INNOVAZIONI IN TEMA DI TERAPIA DEL TROMBOEMBOLISMO VENOSO

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TERAPIA DEL TROMBOEMBOLISMO VENOSO

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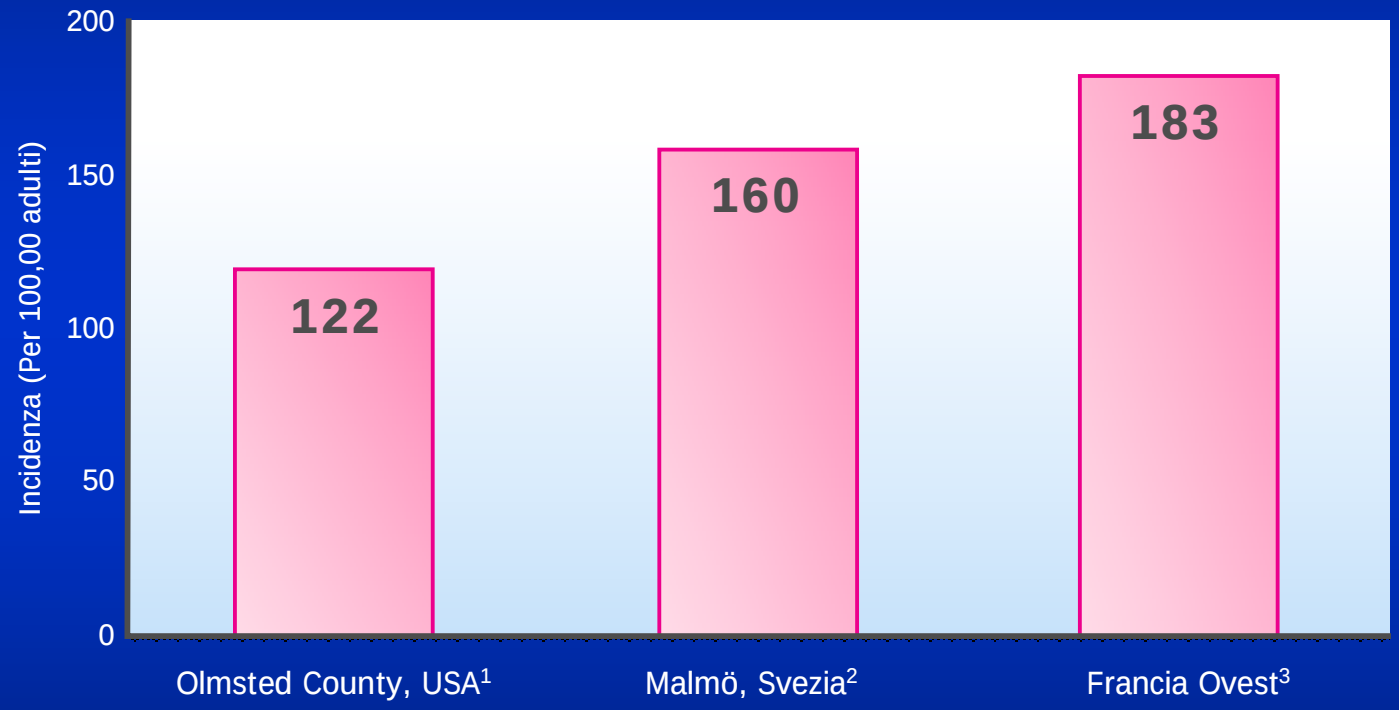
FERRARA

La Malattia Tromboembolica Venosa

- Malattia vascolare frequente
- Debilitante e costosa
- Ampia popolazione a rischio
- Elevata incidenza

Epidemiologia
Incidenza della TVP



1. Heit JA et al. *Arch Intern Med.* 2000;160:761-768.
2. Nordstrom M et al. *J Intern Med.* 1992;232:155-160.
3. Oger E; for EPI-GETBO Study Group. *Thromb Haemost.* 2000;83:657-660.

Percorsi terapeutici del TEV

- TVP arti inferiori/superiori
- Embolia polmonare
- Tromboflebite superficiale
- TV in sedi atipiche (mesenterica, cerebrale, retinica, etc)

