RIVAROXABAN

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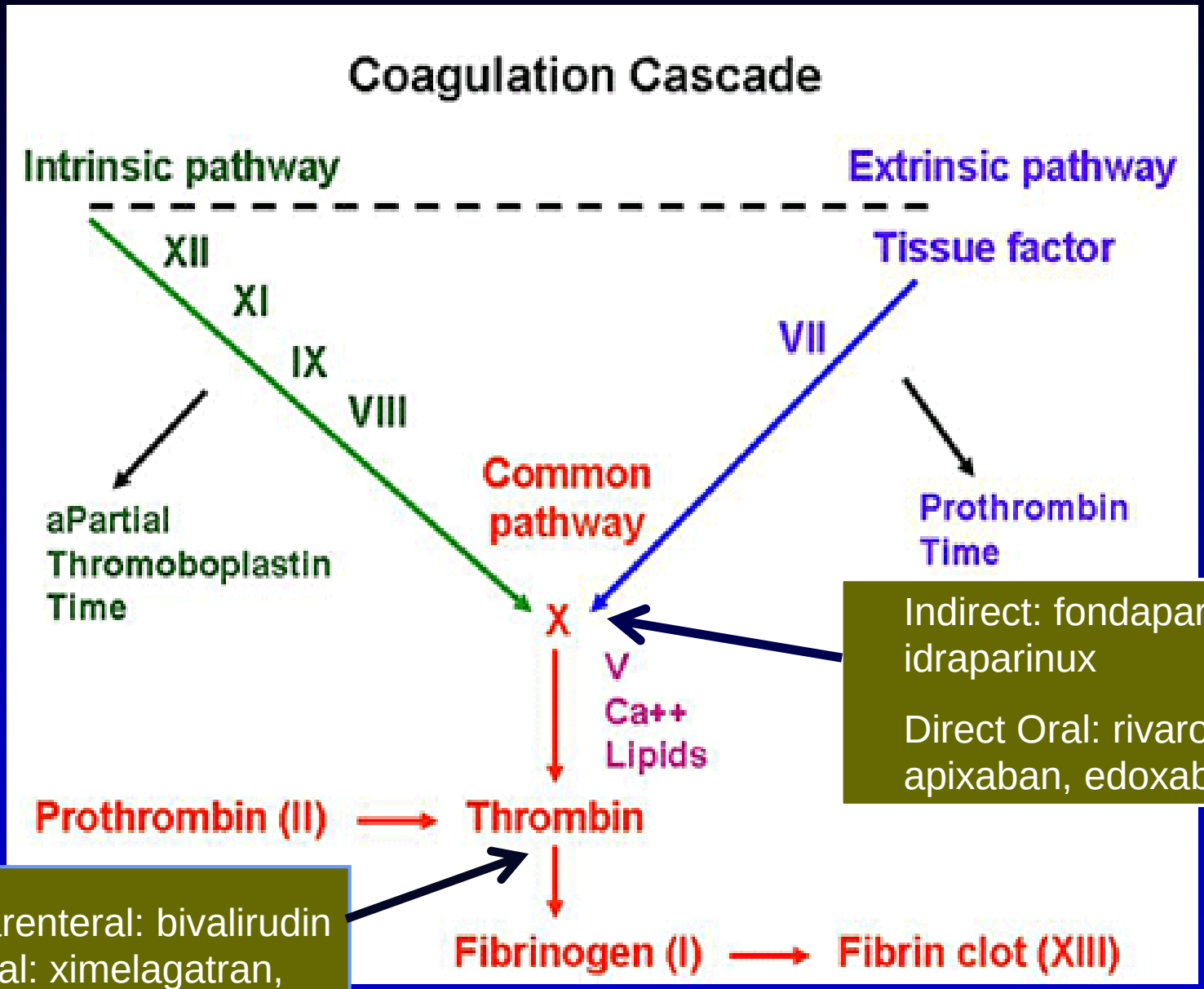
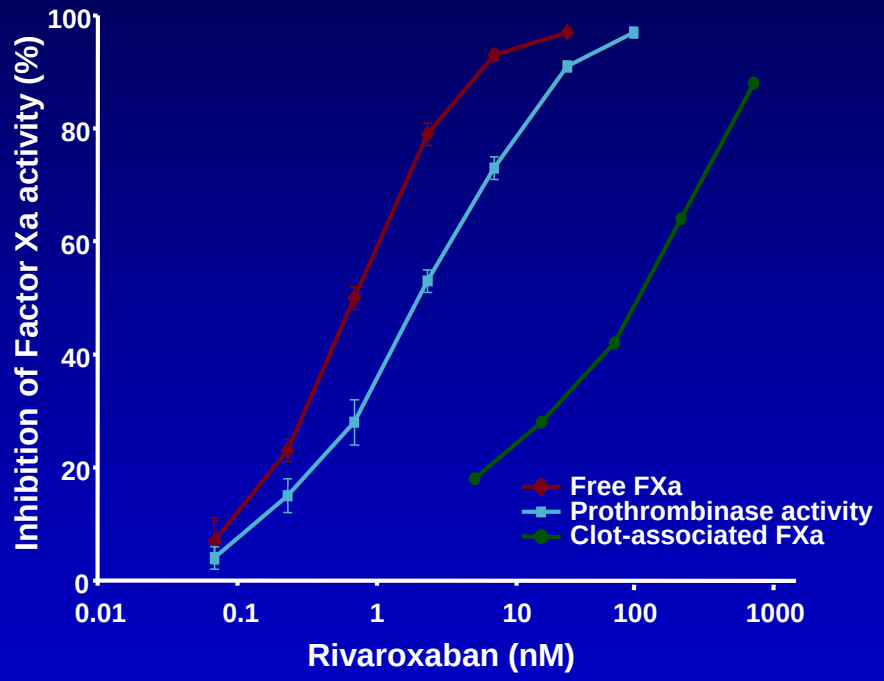
The ‘ideal’ oral anticoagulant

- Oral, preferably once daily
- Rapid onset and offset of action
- Predictable PK and PD
- Low propensity for food and drug interactions
- Fixed doses
- Wide therapeutic window
- Easy to use with no need for monitoring


Coagulation Cascade
Intrinsic pathway
Extrinsic pathway
XII
XI
IX
VIII
Tissue factor
VII
aPartial Thromoboplastin Time
Common pathway
Prothrombin Time
X
V
Ca++
Lipids
Prothrombin (II)
Thrombin
Fibrinogen (I)
Fibrin clot (XIII)
Indirect: fondaparinux, idraparinux
Direct Oral: rivaroxaban, apixaban, edoxaban
Direct Parenteral: bivalirudin
Direct Oral: ximelagatran, dabigatran, AZD0837

Rivaroxaban: oral direct Factor Xa inhibitor

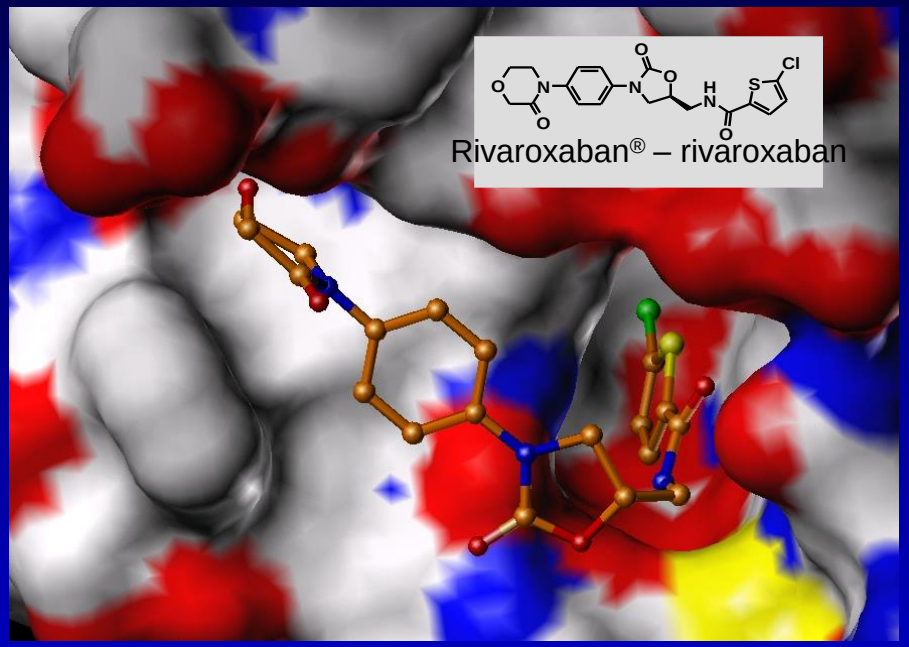
- Specific, competitive, direct FXa inhibitor
- Inhibits free and clot-associated FXa activity, and prothrombinase activity
- Inhibits thrombin generation via inhibition of FXa activity
  - Prolongs time to thrombin generation
  - Inhibits peak thrombin generation
  - Reduces the total amount of thrombin generated
- Does not require a cofactor



