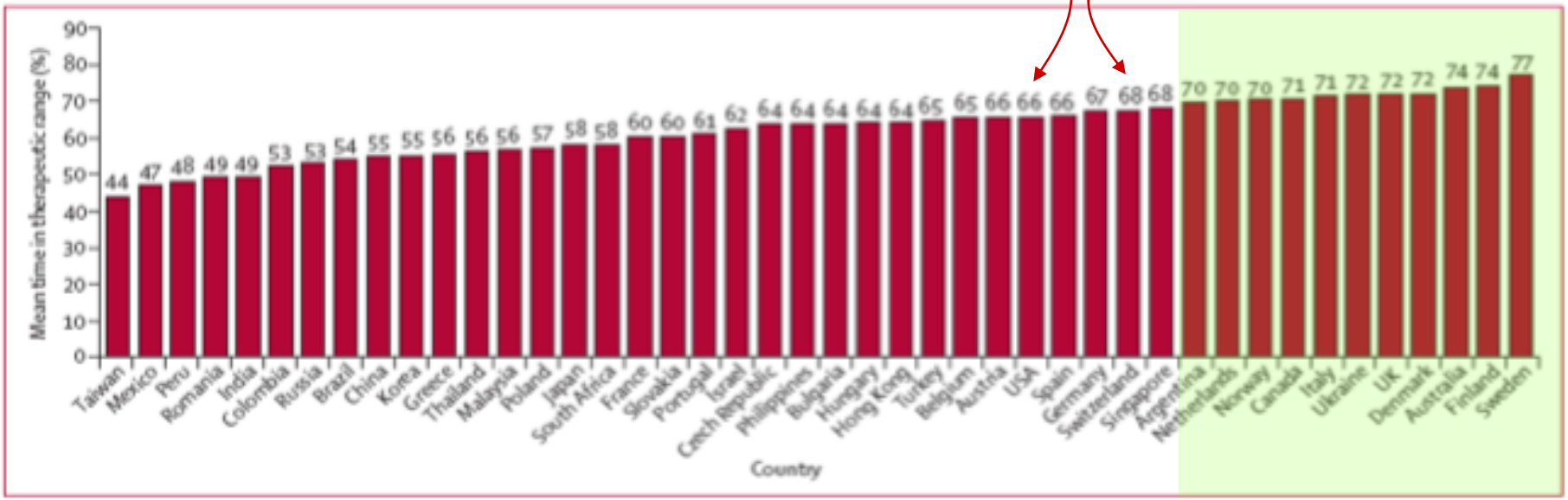


6,108 patients with nonvalvular atrial fibrillation
- 2,235 (36.6%) with ≥ 5 INR readings
- 486 (21.7%) had CHADS2 score ≥2

Morgan CLI
Thrombosis Research
124: 37-41, 2009

RE-LY Trial

„mean time in therapeutic range“ according to country



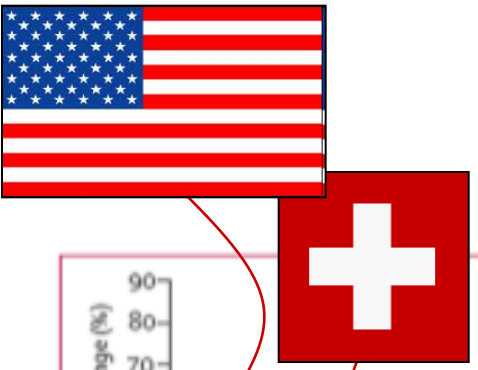
INR
Too low : 2 thirds
Too high: 1 third