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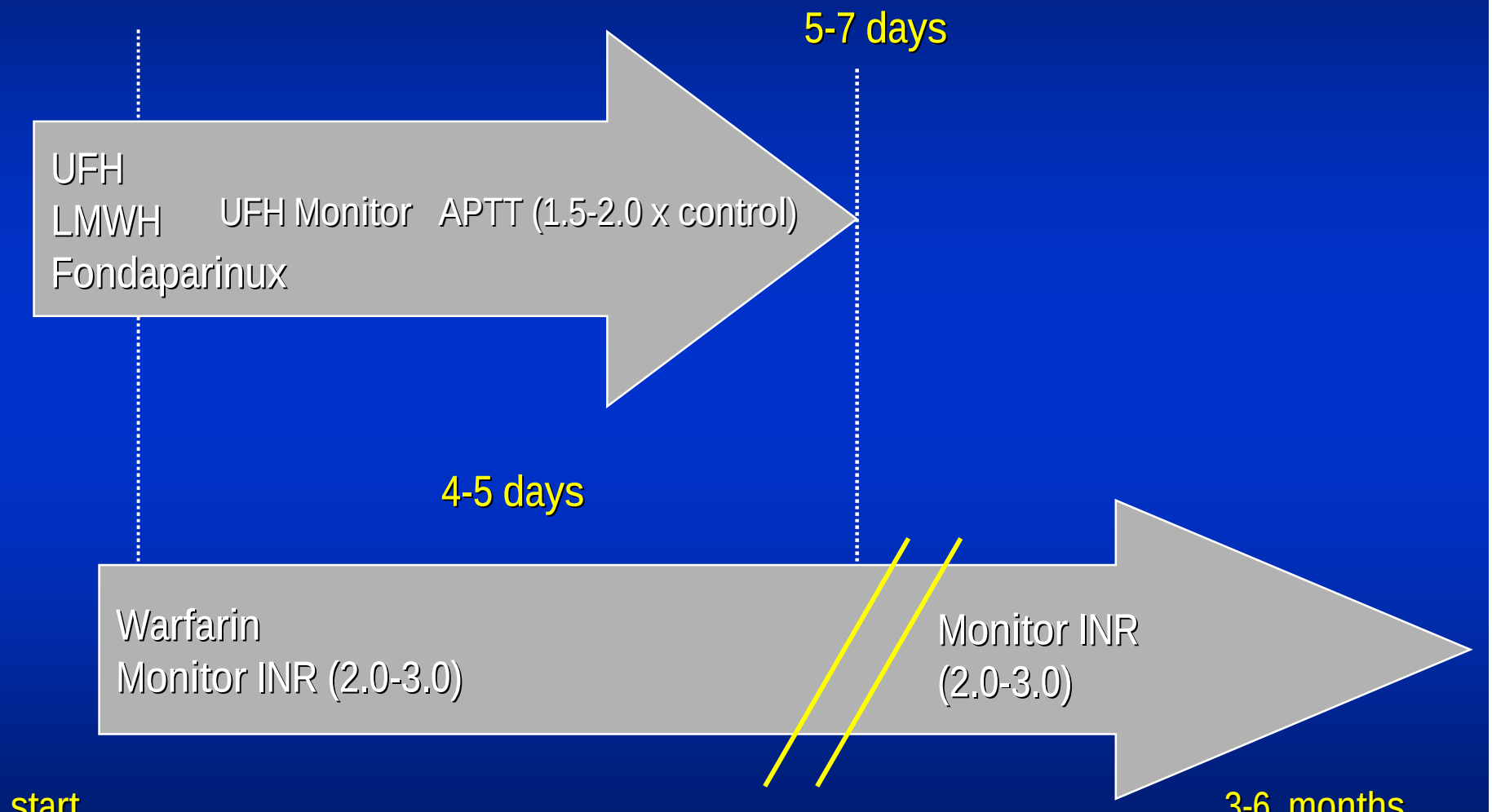
OBBIETTIVI DELLA TERAPIA DEL TEV

- Prevenire la morte da embolia polmonare
- Prevenire le recidive
- Migliorare la sintomatologia clinica (es. dispnea, dolore, edema, etc)
- Prevenire l'ipertensione polmonare tromboembolica cronica e la sindrome post-trombotica

TERAPIA DEL TEV

- Eparina non frazionata
- Eparina a basso peso molecolare
- Fondaparinux
- Antagonisti vitamina K
- Trombolitici
- Filtri cavali
- Trombectomia, embolectomia meccanica
- Terapia chirurgica
- Nuovi farmaci anticoagulanti

Initial and long term treatment of VTE



Kearon, Chest, 2008

Limiti degli attuali farmaci antitrombotici

ANTICOAGULANTI ORALI

Intervallo terapeutico ristretto

Somministrazione solo orale

Significativa interazione con gli alimenti e i farmaci

Necessità di frequenti controlli laboratoristici

Lento on e off-set d'azione

Limitata efficacia e elevato rischio emorragico in alcune categorie di pazienti (es. p.ti neoplastici)

ENF/EBPM

Somministrazione solo parenterale

Rischio di HIT e osteopenia

Necessità di monitoraggio laboratoristico in alcuni casi

Perché nuovi farmaci antitrombotici; caratteristiche dell'anticoagulante "ideale"

- Efficacia e sicurezza
- Scarsità di effetti collaterali
- Azione facilmente e rapidamente reversibile
- Effetto prevedibile, monitoraggio non necessario
- Semplicità della via, della modalità e del numero delle sommistrazioni
- Buona compliance del paziente (con conseguente ottimizzazione della efficacia e sicurezza)

Desirable Qualities of a New Anticoagulant

- At least as effective as current agents
- At least as safe as current agents
- Oral application
- Fixed dosing
- Predictable pharmakodynamic effect
- No need for routine anticoagulation monitoring
- No drug-food and limited drug-drug interactions
- Rapid onset and offset of action

Initial Treatment of VTE

Recommendations from 8th Edition of the ACCP Evidence-Based Guidelines (2008)	
UFH	§ IV UFH, SC UFH, or fixed-dose SC UFH (All Grade 1A) § Treat for ≥5 days and until INR is stable and ≥2.0 for 24 hours (Grade 1C)
LMWH	§ Treat for ≥5 days and until INR is stable and ≥2.0 for 24 hours (Grade 1C)
Fondaparinux	§ Treat for ≥5 days and until INR is stable and ≥2.0 for 24 hours (Grade 1C)
Warfarin	§ Initiate together with LMWH, UFH, or fondaparinux on first treatment day (Grade 1A)

Kearon, Chest, 2008

Antithrombotic Therapy for Venous Thromboembolic Disease

- For patients with objectively confirmed DVT or non-massive PE, we recommend acute treatment with subcutaneous LMWH, fondaparinux or **alternatively** intravenous UFH **(both Grade 1A)**.