Perzborn *et al. J Thromb Haemost* 2005; *ICT* 2004; Depasse *et al*. *ISTH* 2005; Kubitza *et al*. *Clin Pharmacol Ther* 2005; *Br J Clin Pharmacol*, 2007; Graff *et al*

Rivaroxaban: oral direct Factor Xa inhibitor

- Predictable pharmacology
- High bioavailability
- Low risk of drug–drug interactions
- Fixed dose
- No requirement for monitoring



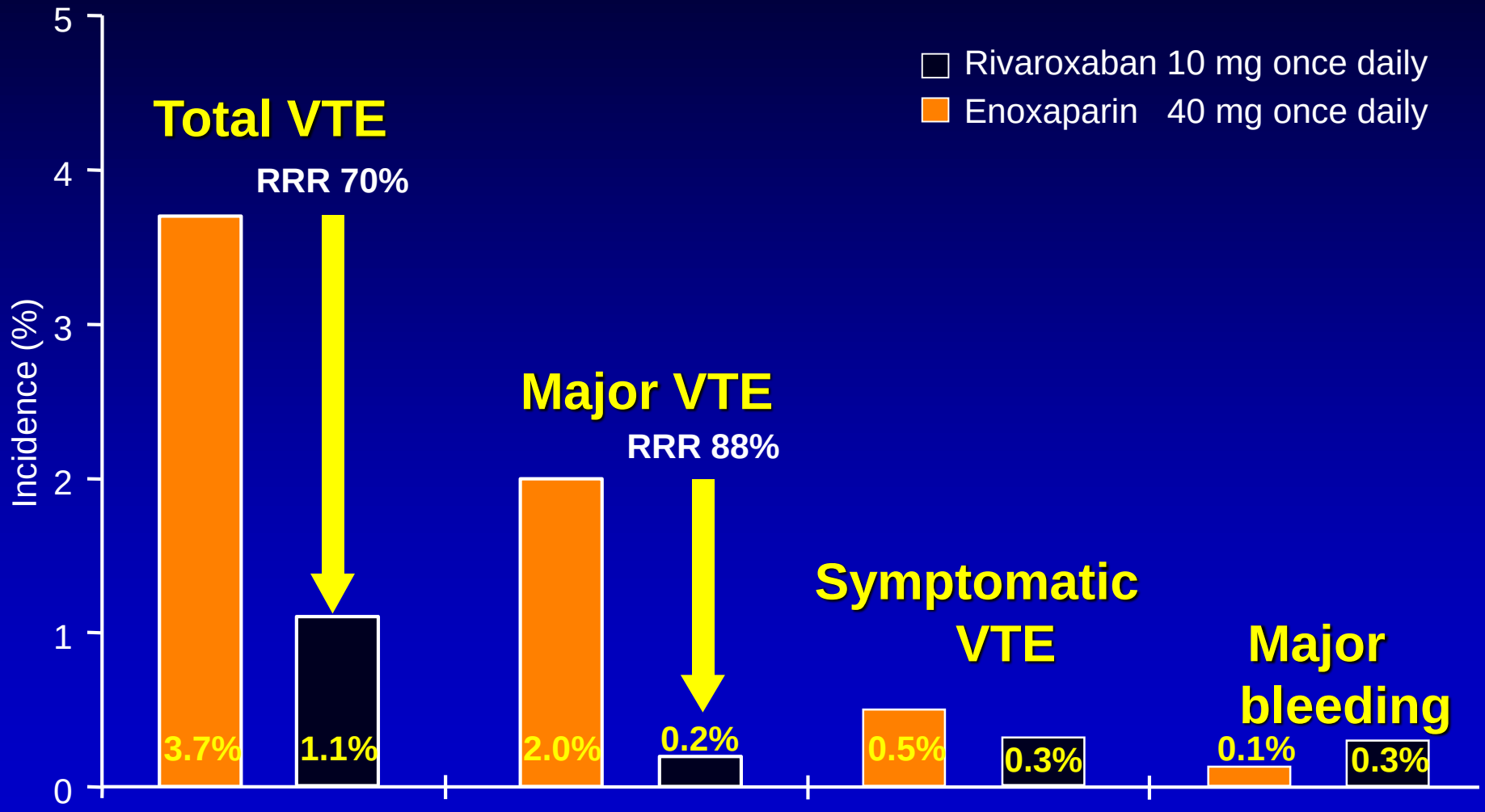
Perzborn *et al.* 2005; Kubitza *et al.* 2005; 2006; 2007; Roehrig *et al*, 2005

Clinical trials with Rivaroxaban:

	Phase II	Phase III
VTE prevention after major orthopaedic surgery	▪ ODIXa-HIP1 ▪ ODIXa-HIP2 ▪ ODIXa-KNEE ▪ ODIXa-OD-HIP	RECORD ▪ RECORD1 ▪ RECORD2 ▪ RECORD3 ▪ RECORD4
VTE prevention in hospitalized medically ill patients		MAGELLAN
VTE treatment	▪ ODIXa-DVT ▪ EINSTEIN-DVT	EINSTEIN ▪ EINSTEIN-DVT ▪ EINSTEIN-PE ▪ EINSTEIN-EXT
Stroke prevention in atrial fibrillation		ROCKET AF Japanese Phase III study
Secondary prevention of acute coronary syndromes	ATLAS ACS TIMI 46	
	~8,000	**>42,000**

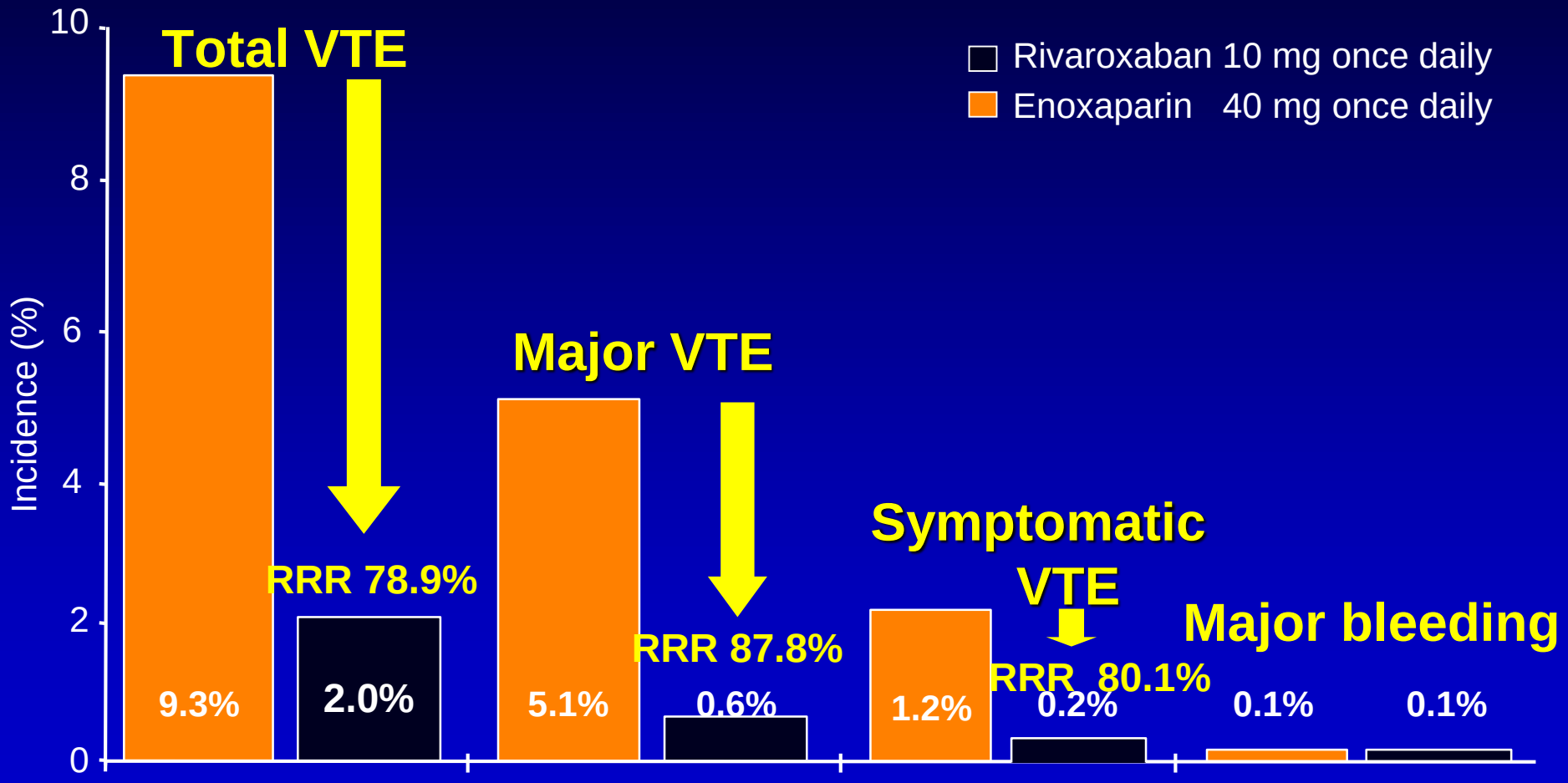
Oral rivaroxaban compared with subcutaneous enoxaparin for extended thromboprophylaxis after total hip arthroplasty