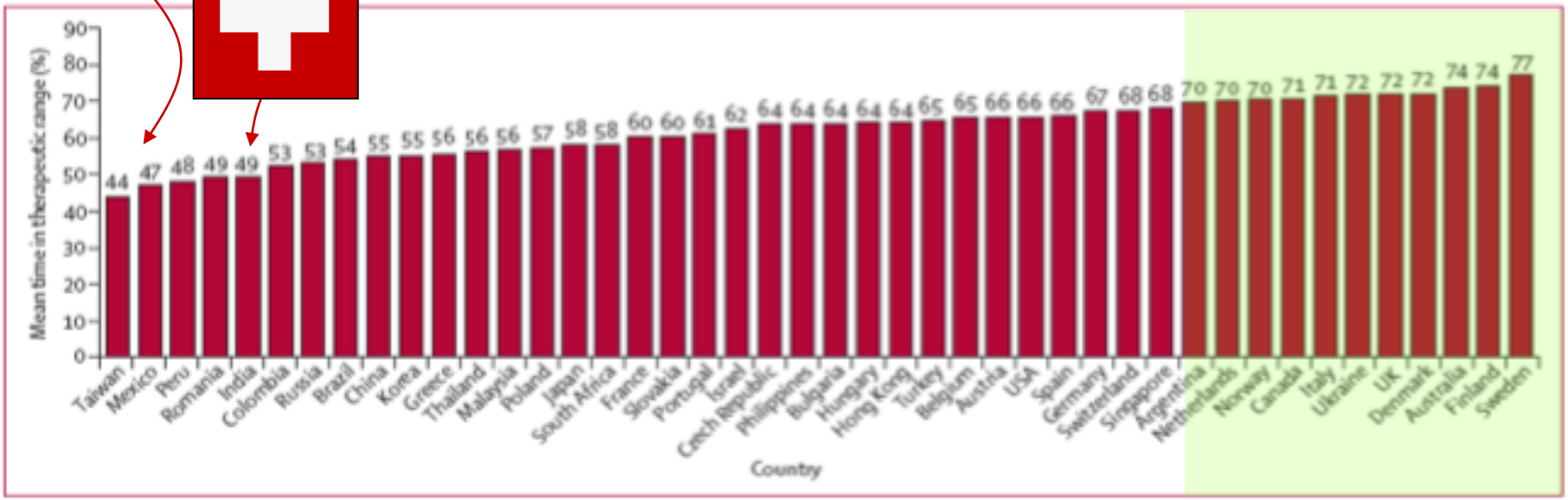
Wallentin et al. Lancet 2010;376:975

RE-LY Trial

„mean time in therapeutic range“ according to country

Real Life





INR
Too low : 2 thirds
Too high: 1 third

Wallentin et al. Lancet 2010;376:975

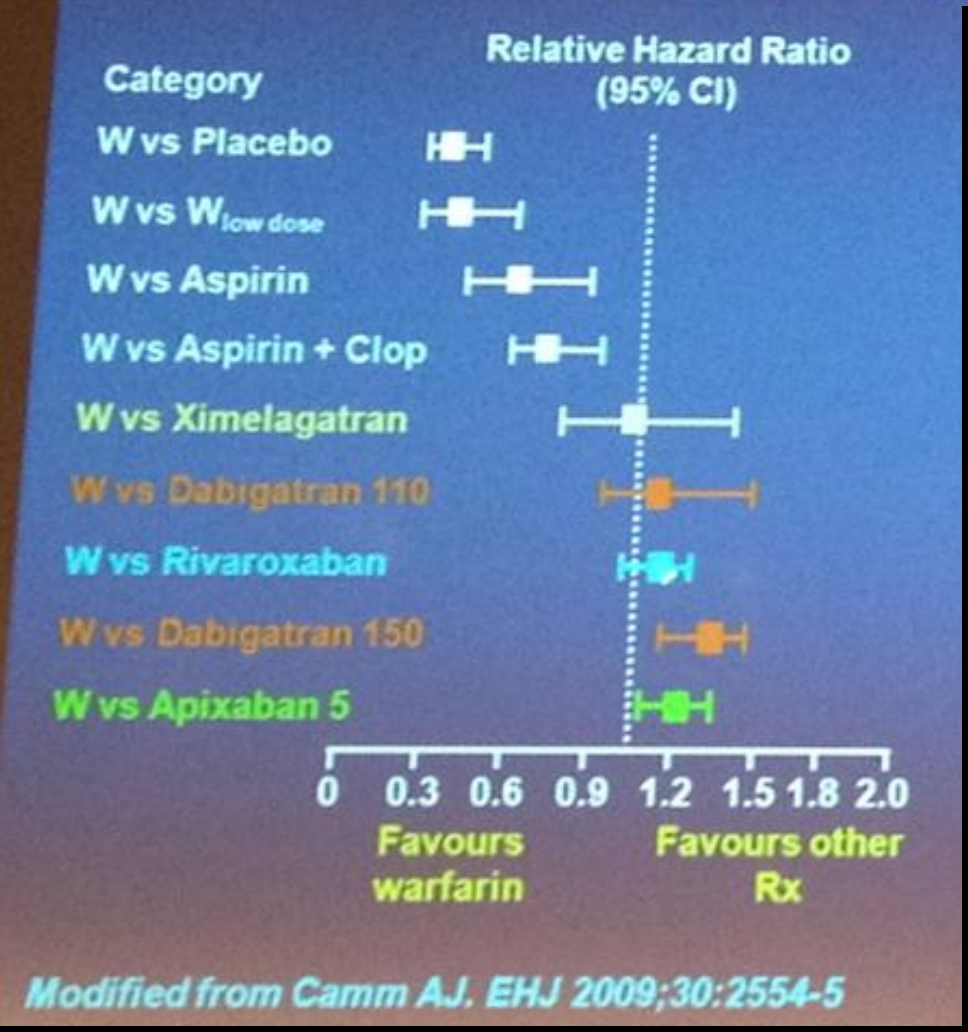
New Oral Anticoagulants – Pharmacokinetics and Studies*

Class	Manufacturer	Substance	Product name	SPAF Dose	Study
Factor IIa (Thrombin) Inhibitor	Boehringer Ingelheim	Dabigatran[1]	Pradaxa	2x/d	RE-LY[1a]
Factor Xa Inhibitors	Bayer	Rivaroxaban[2]	Xarelto	1x/d	ROCKET-AF[2a]
	Pfizer/BMS	Apixaban[3]	Eliquis	2x/d	ARISTOTLE[3a] AVERROES[3b]
	Daiichi-Sankyo	Edoxaban	Lixiana	1x/d[4]	ENGAGE-AF TIMI 48[4a]

1. Fachinformation D_Aug 2011;
1a. Conolly et al. N Engl J Med 2009; 361:1139-51;
2. Fachinformation Rivaroxaban 10 mg;
2a. Rationale & Design: Patel MR et al. Am Heart J 2010;159:340-347;
3. Eikelboom und Weitz, Circulation 2007;116:131-133;
3a. Rationale & Design: Lopes DR et al. Am Heart J 2010;159:331-9;
3b. Conolly J et al. N Engl J Med 2011
4. Steffel J et al. Eur Heart J 2011;
4a. Rationale & Design: Ruff TC et al. Am Heart J 2010;160:635-641;