- For patients with acute VTE and severe renal failure, we suggest IV UFH over LMWH **(Grade 2C)**

- For patients with a high clinical suspicion of PE, we recommend treatment with anticoagulants while awaiting the outcome of diagnostic tests (**Grade 1C**)

Kearon, Chest, 2008

Antithrombotic Therapy for Venous Thromboembolic Disease

- For most patients with PE, we recommend clinicians **not** use systemic thrombolytic therapy (**Grade1A**)
- In **selected patients**, we suggest systemic administration of thrombolytic therapy (**Grade 2B**)
- For patients who are **hemodynamically unstable**, we suggest use of thrombolytic therapy (**Grade 2B**)

Kearon, Chest, 2008

Antithrombotic Therapy for Venous Thromboembolic Disease

- We suggest clinicians **not** use local administration of thrombolytic therapy via a catheter (Grade 1C)

- For patients with PE who receive thrombolytic regimens, we suggest use of thrombolytic regimens with a short infusion time over those with prolonged infusion times (Grade 2C)

Kearon, Chest, 2008

Treatment of PE in Hemodynamically Unstable Patients

Systemic and local thrombolytic therapy

- Thrombolytic therapy is *not recommended* in the majority of patients with PE (Grade 1B)
- All PE patients should undergo rapid risk stratification (Grade 1C)
- For patients with evidence of hemodynamic compromise, thrombolytic therapy is recommended unless there are major contraindications owing to bleeding risk (Grade 1B)
- Selected high-risk patients without hypotension, and at low risk for bleeding, are candidates for thrombolytic therapy (Grade 2B)
- Short infusion preferred over long infusion (Grade 1B)
- Administer treatment via peripheral vein rather than placing a pulmonary artery catheter (Grade 1B)

Kearon, Chest, 2008

Clinical management of acute PE

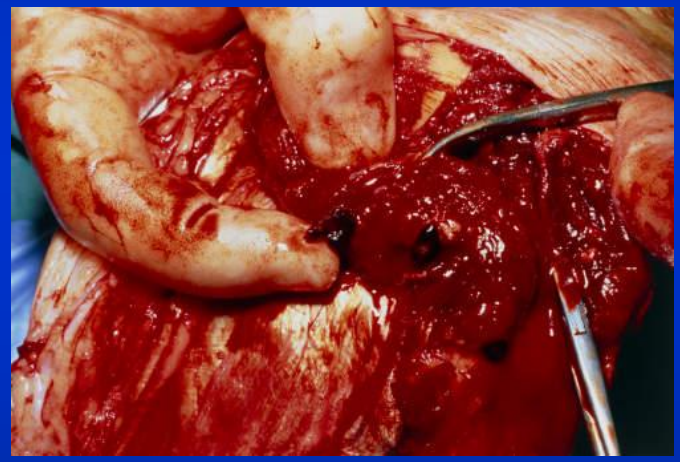
RISK \ MARKERS		CLINICAL	RV dysfunction	Myocardial Injury	Treatment implications
HIGH (Clinically Massive PE)		**+**			**Thrombolysis or embolectomy**
NON HIGH	**INTERMEDIATE**	**-**	**+**	**+**	**Hospital treatment**
			+	**-**	
			-	**+**	
	LOW	**-**	**-**	**-**	**consider early discharge or ambulatory treatment**

ESC Guidelines, Eur Heart J, 2008

Treatment of PE in Hemodynamically Unstable Patients

Pulmonary embolectomy

May be used in selected, highly compromised patients who are unable to receive thrombolytic therapy (Grade 2C)



Kearon, Chest, 2008

Treatment of VTE: Vena cava filters

- For patients with acute proximal DVT if anticoagulant therapy is not possible because of risk of bleeding, we recommend placement of an IVC filter (Grade 1C).
- For patients with acute DVT who have an IVC filter inserted as an alternative to anticoagulation, we recommend that they should subsequently receive a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 1C).

Kearon, Chest, 2008

Long-term Treatment of DVT/PE

Recommendations from 8th Edition of the ACCP Evidence-Based Guidelines (2008)	
First-episode secondary to transient risk factor	Warfarin for 3 months (Grade 1A)
Unprovoked DVT	Treatment with warfarin for at least 3 months (Grade 1A); consider long-term anticoagulant therapy (Grade 1C) In patients with first unprovoked DVT that is a proximal DVT, without bleeding risk factors, long-term treatment is recommended (Grade 1A) In patients with first unprovoked DVT that is distal, 3 months of anticoagulant therapy is sufficient (Grade 1C)
Second unprovoked DVT	Long-term treatment is recommended (Grade 1A)
Cancer	LMWH for first 3 to 6 months of long-term anticoagulant therapy (Grade 1A); consider indefinite therapy or until cancer is resolved (Grade 1C)