RECORD1: summary



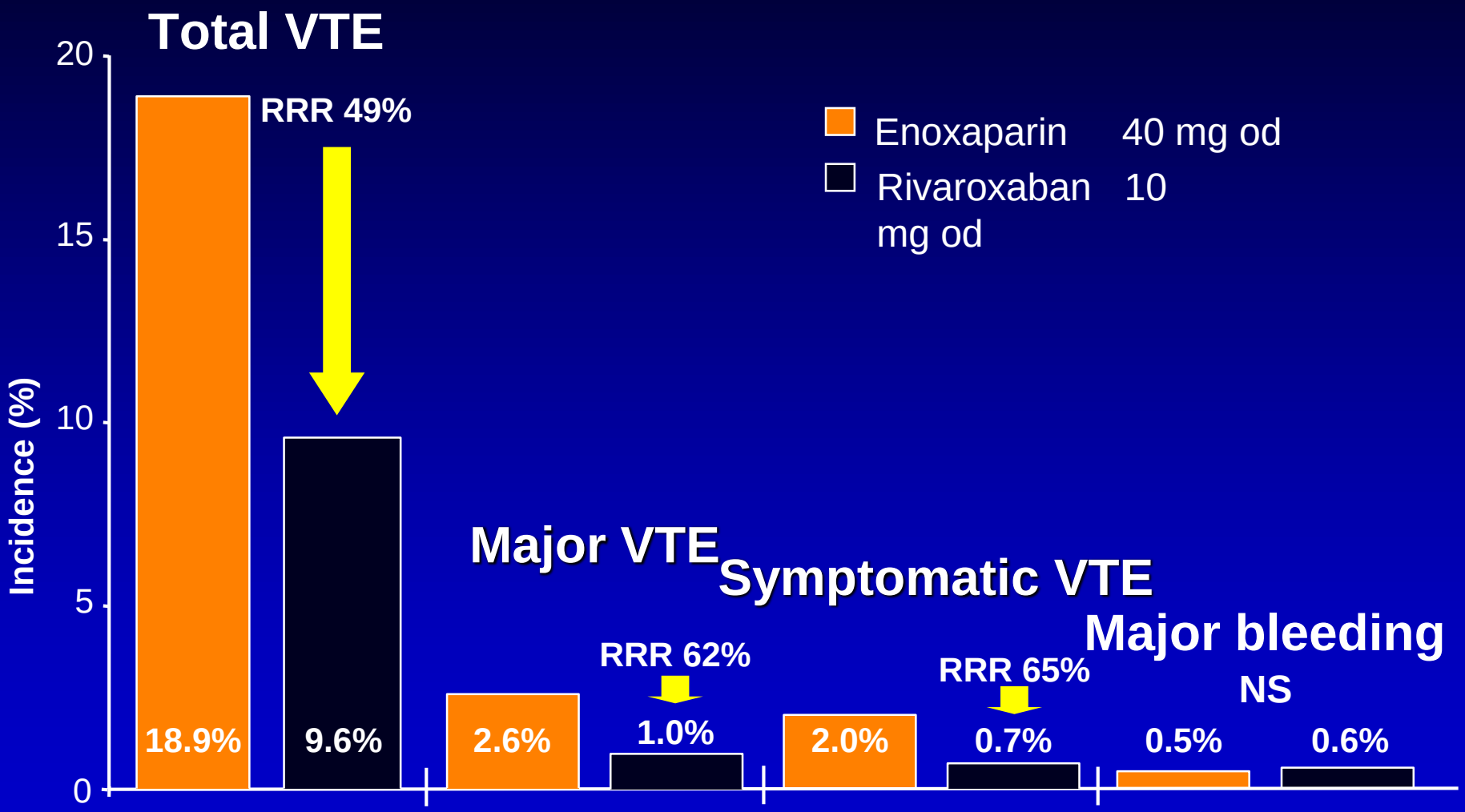
Extended thromboprophylaxis with rivaroxaban compared with short-term thromboprophylaxis with low molecular weight heparin after total hip arthroplasty

RECORD2: summary

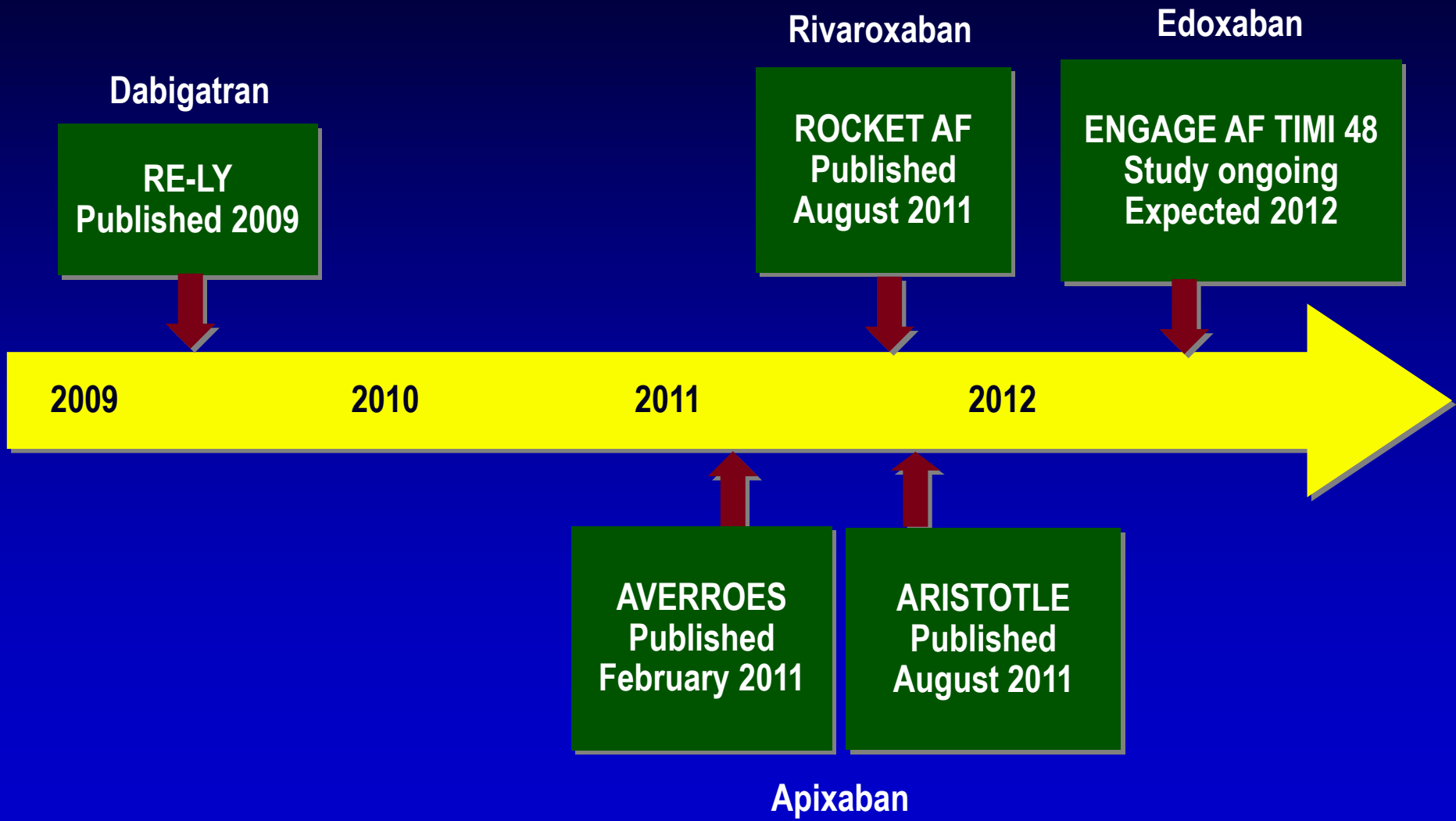


Rivaroxaban for the prevention of venous thromboembolism in total knee arthroplasty surgery