Stroke Prevention: Anticoagulant Effect

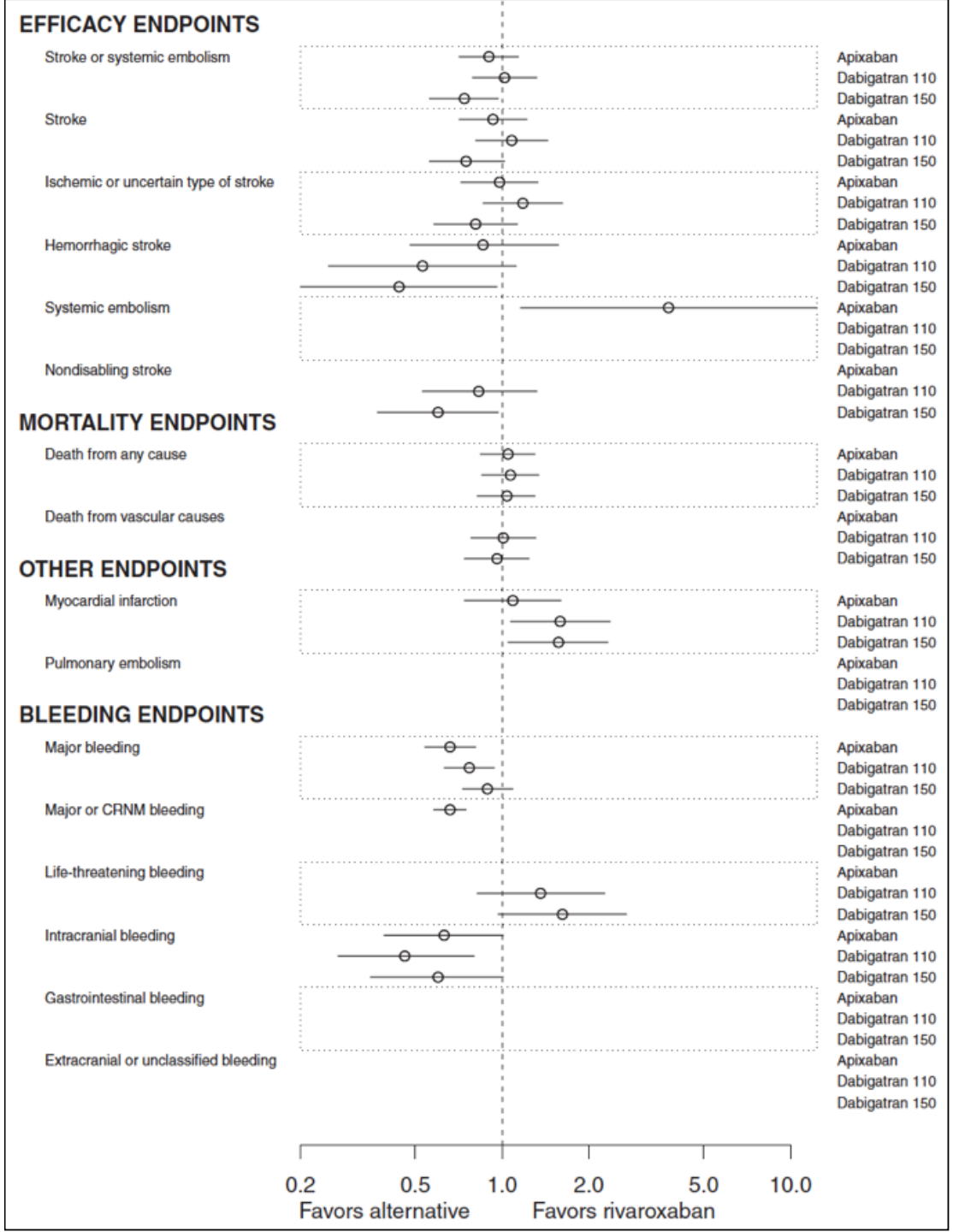
Meta-analysis of stroke or systemic embolism



Modified from Camm AJ. EHJ 2009;30:2554-5

New Oral Anticoagulants
Indirect Comparison

Lip GYH, JACC;60:2012



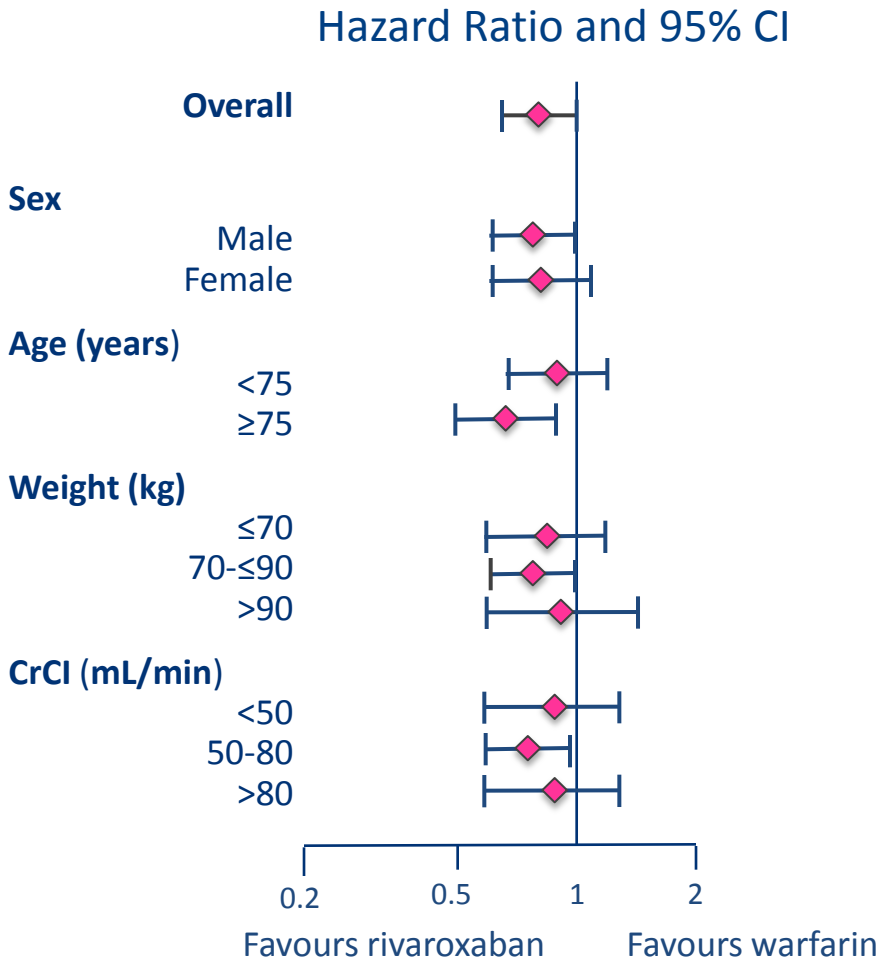
ESC 2012 guidelines
NOACs are preferred to VKAs for SPAF

- All NOACs (dabigatran, rivaroxaban and apixaban)
  - are preferred to VKAs for SPAF in the majority of patients with non-valvular AF (Class IIa, Level A)
  - Antiplatelets for SPAF are limited to patients who refuse or cannot take any OAC (Class IIa, Level B)
- None of the NOACs is recommended for patients with severe renal impairment CrCl < 30 mL/min (Class III, Level A)
  - Note: rivaroxaban 15 mg od is licensed for CrCl 15-29 mL/min
- VKA (INR 2–3) is the recommended OAC for stroke prevention in valvular AF