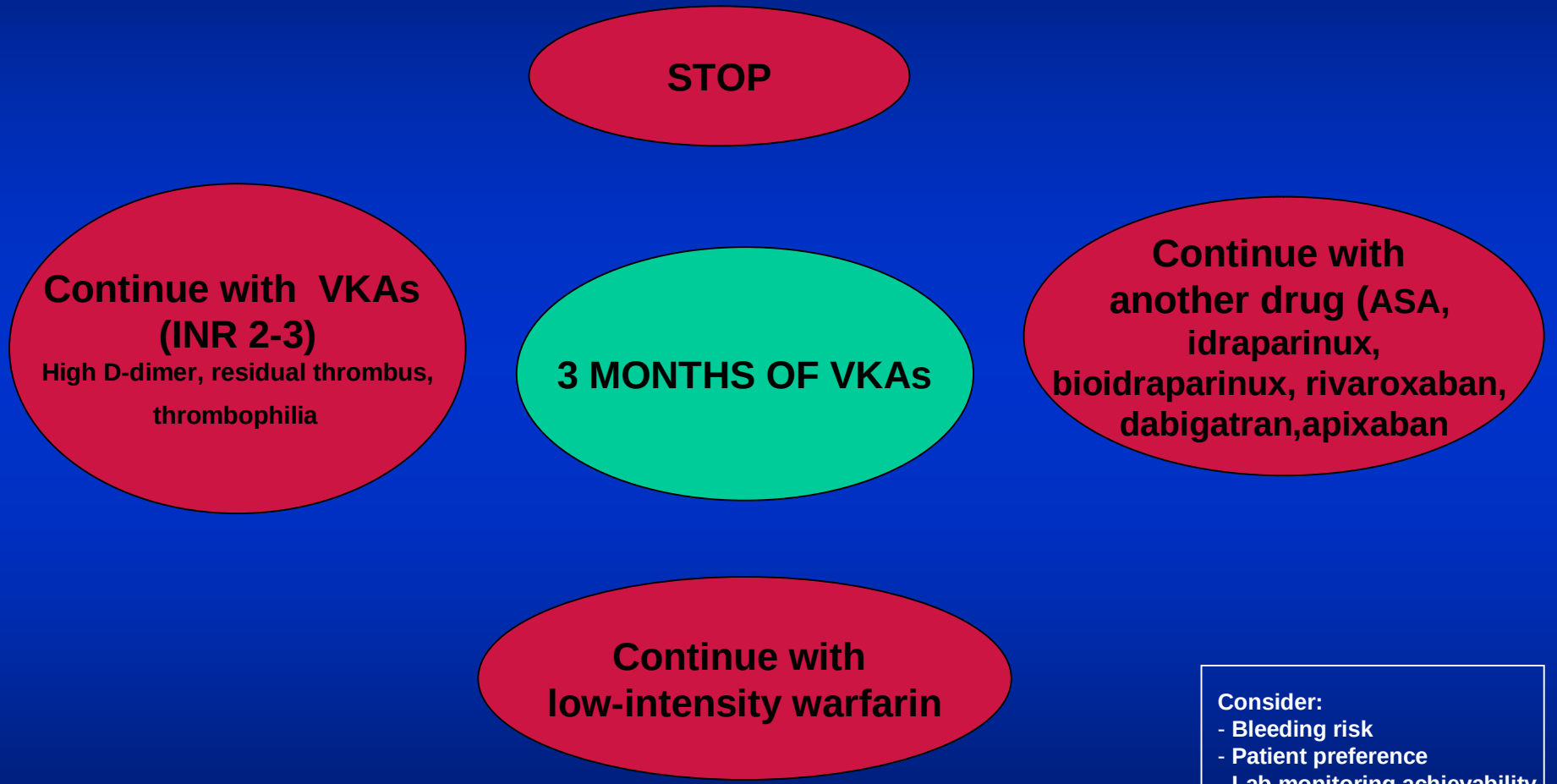
Kearon, Chest, 2008

Long-term Treatment of VTE: Warfarin Dosage

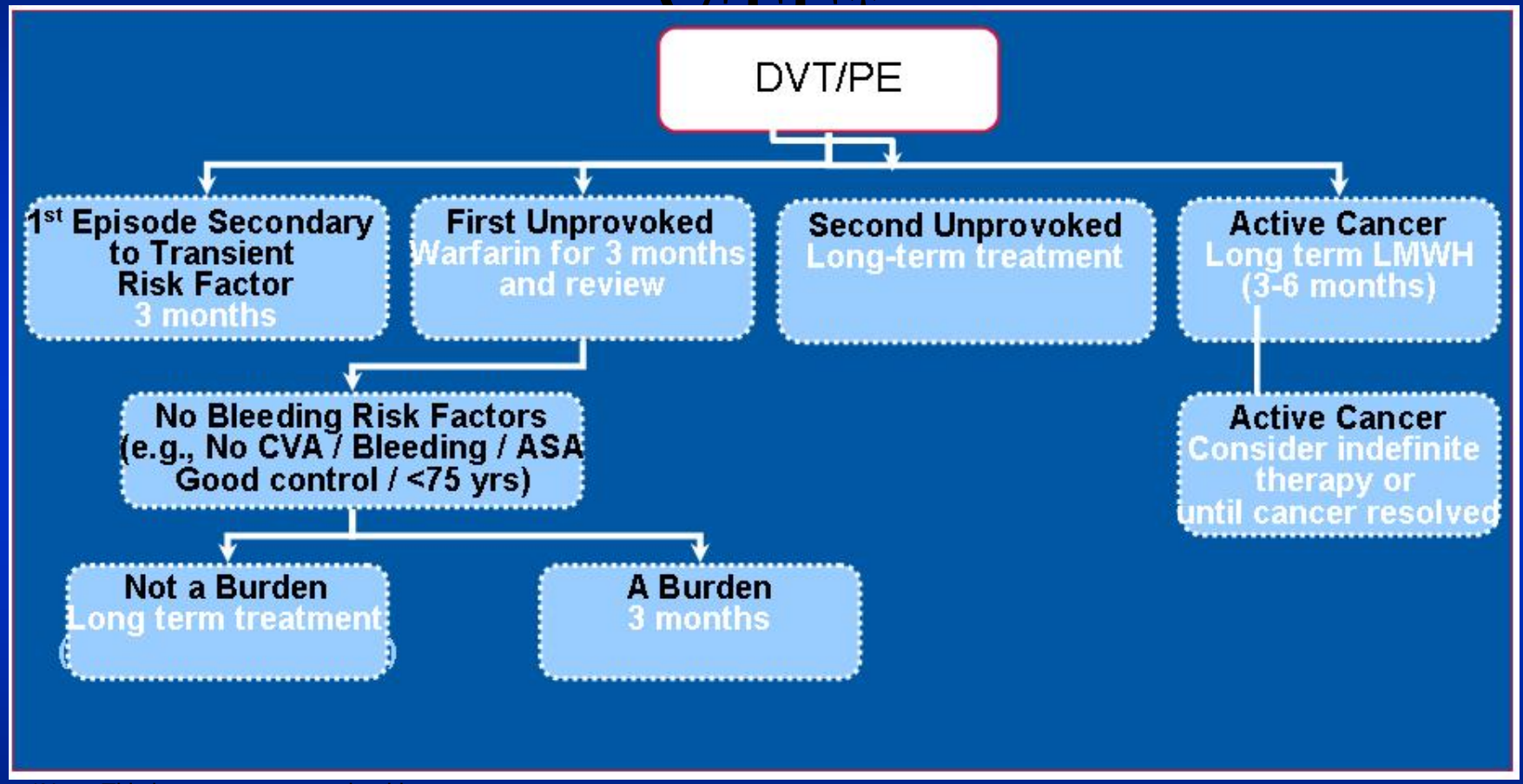
Recommendations from 8th Edition of the ACCP Evidence-Based Guidelines (2008)
Adjusted dose to maintain target INR of 2.5 (range 2.0 to 3.0) for all treatment durations
For patients with unprovoked DVT who have a strong preference for less-frequent INR testing, after first 3 months of conventional-intensity anticoagulation, low-intensity therapy (INR range 1.5 to 1.9) with less frequent INR monitoring is recommended over stopping treatment
Recommend against high-intensity therapy (INR 3.1 to 4.0)

Kearon, Chest, 2008

First unprovoked VTE: what to do after 3 months of VKAs treatment