RECORD3: summary



Atrial Fibrillation
Phase 3 Study Timelines



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

N Engl J Med August 10, 2011

Study Design

Atrial Fibrillation

Risk Factors
- CHF
- Hypertension
- Age ≥ 75
- Diabetes

At least 2 or 3 required*

OR
- Stroke, TIA or Systemic embolus

Randomize
Double Blind / Double Dummy
(n ~ 14,000)

Rivaroxaban

20 mg daily
15 mg for Cr Cl 30-49 ml/min

Warfarin

INR target - 2.5
(2.0-3.0 inclusive)

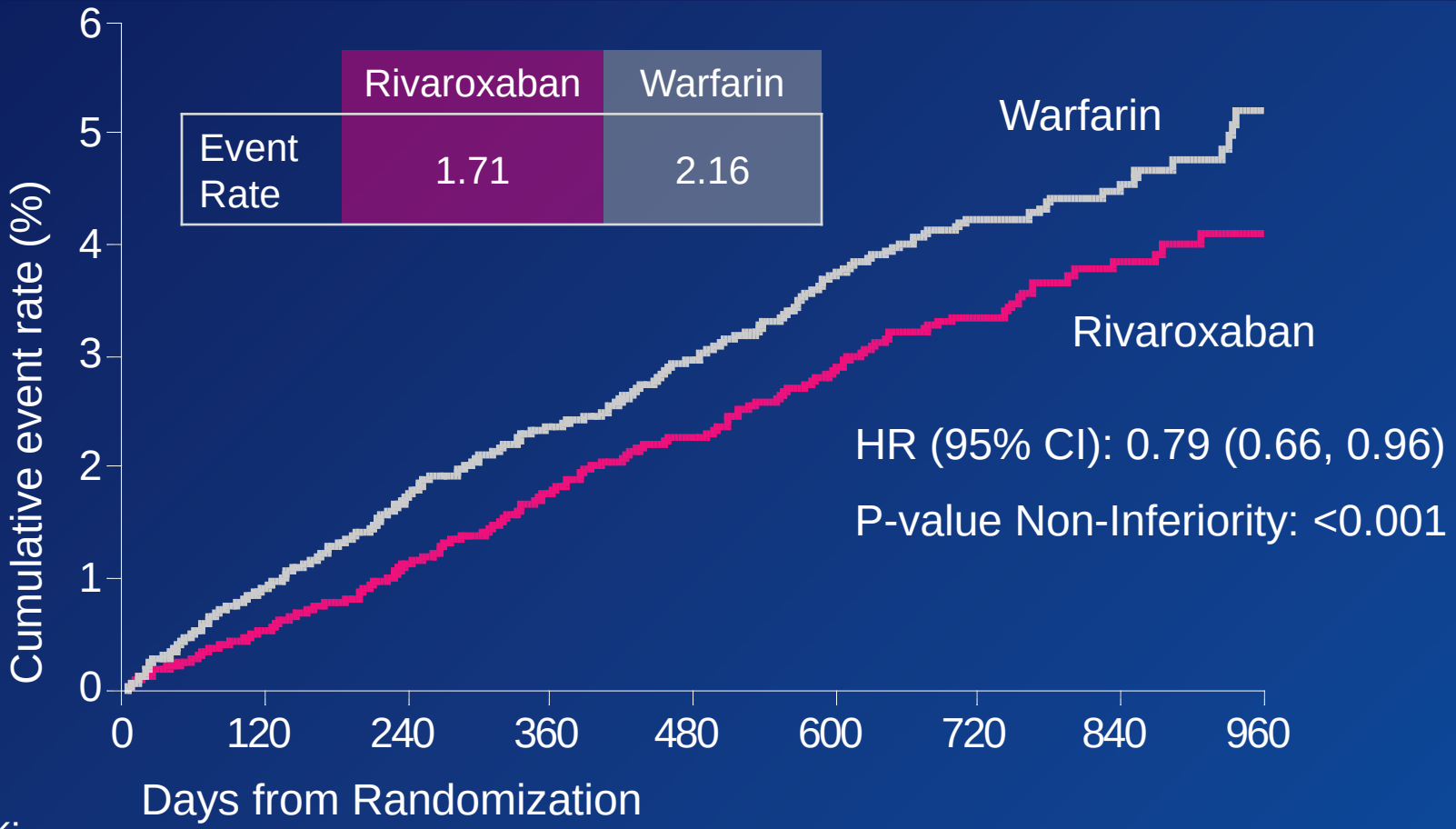
Monthly Monitoring
Adherence to standard of care guidelines

Primary Endpoint: Stroke or non-CNS Systemic Embolism

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

ROCKET AF

Primary Efficacy Outcome
Stroke and non-CNS Embolism



No. at risk:

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

Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

ROCKET AF

Primary Safety Outcomes

	Rivaroxaban	Warfarin		
	Event Rate	Event Rate	HR (95% CI)	P-value
Major and non-major Clinically Relevant	14.91	14.52	1.03 (0.96, 1.11)	0.442
Major	3.60	3.45	1.04 (0.90, 1.20)	0.576
Non-major Clinically Relevant	11.80	11.37	1.04 (0.96, 1.13)	0.345

Event Rates are per 100 patient-years
Based on Safety on Treatment Population

ROCKET AF

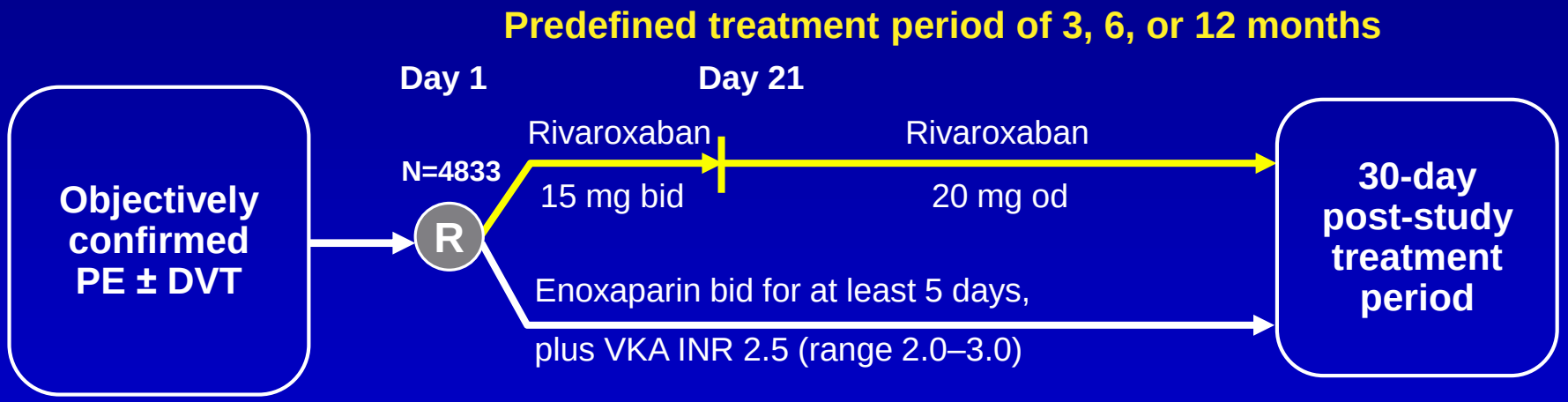
Summary

- **Efficacy**:
  - Rivaroxaban was non-inferior to warfarin for prevention of stroke and non-CNS embolism.
  - Rivaroxaban was superior to warfarin while patients were taking study drug.
  - By intention-to-treat, rivaroxaban was non-inferior to warfarin but did not achieve superiority.
- **Safety**:
  - Similar rates of bleeding and adverse events.
  - Less ICH and fatal bleeding with rivaroxaban.
- **Conclusion**:
  - Rivaroxaban is a proven alternative to warfarin for moderate or high risk patients with AF.