Camm AJ *et al*. *Eur Heart J* 2012

ROCKET AF: Primary Efficacy Endpoints

Influence of patient factors



p-value*
0,92
0,11
0,78
0,72

No significant difference between the sub-groups

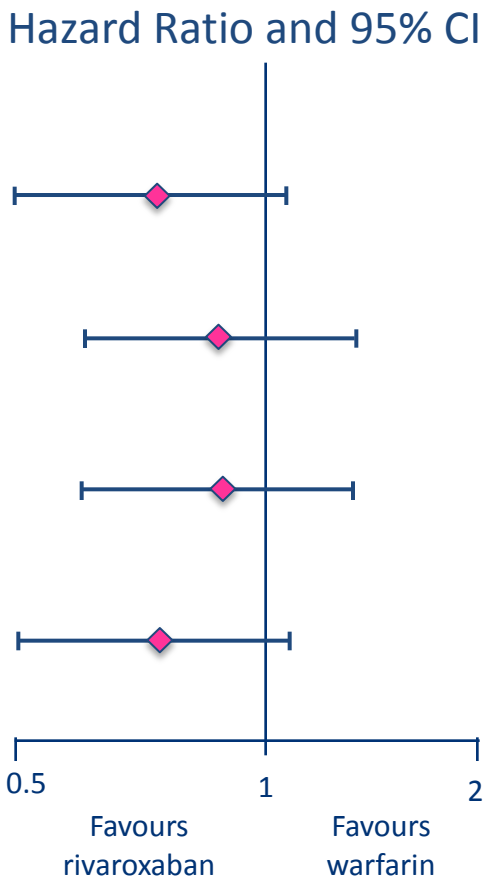
*p-value for interaction
Safety population – on treatment analysis

Patel et al 10.1056/NEJMoa1009638 2011

ROCKET AF: Consistent results even compared to the best treated warfarin patients

Better INR control

Center based INR control*	Rivaroxaban	Warfarin	Hazard ratio
cTTR range	7'061 (% per year)	7'082 (% per year)	(95% CI)
0,0-50,6%	1,8	2,5	0,70 (0,48-1,03)
50,7%-58,5%	1,9	2,2	0,89 (0,62-1,29)
58,6-65,7%	1,9	2,1	0,89 (0,62-1,28)
65,7-100%	1,3	1,8	0,74 (0,49-1,12)



cTTR, centre-based time in therapeutic range
Based on Rosendaal method with all INR values included
Safety population

*p-value for interaction = 0.74
Patel et al 10.1056/NEJMoa1009638 2011

Outcomes of Discontinuing Rivaroxaban Compared With Warfarin

In Patients With Nonvalvular Atrial Fibrillation Treated in Double-Blind Trial

Ischemic Events

	Events per 100 Patient-Yrs (Total Events)			
	Rivaroxaban	Warfarin	Rivaroxaban: Warfarin HR (95% CI)	p Value
Stroke or non-CNS embolism rates				
All discontinuations and interruptions (before end of study)	16.49 (51)	14.05 (44)	1.21 (0.81–1.81)	0.35
Temporary interruptions	6.20 (9)	5.05 (8)	1.28 (0.49–3.31)	0.62
Permanent discontinuations	25.60 (42)	23.28 (36)	1.10 (0.71–1.72)	0.66
After end of study	6.42 (22)	1.73 (6)	3.72 (1.51–9.16)	0.0044
All discontinuations and interruptions (before end of study) + after end of study events	11.20 (73)	7.57 (50)	1.50 (1.05–2.15)	0.026
Stroke, non-CNS embolism, MI, or vascular death				
All discontinuations and interruptions (before end of study)	46.97 (145)	52.50 (164)	0.92 (0.74–1.15)	0.47
Temporary interruptions	9.66 (14)	10.75 (17)	0.95 (0.47–1.94)	0.89
Permanent discontinuations	80.01 (131)	95.28 (147)	0.84 (0.67–1.07)	0.16
After end of study	9.05 (31)	4.03 (14)	2.24 (1.19–4.22)	0.012
All discontinuations and interruptions (before end of study) + after end of study events	27.02 (176)	26.97 (178)	1.02 (0.83–1.26)	0.85

Bleeds

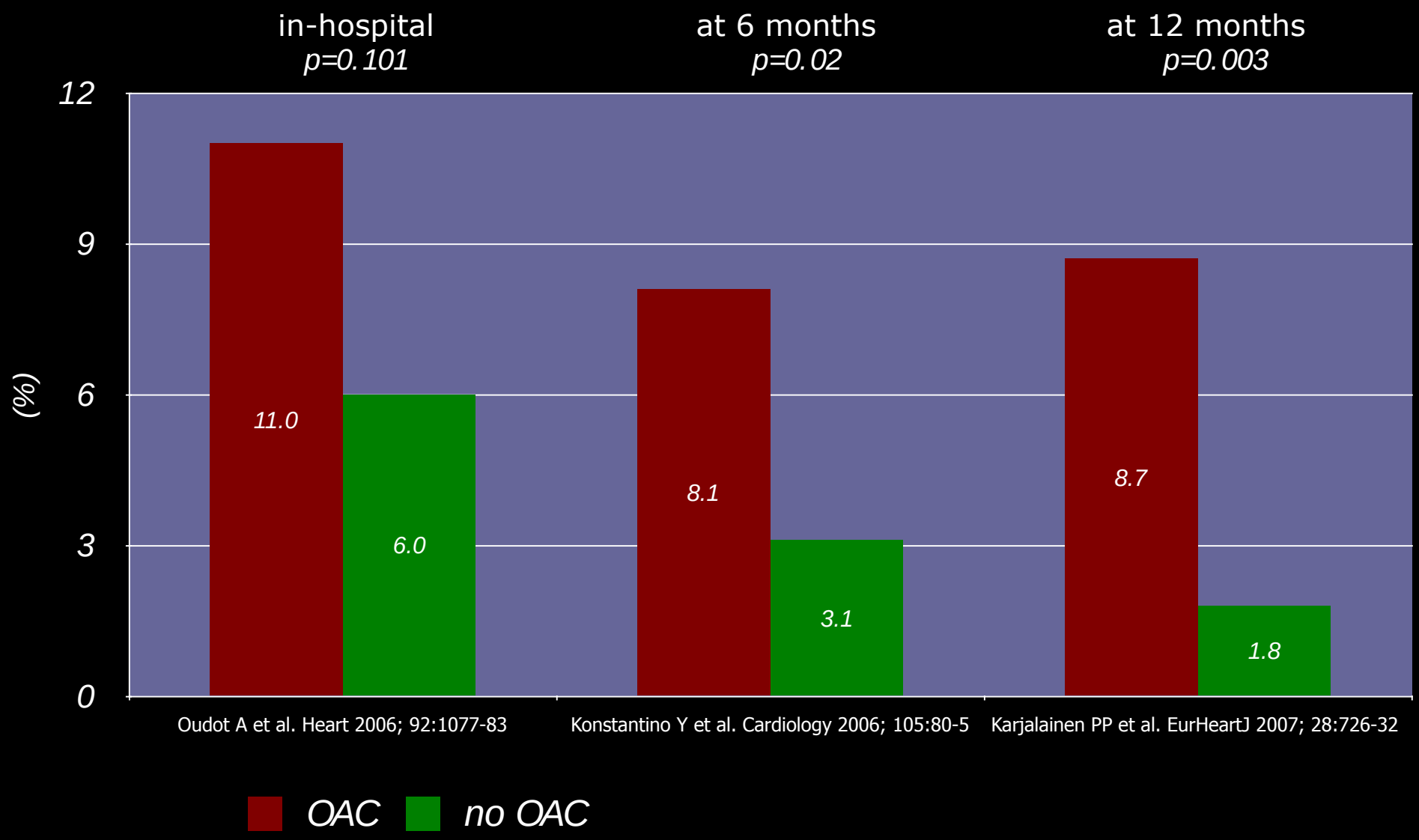
After end of study	7.29 (25)	2.01 (7)	3.62 (1.56–8.36)	0.0026