Duration of Anticoagulation for VTE*



*Note: This is not a treatment algorithm.

ASA=aspirin; CVA=central venous access; DVT=deep vein thrombosis; LMWH=low molecular weight heparin; PE=pulmonary embolism; VTE=venous thromboembollism

Kearon C et al. *Chest*. 2008;133:454S-545S.

TERAPIA DEL TEV: ASPETTI PARTICOLARI

- Popolazioni “speciali” (cancro, gravidanza)
- Filtri cavali
- Trattamento della trombosi venosa superficiale
- Nuovi farmaci anticoagulanti

TERAPIA DEL TEV: ASPETTI PARTICOLARI

- Pazienti neoplastici
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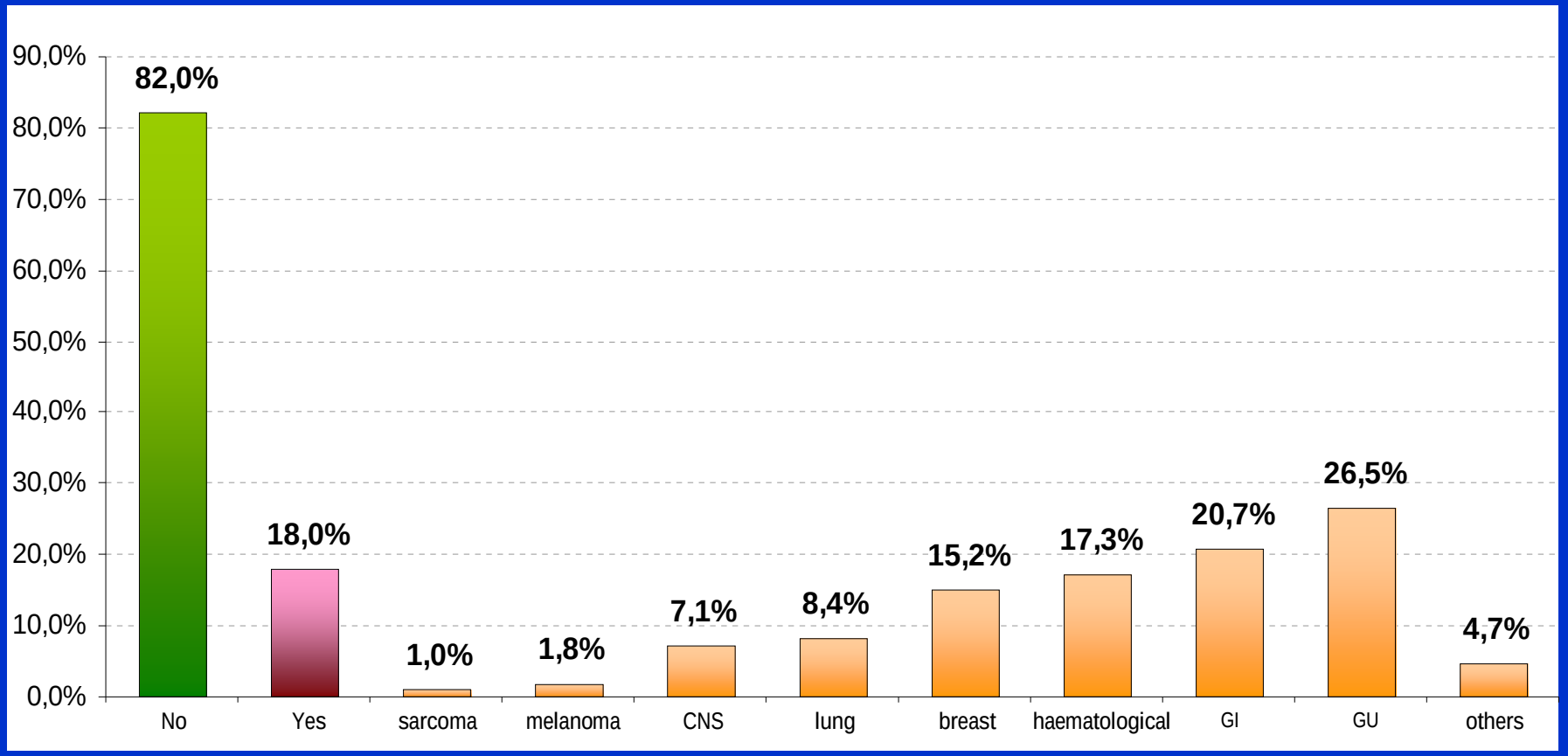
Management of cancer associated VTE
Findings from the MASTER Registry