EINSTEIN PE: study design

Randomized, open-label, event-driven, non-inferiority study

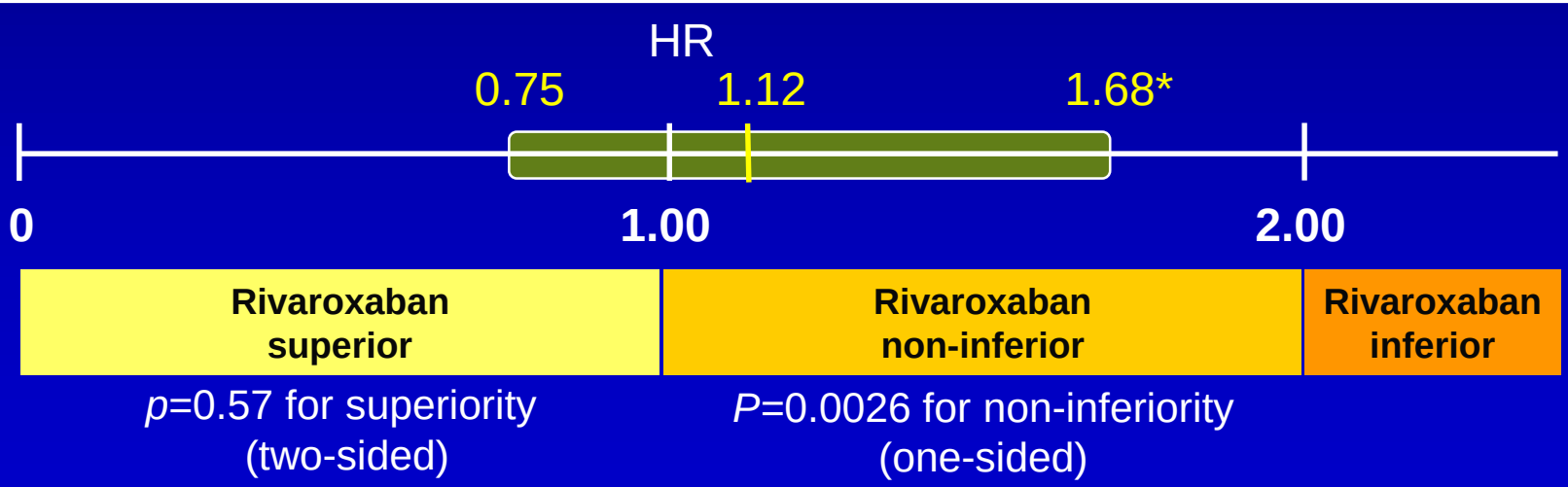
- **Up to 48 hours' heparins/fondaparinux treatment permitted before study entry**
- **88 primary efficacy outcomes needed**
- **Non-inferiority margin: 2.0**



- Primary efficacy outcome: first recurrent VTE
- Principal safety outcome: first major or nonmajor clinically relevant bleeding

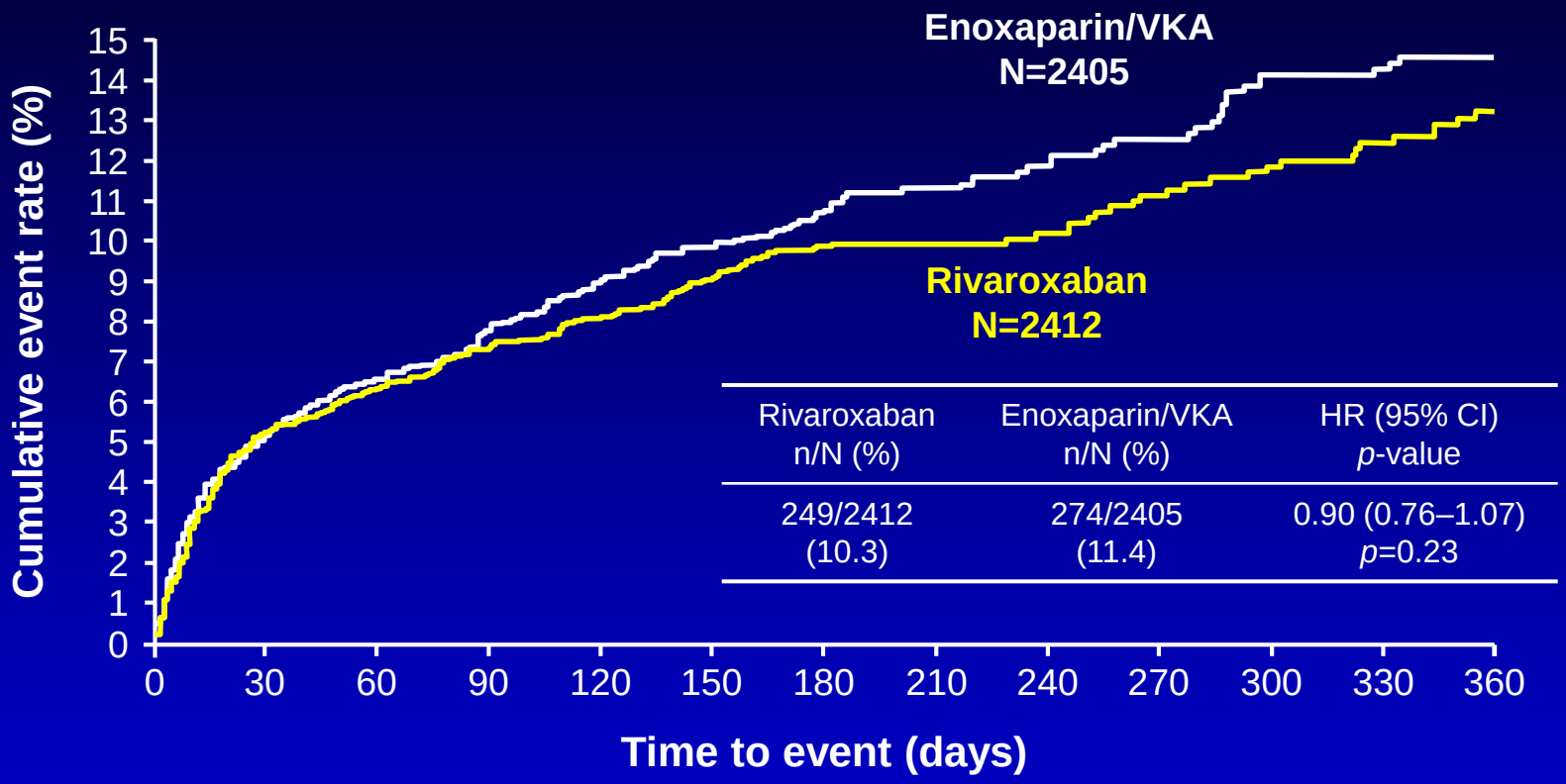
EINSTEIN PE: primary efficacy outcome analysis

	Rivaroxaban (N=2419)		Enoxaparin/VKA (N=2413)	
	n	(%)	n	(%)
First symptomatic recurrent VTE	**50**	**(2.1)**	**44**	**(1.8)**
Recurrent DVT	18	(0.7)	17	(0.7)
Recurrent DVT + PE	0		2	(<0.1)
Non-fatal PE	22	(0.9)	19	(0.8)
Fatal PE/unexplained death where PE cannot be ruled out	10	(0.4)	6	(0.2)



*Potential relative risk increase <68.4%; absolute risk difference 0.24% (–0.5 to 1.02)

EINSTEIN PE: principal safety outcome – major or non-major clinically relevant bleeding



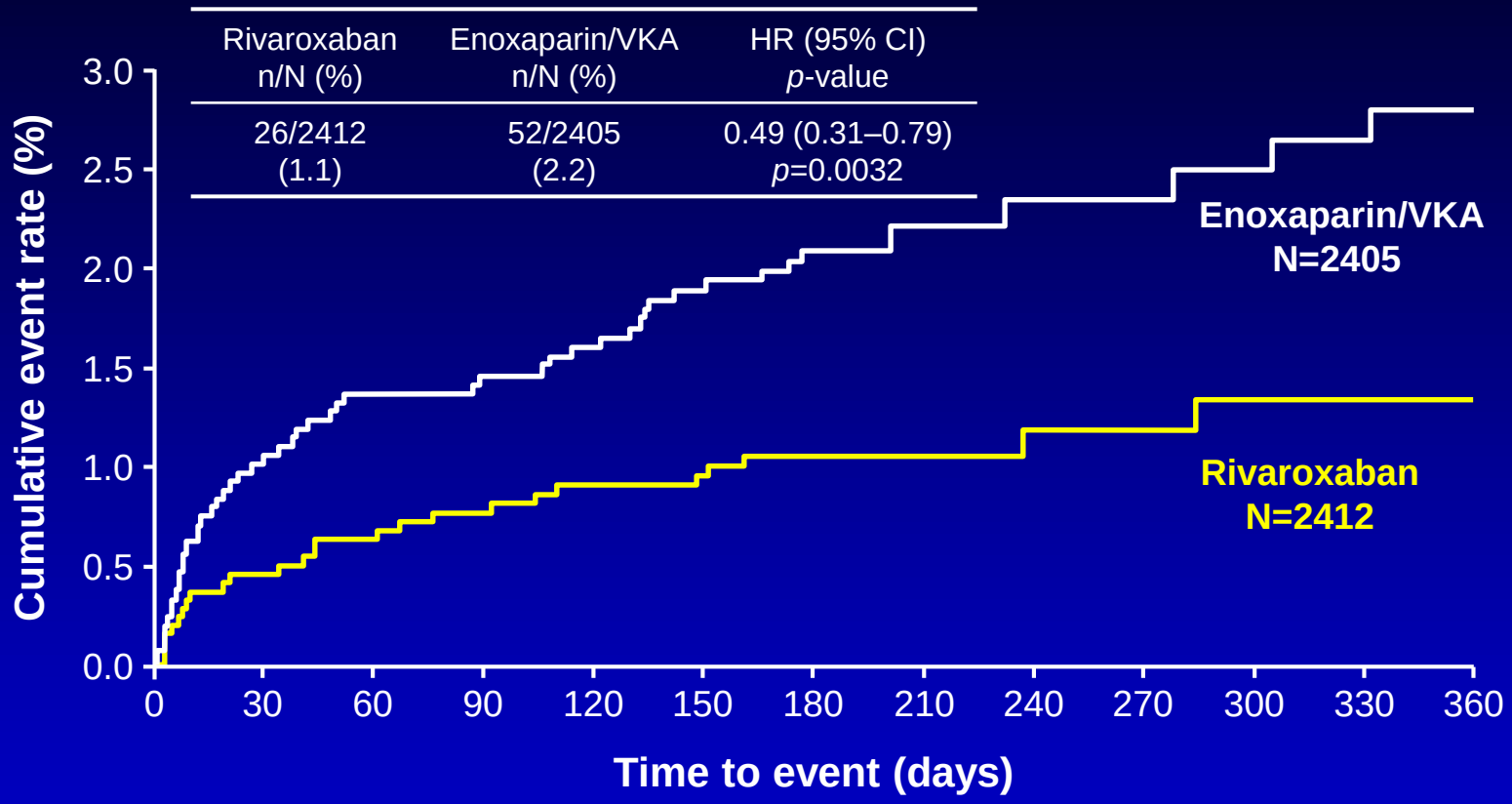
Rivaroxaban n/N (%)	Enoxaparin/VKA n/N (%)	HR (95% CI) *p*-value
249/2412 (10.3)	274/2405 (11.4)	0.90 (0.76–1.07) *p*=0.23