No official recommendations
Personal recommendations
- Rivaroxaban to vitamin K antagonist (VKA): stop rivaroxaban, start VKA, and bridge with low-dose LMWH to INR ≥ 2.0
- VKA to Rivaroxaban: start rivaroxaban at INR ≤ 2.5

Patel MR for ROCKET AF, J Am Coll Cardiol 2013;61:651–8

Mortality of patients with ACS / chronic CAD receiving OAC*

*Oral anticoagulation with vitamin K antagonist



ESC Guidelines for ST-segment elevation acute myocardial infarction

The recent Anti-Xa Therapy to Lower cardiovascular events in Addition to Standard therapy in subjects with Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) trial tested the addition of rivaroxaban, a factor Xa antagonist to aspirin and clopidogrel following ACS.262 In that trial, a low dose of rivaroxaban (2.5 mg twice daily) reduced the composite primary endpoint of cardiovascular death, myocardial infarction and stroke, but also all-cause mortality. Interestingly, stent thrombosis was reduced by one third. This was associated with threefold increases in non-CABG-related major bleeding, and intracranial haemorrhage. Importantly, the high dose of rivaroxaban (5 mg twice daily) was not associated with similar benefits and was associated with a major increase in the risk of

In selected patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered if the patient is at low bleeding risk. | IIb | B | 262

trial, in selected patients at low bleeding risk, the 2.5 mg dose of rivaroxaban may be considered in patients who receive aspirin and clopidogrel after STEMI. However, a phase III trial of another factor Xa antagonist (apixaban), the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE-2) trial,263 failed to find similar benefits of adding a high dose of apixaban to single or DAPT in a very-high-risk ACS population. Finally, darexaban and dabigatran were both tested in phase-II dose-ranging trials in post ACS patients,264,265 with, in both cases, dose-dependent increases in major bleeding but no signal of added efficacy when adding anticoagulant therapy to antiplatelet therapy in this setting.

In conclusion, the role of novel anticoagulants in combination with DAPT in secondary prevention of STEMI remains under discussion. The substantial mortality benefit seen with a low dose of rivaroxaban combined with aspirin and clopidogrel is intriguing but interpretation of the totality of evidence for the class is difficult.

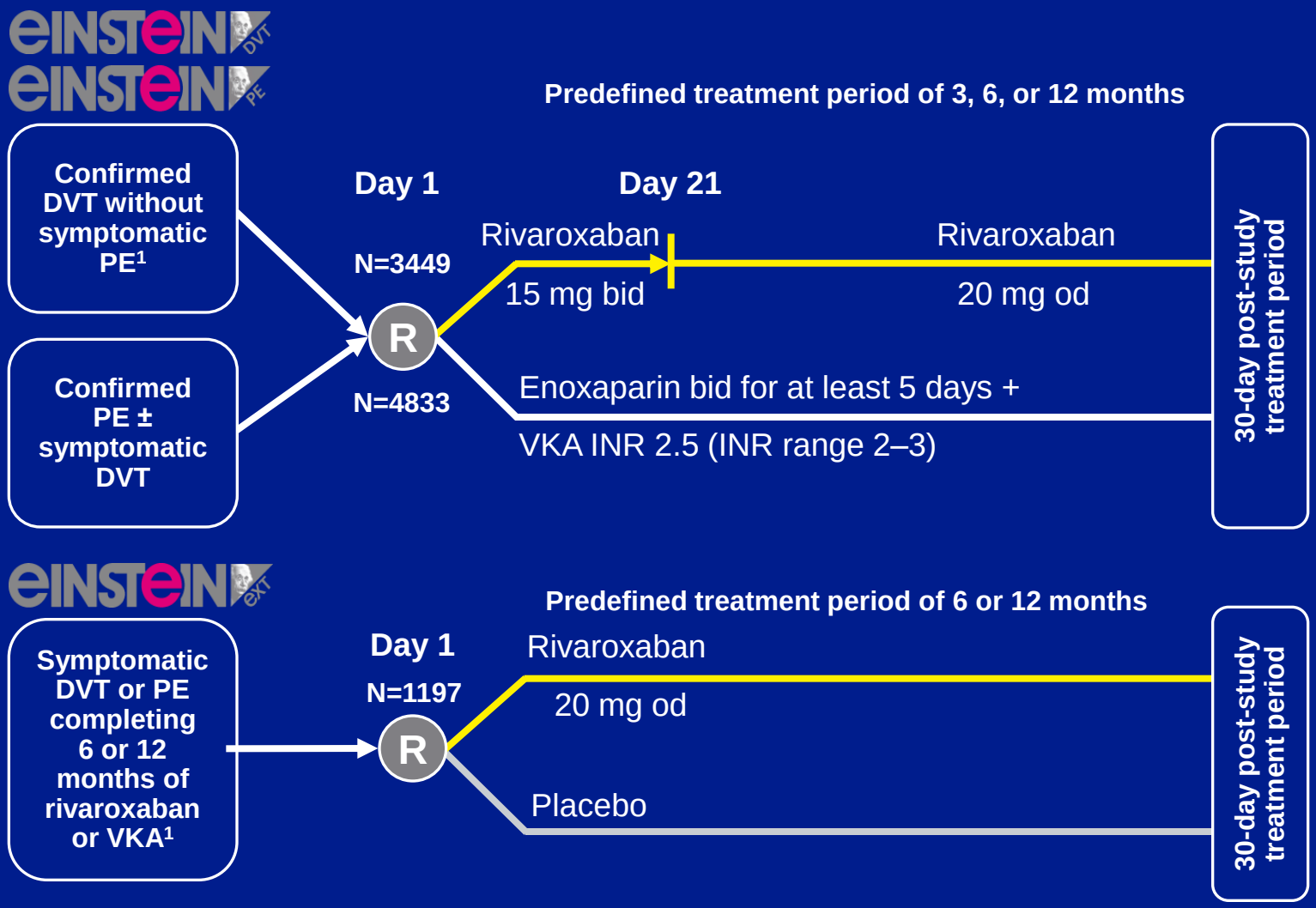
Steg PG, Europ Heart J (2012) 33, 2569–2619