Known cancer: 381/2119 patients



Imberti, Haematologica, 2008

Management of cancer associated VTE Findings from the MASTER Registry

- Cancer-associated VTE: 424/2119 (20%)
- Treatment of the acute phase of VTE

	cancer (%)	non-cancer (%)	p-value
Major bleeding:	3.3	1.1	0.001
IVC filter:	7.3	4.1	0.005

Imberti, Haematologica, 2008

Oral anticoagulant therapy in cancer patients

Warfarin therapy is complicated in cancer patients

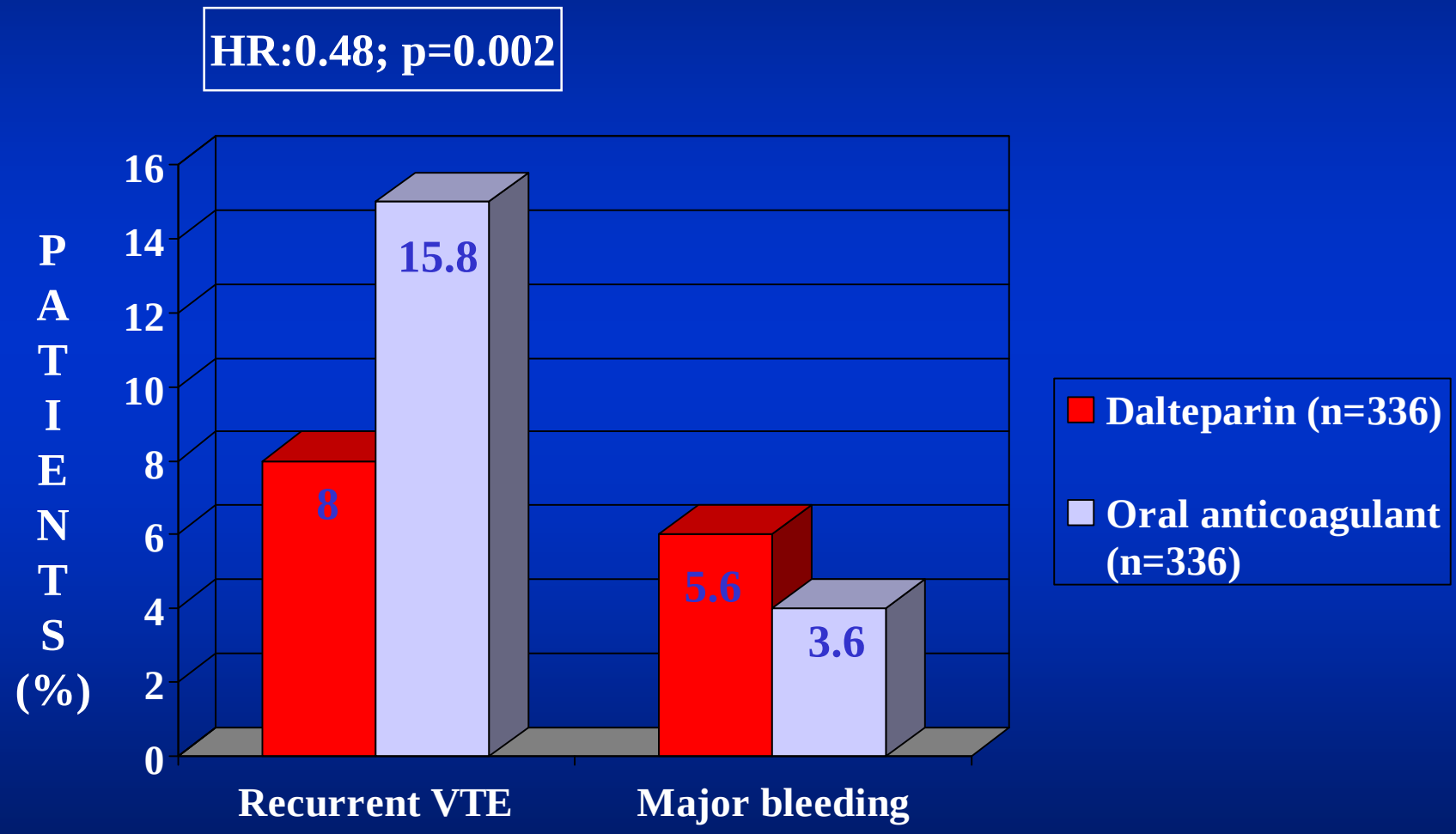
- difficult to maintain tight therapeutic INR level (anorexia, vomiting, drug interactions)
- venous access problematic
- frequent interruptions for thrombocytopenia and invasive procedures
- increased risk of recurrence and bleeding