Number of patients at risk

Rivaroxaban	2412	2183	2133	2024	1953	1913	1211	696	671	632	600	588	313
Enoxaparin/VKA	2405	2184	2115	1990	1923	1887	1092	687	660	620	589	574	251

Safety population

EINSTEIN PE: major bleeding



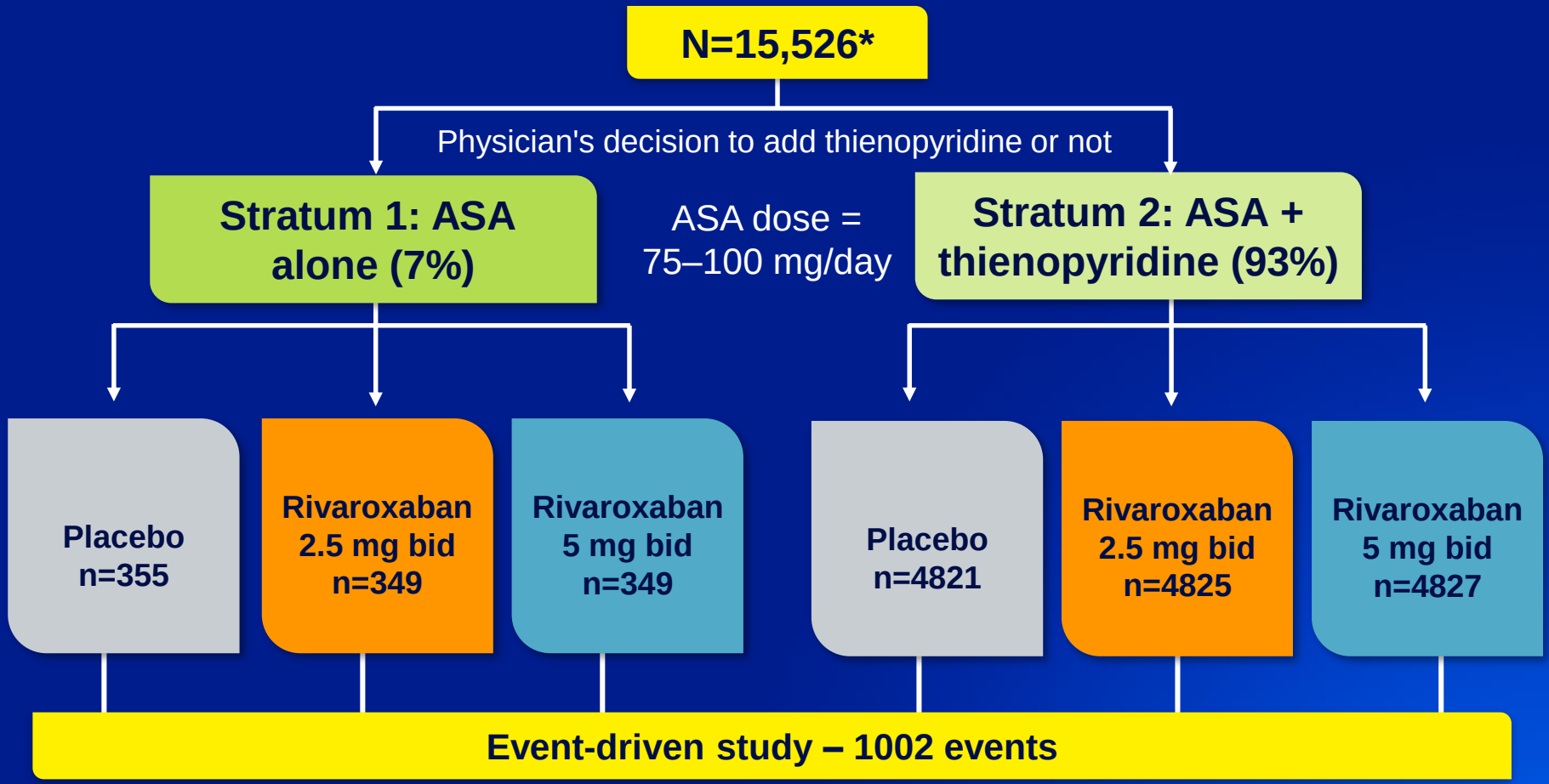
Number of patients at risk													
Rivaroxaban	2412	2281	2248	2156	2091	2063	1317	761	735	700	669	659	350
Enoxaparin/VKA	2405	2270	2224	2116	2063	2036	1176	746	719	680	658	642	278

Safety population

EINSTEIN PE: conclusions

- **In patients with acute symptomatic PE with or without DVT, rivaroxaban showed:**
  - **Non-inferiority to LMWH/VKA for efficacy**
  - **Similar findings for principal safety outcome**
  - **Superiority for major bleeding**
  - **Consistent efficacy and safety results irrespective of age, body weight, gender, kidney function and cancer**
  - **No evidence for liver toxicity**