Table 22 Routine therapies in the acute, subacute and long term phase of ST-segment elevation myocardial infarction

Recommendations	Class[a]	Level[b]	Ref[c]
Active smokers with STEMI must receive counselling and be referred to a smoking cessation programme.	I	B	225
Each hospital participating in the care of STEMI patients must have a smoking cessation protocol.	I	C	-
Exercise-based rehabilitation is recommended.	I	B	232, 233
Antiplatelet therapy with low dose aspirin (75–100 mg) is indicated indefinitely after STEMI.	I	A	237
In patients who are intolerant to aspirin, clopidogrel is indicated as an alternative to aspirin.	I	B	243
DAPT with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended (over aspirin and clopidogrel) in patients treated with PCI.	I	A	109, 110
DAPT with aspirin and an oral ADP receptor antagonist must be continued for up to 12 months after STEMI, with a strict minimum of:	I	C	245–247, 283
• 1 month for patients receiving BMS	I	C	
• 6 months for patients receiving DES	IIb	B	
In patients with left ventricular thrombus, anticoagulation should be instituted for a minimum of 3 months.	IIa	B	344–346
In patients with a clear indication for oral anticoagulation (e.g. atrial fibrillation with CHA_2DS_2-VASc Score ≥2 or mechanical valve prosthesis), oral anticoagulation must be implemented in addition to antiplatelet therapy.	I	C	-
If patients require triple antithrombotic therapy, combining DAPT and OAC, e.g. because of stent placement and an obligatory indication for OAC, the duration of dual antiplatelet therapy should be minimized to reduce bleeding risk.	I	C	-
In selected patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered if the patient is at low bleeding risk.	IIb	B	262
Oral treatment with beta-blockers is indicated in patients with heart failure or LV dysfunction.	I	A	284–288
Intravenous beta-blockers must be avoided in patients with hypotension or heart failure.	III	B	266
Intravenous beta-blockers should be considered at the time of presentation in patients without contraindications, with high blood pressure, tachycardia and no signs of heart failure.	IIa	B	266
A fasting lipid profile must be obtained in all STEMI patients, as soon as possible after presentation.	I	C	-
It is recommended to initiate or continue high dose statins early after admission in all STEMI patients without contraindication or history of intolerance, regardless of initial cholesterol values.	I	A	267
Reassessment of LDL-cholesterol should be considered after 4–6 weeks to ensure that a target value of ≤1.8 mmol/L (70 mg/dL) has been reached.	IIa	C	270
Verapamil may be considered for secondary prevention in patients with absolute contraindications to beta-blockers and no heart failure.	IIb	B	276
ACE inhibitors are indicated starting within the first 24 h of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes or an anterior infarct.	I	A	279
An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure or LV systolic dysfunction, particularly those who are intolerant to ACE inhibitors.	I	B	280, 281
ACE inhibitors should be considered in all patients in the absence of contraindications.	IIa	A	289, 290
Aldosterone antagonists, e.g. eplerenone, are indicated in patients with an ejection fraction ≤40% and heart failure or diabetes, provided no renal failure or hyperkalaemia.	I	B	282

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; BMS = bare metal stent; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; LDL = low-density lipoprotein; LV = left ventricular; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