LMWH for secondary prophylaxis of VTE in cancer patients

STUDY	THERAPY	PATIENTS (n)	LMWH DAILY DOSE	DURATION (months)
Meyer 2002	Enoxaparin OA	71 75	1.5 mg/kg	3
Lee 2003	Dalteparin OA	336 336	200 (150) UI/kg	6
Hull, 2006	Tinzaparin OA	100 100	175 UI/kg	3
Deitcher, 2006	Enoxaparin OA	31 /36 34	a) 1.5 mg/kg b) 1 mg/kg	6

Randomized, open-label, multicenter trials

Low-Molecular-Weight Heparin versus a Coumarin for the prevention of recurrent VTE in cancer (CLOT Study)



Lee, N Engl J Med, 2003

RCTs of Long-term LMWH or OAC Therapy in Cancer Patients With VTE

	Risk ratio	Lower limit	Upper limit	Z value	p value
Meyer[18]	0·704	0·121	4·091	−0·391	0·696
Lee[19]	0·509	0·329	0·789	−3·018	0·003
Hull[20]	0·438	0·188	1·017	−1·920	0·055
Deitcher[21]	0·690	0·124	3·832	−0·425	0·671
Overall	0·509	0·351	0·737	−3·571	<0·0001*

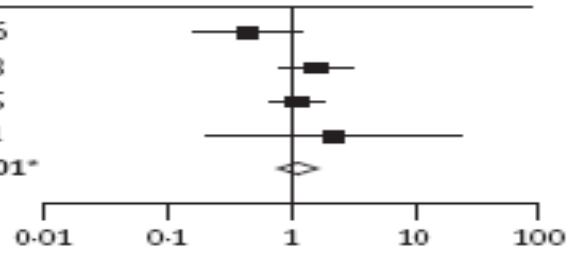


Figure 2: Risk of developing recurrent venous thromboembolism with low-molecular-weight heparin compared with warfarin
Risk ratios pooled by use of fixed-effects model.

	Risk ratio	Lower limit	Upper limit	Z value	p value
Meyer[18]	0·440	0·163	1·186	−1·622	0·105
Lee[19]	1·582	0·781	3·210	1·275	0·202
Hull[20]	1·125	0·700	1·809	0·486	0·627
Deitcher[21]	2·194	0·209	23·014	0·655	0·512
Overall	1·103	0·768	1·584	0·532	0·595

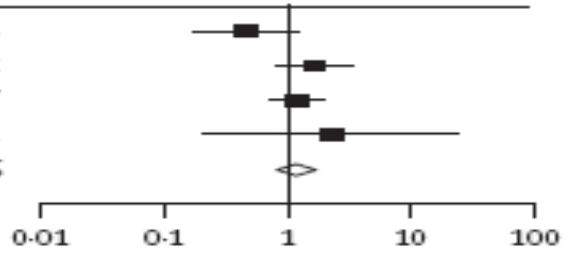


Figure 3: Risk of bleeding with low-molecular-weight heparin compared with warfarin
Risk ratios pooled by use of fixed-effects model.

Noble, Lancet Oncology, 2008

Long-term VTE treatment in cancer patients

For most patients with DVT and cancer, we recommend LMWH for the first 3 to 6 months of long-term anticoagulant therapy (Grade 1A).

Kearon, Chest, 2008

Treatment of specific situation

- Thrombolysis for patients with high risk PE
- CVC- related thrombosis
- Clinically unsuspected VTE events
- Brain metastases or primary cancer of Central Nervous System

Treatment of specific situation

	ASCO	NCCN National Comprehensive Cancer Network®	AIOM ESMO		CHEST
Thombolytic therapy for initial treatment of PE in cancer patients	Restricted to patients with life threatening thrombotic events	Restricted to appropriate candidates with massive DVT or massive-submassive PE with moderate to severe right ventricular dysfunction	Not specified	Restricted to PE with hemodynamic collapse	For patients with evidence of Hemodynamic compromise, unless there are Contraindications owing to bleeding risk (Grade 1B)
CVC-related thrombosis of the upper limb	Not specified	LMWH or VKA for as long as CVC is in place and for at least 3 months after CVC removal	Not specified	LMWH for to 6 months; consider VKA after 6 months as long as cancer is active or CVC in place, anticoagulate for up to 6 weeks after CVC removal	Not specified
Clinically unsuspected PE or DVT	Not specified	Not Specified	Not specified	Not specified	Not specified
Brain Metastases or CVS primary cancer	Not specified	Not specified	Not specified	Not specified	Not specified

Treatment of VTE in cancer patients: unsolved clinical problems SISET Guidelines

- Home- treatment of VTE
- Selected population with very high-haemorragic risk (i.e. patients with severe thrombocytopenia)
- Optimal duration of long-term anticoagulation
- Optimal treatment of recurrences while anticoagulant therapy
- Possible role of new anticoagulants