ATLAS ACS 2 TIMI 51

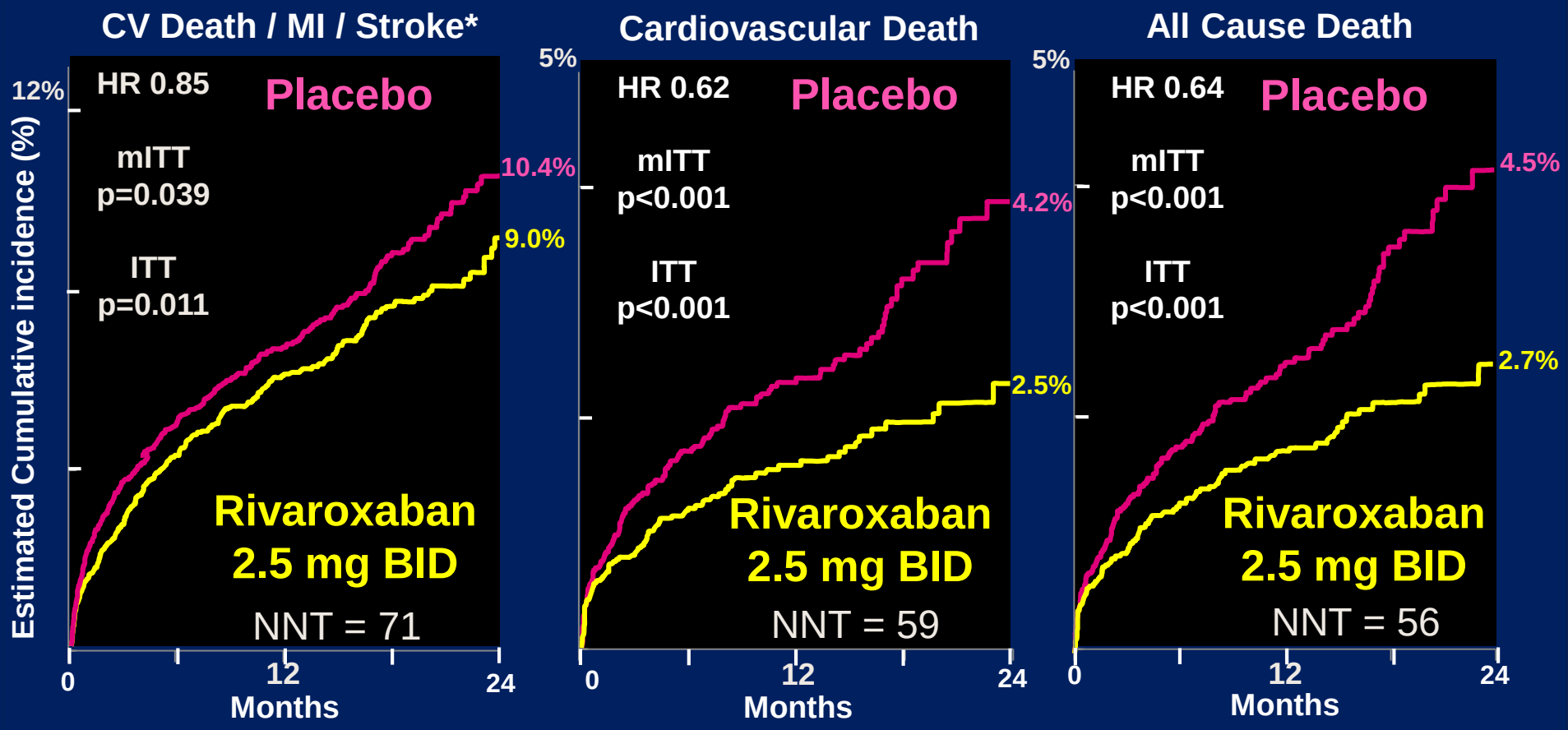


*184 patients were excluded from the efficacy analyses prior to unblinding because of trial misconduct at three sites

Mega *et al*, 2011

ATLAS ACS 2 TIMI 51

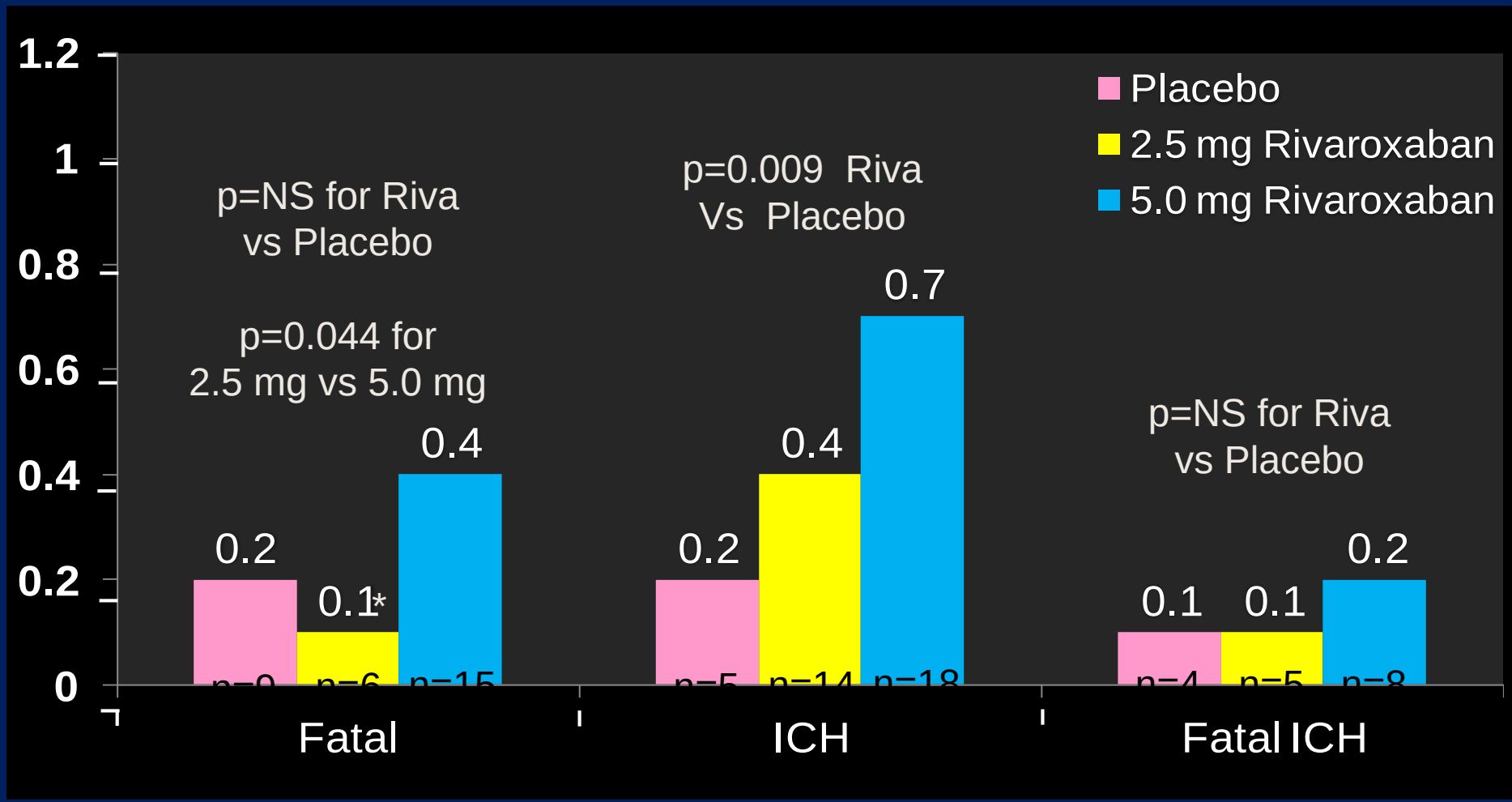
PRIMARY EFFICACY ENDPOINTS: 2.5 mg PO BID In Patients Treated with ASA + Thienopyridine



*: First occurrence of cardiovascular death, MI, stroke (ischemic, hemorrhagic, and uncertain) as adjudicated by the CEC
Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches; NNT=Number needed to treat.

ATLAS ACS 2 TIMI 51

TREATMENT-EMERGENT FATAL BLEEDS AND ICH



*Among patients treated with aspirin + thienopyridine, there was an increase in fatal bleeding among patients treated with 5.0 mg of Rivaroxaban (15/5110) vs 2.5 mg of Rivaroxaban (5/5115) (p=0.02)

ATLAS ACS 2 TIMI 51

SUMMARY-EFFICACY

- The primary efficacy endpoint of CV death, MI and stroke was reduced when added to standard therapy for both rivaroxaban doses combined, and for the 2.5 and 5.0 mg BID doses separately

- CV and all cause death were reduced for both rivaroxaban doses combined, and for the 2.5 mg BID dose .

SUMMARY- SAFETY

- There was a dose dependent increase in bleeding associated with rivaroxaban (2.5 mg < 5.0 mg).

- Although ICH was increased with rivaroxaban, there was no excess risk of fatal ICH or fatal bleeding associated with rivaroxaban compared to placebo.

- No evidence of drug induced liver injury or rebound (post-treatment) ischemic events

Risk-Based Antithrombotic Therapy (cont'd)

Recommendations	COR	LOE
For patients with nonvalvular AF with prior stroke, transient ischemic attack, or a CHA_2DS_2-VASc score of 2 or greater, oral anticoagulants are recommended. Options include:		
• warfarin (INR 2.0 TO 3.0), or	I	A
• dabigatran, or	I	B
• rivaroxaban, or	I	B
• apixaban.	I	B
Among patients treated with warfarin, the INR should be determined at least weekly during initiation of antithrombotic therapy and at least monthly when anticoagulation (INR in range) is stable.	I	A
For patients with nonvalvular AF unable to maintain a therapeutic INR level with warfarin, use of a direct thrombin or factor Xa inhibitor (dabigatran, rivaroxaban, or apixaban) is recommended.	I	C
Re-evaluation of the need for and choice of antithrombotic therapy at periodic intervals is recommended to reassess stroke and bleeding risks.	I	C

Risk-Based Antithrombotic Therapy (cont'd)

Recommendations	COR	LOE
Bridging therapy with UFH or LMWH is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions on bridging therapy should balance the risks of stroke and bleeding.	I	C
For patients with AF without mechanical heart valves who require interruption of warfarin or new anticoagulants for procedures, decisions about bridging therapy (LMWH or UFH) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated.	I	C
Renal function should be evaluated before initiation of direct thrombin or factor Xa inhibitors and should be re-evaluated when clinically indicated and at least annually.	I	B
For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF.	I	C

Risk-Based Antithrombotic Therapy (cont'd)

Recommendations	COR	LOE
In patients with AF undergoing percutaneous coronary intervention,† bare-metal stents may be considered to minimize the required duration of dual antiplatelet therapy. Anticoagulation may be interrupted at the time of the procedure to reduce the risk of bleeding at the site of peripheral arterial puncture.	IIb	C
Following coronary revascularization (percutaneous or surgical) in patients with AF and a CHA_2DS_2-VASc score of 2 or greater, it may be reasonable to use clopidogrel (75 mg once daily) concurrently with oral anticoagulants but without aspirin.	IIb	B
The direct thrombin inhibitor dabigatran and the factor Xa inhibitor rivaroxaban are not recommended in patients with AF and end-stage CKD or on dialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits.	III: No Benefit	C
The direct thrombin inhibitor dabigatran should not be used in patients with AF and a mechanical heart valve.	III: Harm	B

†See the 2011 percutaneous coronary intervention guideline for type of stent and duration of dual antiplatelet therapy recommendations.