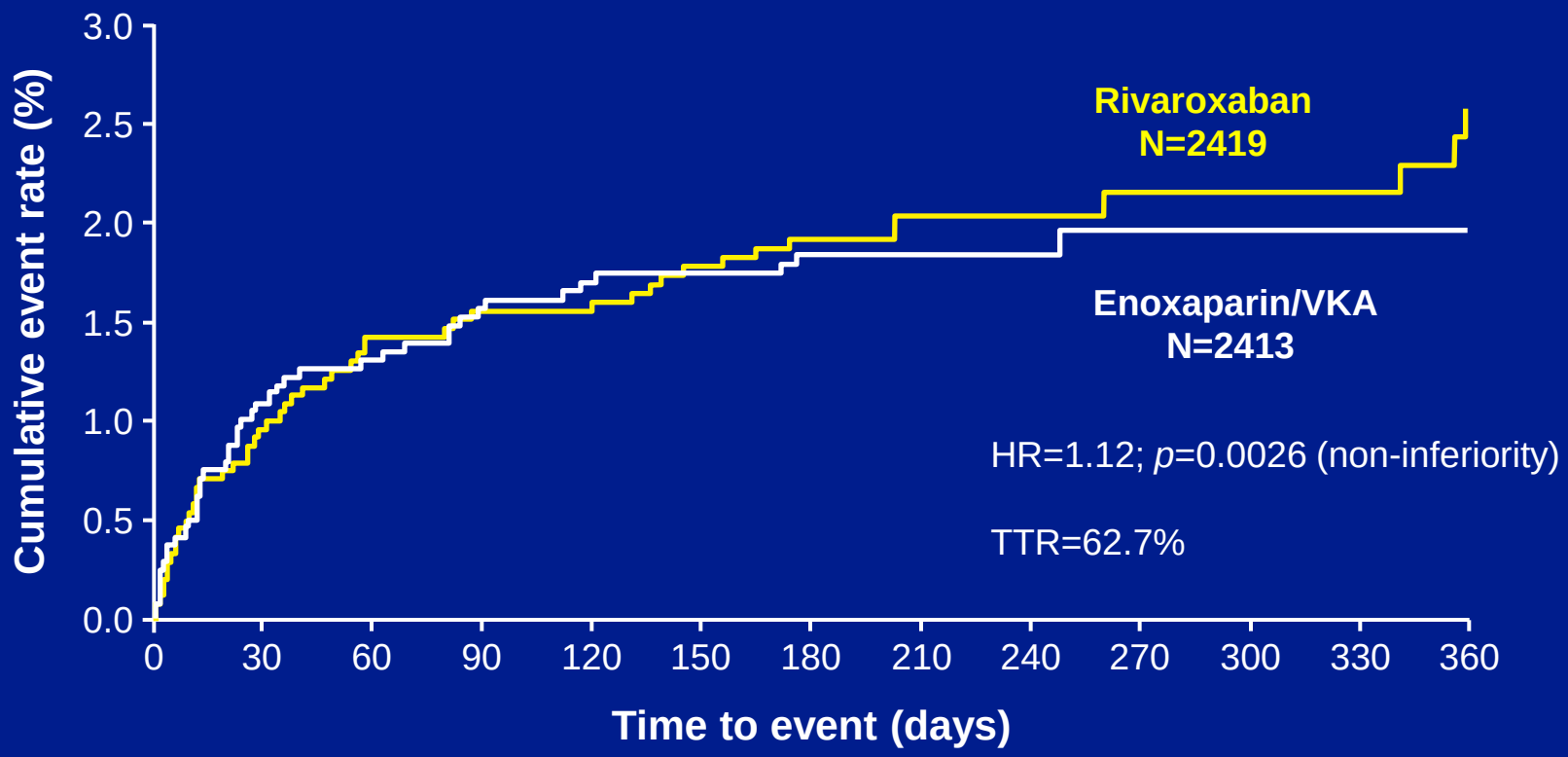
EINSTEIN study program



1. The Einstein Investigators *NEJM* 2010;363:2499–2510

L.CH.HC.04.2012.0120-EN

EINSTEIN PE: primary efficacy outcome: time to first event

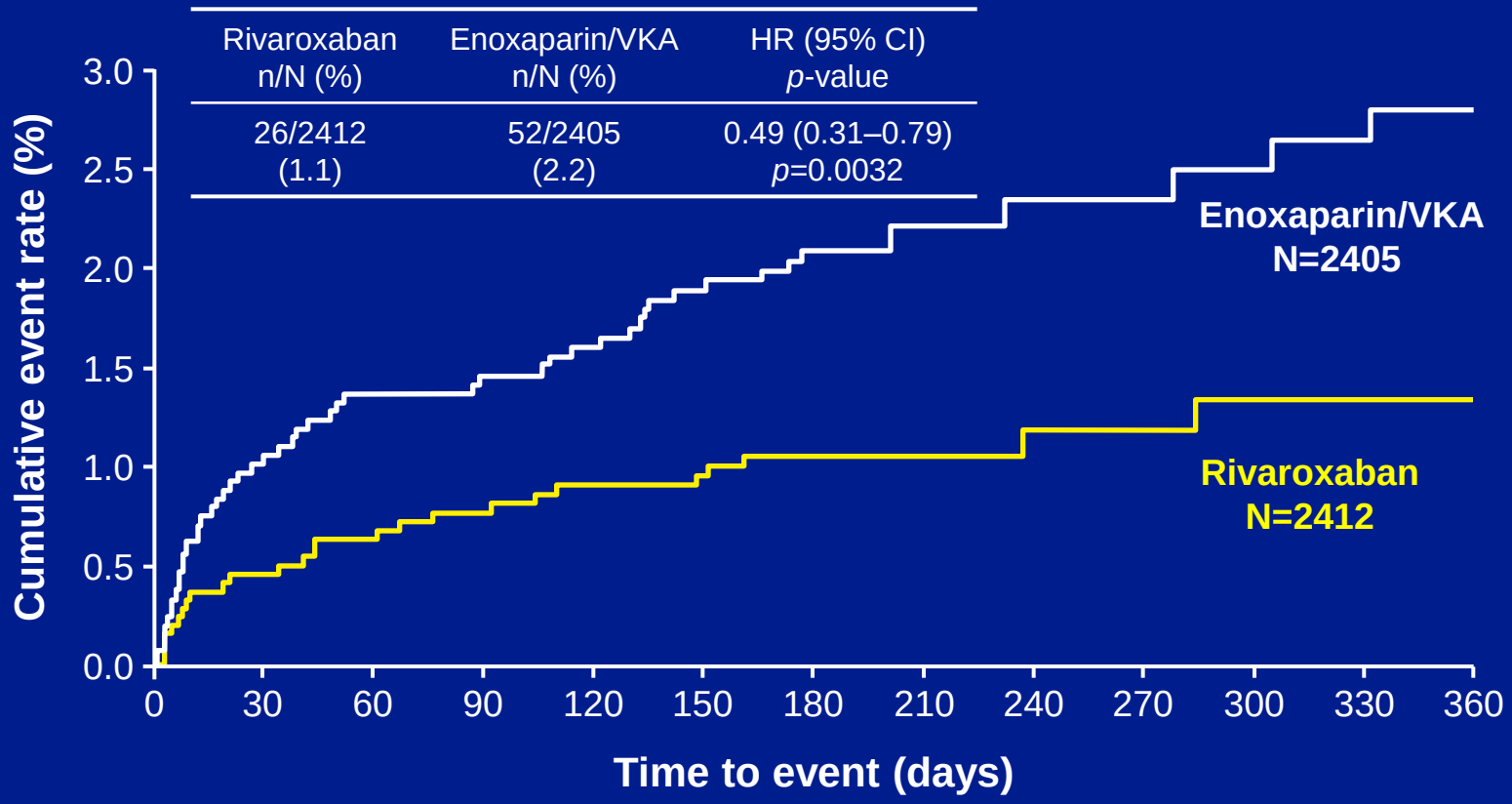


Number of patients at risk													
Rivaroxaban	2419	2350	2321	2303	2180	2167	2063	837	794	785	757	725	672
Enoxaparin/VKA	2413	2316	2295	2274	2155	2146	2050	835	787	772	746	722	675

ITT population

L.CH.HC.04.2012.0120-EN

EINSTEIN PE: major bleeding



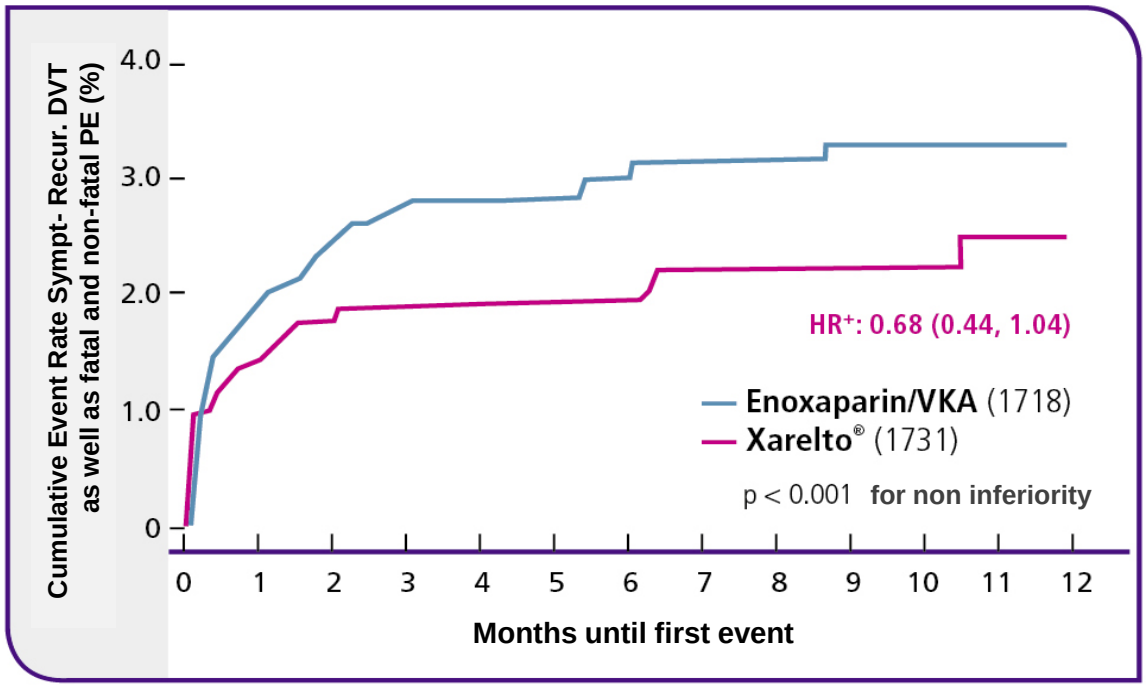
Number of patients at risk													
Rivaroxaban	2412	2281	2248	2156	2091	2063	1317	761	735	700	669	659	350
Enoxaparin/VKA	2405	2270	2224	2116	2063	2036	1176	746	719	680	658	642	278

Safety population

L.CH.HC.04.2012.0120-EN

Deep Vein Thrombosis– Study Results

Xarelto® - Effective Treatment of DVT with a new Single-Drug-Therapy[5]



EINSTEIN DVT

+Hazard Ratio

Xarelto rivaroxaban

Rivaroxaban for Thromboprophylaxis in Acutely Ill Medical Patients

Cohen AT for MAGELLAN Trial, N Engl J Med 2013;368:513-23

- ≥ 40 years
- Hospitalized for an acute medical
- Randomized to