Dose Selection of Oral Anticoagulant Options for Patients With Nonvalvular AF and CKD

(Based on Prescribing Information for the United States)*

Renal Function	Warfarin	Dabigatran†	Rivaroxaban†	Apixaban†
Normal/mild impairment	Dose adjusted for INR 2.0–3.0	150 mg BID (CrCl >30 mL/min)	20 mg QD with the evening meal (CrCl >50 mL/min)	5.0 or 2.5 mg BID‡
Moderate impairment	Dose adjusted for INR 2.0–3.0	150 mg BID (CrCl >30 mL/min)	15 mg QD with the evening meal (CrCl 30–50 mL/min)	5.0 or 2.5 mg BID‡
Severe impairment	Dose adjusted for INR 2.0–3.0 §	75 mg BID‖ (CrCl 15–30 mL/min)	15 mg QD with the evening meal (CrCl 15–30 mL/min)	No recommendation¶
End-stage CKD not on dialysis	Dose adjusted for INR 2.0–3.0 §	Not recommended¶ (CrCl <15 mL/min)	Not recommended¶ (CrCl <15 mL/min)	No recommendation¶
End-stage CKD on dialysis	Dose adjusted for INR 2.0–3.0 §	Not recommended¶ (CrCl <15 mL/min)	Not recommended¶ (CrCl <15 mL/min)	No recommendation¶#

Prevention of Thromboembolism (cont'd)

Recommendations	COR	LOE
Following cardioversion for AF of any duration, the decision about long-term anticoagulation therapy should be based on the thromboembolic risk profile.	I	C
For patients with AF or atrial flutter of 48 hours' duration or longer or of unknown duration who have not been anticoagulated for the preceding 3 weeks, it is reasonable to perform TEE before cardioversion and proceed with cardioversion if no LA thrombus is identified, including in the LAA, provided that anticoagulation is achieved before TEE and maintained after cardioversion for at least 4 weeks.	IIa	B
For patients with AF or atrial flutter of 48 hours' duration or longer or when duration of AF is unknown, anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for at least 3 weeks before and 4 weeks after cardioversion.	IIa	C

ESC 2014
Acute Phase Treatment after Pulmonary Embolism (intermediate/low risk)

As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) is recommended.

Recommendations for acute phase treatment

Recommendations	Class[a]	Level[b]	Ref[c]
PE without shock or hypotension (intermediate-or low-risk)[d]			
Anticoagulation: combination of parenteral treatment with VKA			
Initiation of parenteral anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is in progress.	I	C	352
LMWH or fondaparinux is the recommended form of acute phase parenteral anticoagulation for most patients.	I	A	273, 274, 281, 353
In parallel to parenteral anticoagulation, treatment with a VKA is recommended, targeting an INR of 2.5 (range 2.0–3.0).	I	B	352, 354
Anticoagulation: new oral anticoagulants			
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) is recommended.	I	B	296

ESC 2014 Anticoagulation after pulmonary embolism

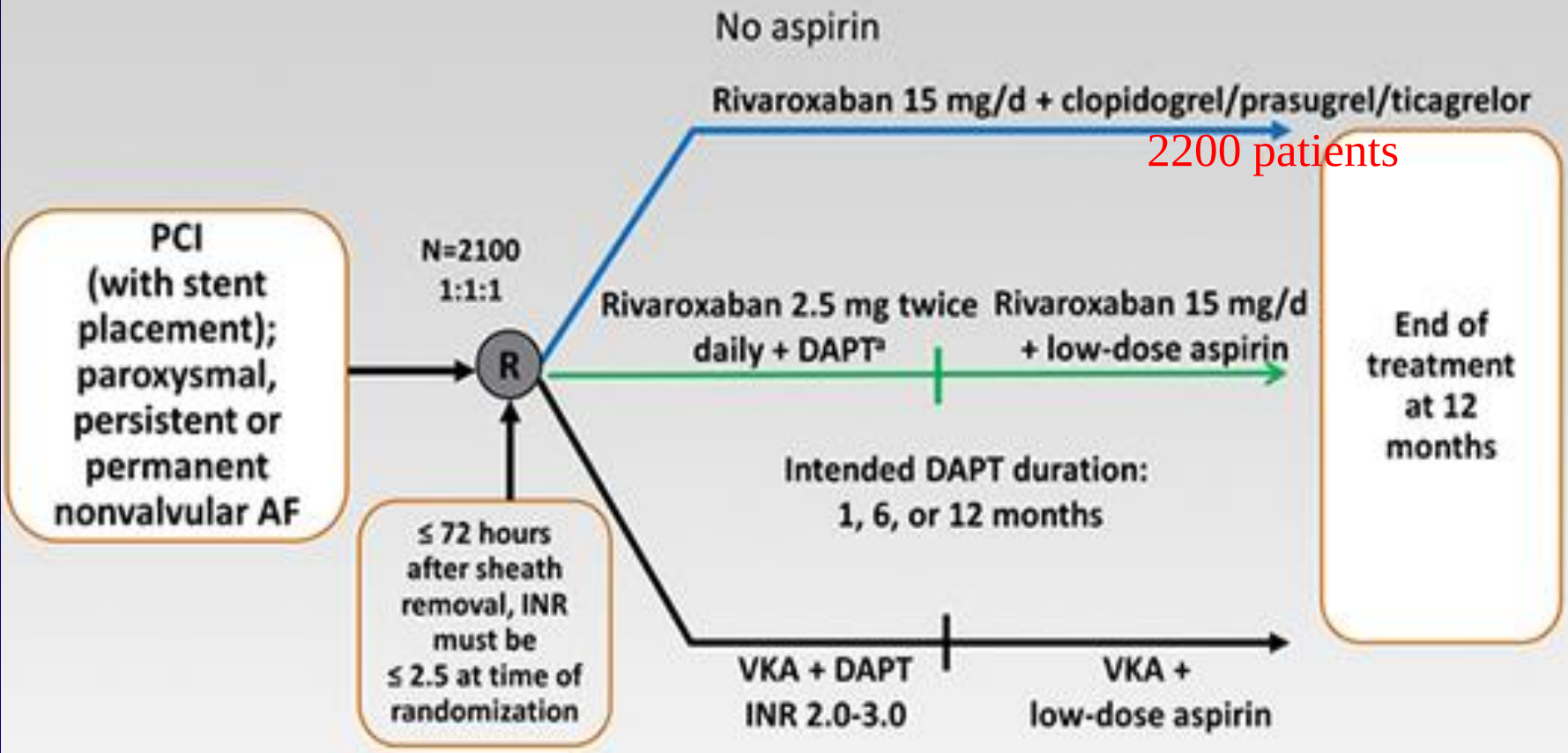
Rivaroxaban (20 mg once daily) should be considered as an alternative to VKA if extended anticoagulation treatment is necessary

Recommendations	Class[a]	Level[b]	Ref[c]
For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is recommended for 3 months.	I	B	358
For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months.	I	A	363, 372–374
Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk .	IIa	B	375
Anticoagulation treatment of indefinite duration is recommended for patients with a second episode of unprovoked PE	I	B	360
Rivaroxaban (20 mg once daily), dabigatran (150 mg twice daily, or 110 mg twice daily for patients ≥80 years of age or those under concomitant verapamil treatment) or apixaban (2.5 mg twice daily) should be considered as an alternative to VKA (except for patients with severe renal impairment) if extended anticoagulation treatment is necessary.[d]	IIa	B[e]	295, 370, 371

Recommendation in ACS

NICE appraisal committee states that rivaroxaban 2.5 mg twice daily with aspirin alone or aspirin plus clopidogrel or ticlopidine is an option for biomarker-confirmed ACS patients without a prior history of stroke or transient ischemic attack. Before starting treatment, clinicians should carefully assess the patient's risk of bleeding

PIONEER AF-PCI



Primary outcome measures: clinically significant bleeding (composite of TIMI major, minor bleeding, and bleeding) requiring medical attention.
Secondary outcome measures: composite of CV death, MI, and stroke

a. DAPT = low-dose aspirin + clopidogrel, prasugrel, or ticagrelor

Thank You