  - subcutaneous enoxaparin 40 mg once daily, for 10 ± 4 days and oral placebo for 35 ± 4 days
  - subcutaneous placebo for 10 ± 4 days and oral rivaroxaban 10 mg once daily, for 35 ± 4 days

In 8,101 acutely ill medical patients

- Rivaroxaban was noninferior to enoxaparin for standard-duration thromboprophylaxis.
- Extended-duration rivaroxaban reduced the risk of venous thromboembolism.
- Rivaroxaban was associated with an increased risk of bleeding.

Rivaroxaban Use at the University Hospital of Bern, Switzerland

	2011					2012				
	1.2011	2.2011	3.2011	4.2011	TOTAL	1.2012	2.2012	3.2012	4.2012	TOTAL
MARCOUMAR[1] 3 mg	9525	6375	9350	7125	**32375**	10275	9475	6700	9150	**35600**
SINTROM[2] MITIS 1 mg	1800	1600	1000	1500	**5900**	1900	1200	700	700	**4500**
SINTROM[2] 4 mg	40	100	180	20	**340**	20	60	100	40	**220**
XARELTO[3] 10 mg						20	130	180	200	**530**
XARELTO[3] 15 mg							40	90	170	**300**
XARELTO[3] 20 mg							110	300	360	**770**
PRADAXA[4] 110 mg								120	60	**180**
PRADAXA[4] 150 mg								60	120	**180**

[1] Phenprocoumon
[2] Acenocoumarol
[3] Rivaroxaban
[4] Dabigatran etexilate


Xarelto
Simple Protection for Many Patients
TCT
1803
Xarelto
Simple Protection for Many Patients