Imberti, Th Res, 2009

LMWH for acute and long-treatment of VTE in haematological malignancies and severe thrombocytopenia

STUDY	THERAPY	NUMBER OF PATIENT	DISEASE	PLATELET ($\times 10^9$ /L)
Imberti, 2004	Enoxaparin	4	AL	55.75 (mean)
Herishanu, 2004	Enoxaparin	5	AL, MM, NHL	4-22
Drakos, 1992	Enoxaparin	5	BMT	15-126

Imberti, Tumori, 2004
Herishanu, Leuk Lymph, 2004
Drakos, Cancer, 1992

Dose escalation of low molecular weight heparin to manage recurrent venous thromboembolic events despite systemic anticoagulation in cancer patients

- Retrospective cohort study
- 70 cancer outpatients with a recurrent VTE while receiving an anticoagulant (67% LMWH, 33% VKAs)
- Treatment:

- If VKAs: therapeutic dose of LMWHs for 1 months, then maintenance dose
- If LMWHs (therapeutic dose): 20-25% increased dose for ar least 4 weeks
- If LMWHs (maintenance dose): therapeutic dose for 6-12 weeks
- If LMWHs (low dose): therapeutic dose of LMWHs for 1 months, then maintenance dose

- 6 recurrences (8.6%), 3 major bleeding (4.3%) during the 3-months follow-up period

Carrier, J Thromb Haemost, 2008

VTE treatment in cancer patients: phase III RCTs with new anticoagulants

STUDY	TREATMENT	PATIENTS	CANCER	%
MATISSE DVT	Fondaparinux	2205	237	11%
MATISSE PE	Fondaparinux	2213	240	11%
VAN GOGH DVT	Idraparinux	2904	421	14.5%
RECOVER	Dabigatran	2564	121	4.7%
EINSTEIN	Rivaroxaban	3449	207	6%
EINSTEIN E	Rivaroxaban	1196	54	4.5%
EQUINOX	Idrabiotaparinux	755	39	5.1%

Conclusion

- Treatment of VTE in cancer is more problematic and difficult than in general population

- LMWHs are the treatment of choice for the initial and long-term treatment of VTE:

- Monitoring not required
- Parenteral administration
- Once daily S.C. injection
- Rapid onset/offset of action
- Home treatment
- Possible antitumoral activity (survival improvement)

Conclusion

- Unsolved clinical issues in long-term treatment with LMWH :

- Optimal doses need better definition
- Optimal duration is uncertain
- Management of VTE recurrences during full-dose of anticoagulation is still matter of debate

TERAPIA DEL TEV: ASPETTI PARTICOLARI

- Pazienti neoplastici
- Gravidanza
- Nuovi farmaci anticoagulanti

VTE treatment in pregnancy

Population	Recommendation
Women with acute VTE	Adjusted-dose SC LMWH or adjusted-dose IV UFH for ≥5 days (Grade 1A) Continue subcutaneous LMWH or UFH throughout pregnancy (Grade 1B) and for at least 6 weeks postpartum (Grade 2C) (for a minimum duration of therapy of 6 months)

Bates, Chest, 2008

Terapia a lungo termine del TEV: modalità di somministrazione e dosaggio

- La emivita delle EBPM è ridotta in gravidanza; la somministrazione bid sarebbe quindi preferibile
- La necessità di adeguare la posologia durante il corso della gravidanza è controversa:

a) dosaggio fisso
b) In base all' incremento ponderale ?
c) In base ai valori dell'anti-Xa ?

Terapia a lungo termine del TEV: dosaggio

"In the absence of large studies using clinical end-points demonstrating that there is a an optimal "therapeutic anti-Xa LMWH range" or that dose-adjustments increase the safety or efficacy of therapy, any of these approaches is reasonable and definitive advice cannot be provided"

Bates, Chest, 2008

Terapia a lungo termine del TEV: monitoraggio

- Il monitoraggio sistematico dell'attività anti-Xa non è raccomandato:

a) Corrispondenza tra livelli "terapeutici" di anti-Xa ed efficacia/sicurezza clinica non dimostrata

b) Differenza tra i vari reagenti disponibili in commercio

c) Esame disponibile non in tutti gli ospedali

d) Possibili eccezioni: pazienti obese, con insufficienza renale, notevoli incrementi ponderali in gravidanza

TERAPIA DEL TEV: ASPETTI PARTICOLARI

- Popolazioni “speciali” (cancro, gravidanza)
- Filtri cavali
- Trattamento della trombosi venosa superficiale
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Background
filtri cavali definitivi

• Nell'unico studio randomizzato pubblicato, il filtro cavale definitivo in aggiunta alla profilassi secondaria farmacologica ha consentito una riduzione iniziale delle EP, ma si e'associato ad un aumento delle recidive delle TVP nel follow-up, senza alcuna differenza in termini di mortalita'

Decousus, N Engl J Med, 1998

• Durata TAO ?

• Pazienti giovani ?

Filtri cavali temporanei

- Assenza di trials clinici randomizzati controllati
- Casistiche limitate, eterogenee
- Gestione problematica e costosa
- Permanenza limitata nel tempo, non superiore a una settimana
- Elevato rischio di trombosi (necessita' terapia anticoagulante), infezione, migrazione e embolizzazione alla rimozione
- Indicazione più frequente è nei pazienti con TVP in atto con temporanea controindicazione assoluta alla anticoagulazione (es. politrauma)

Retrievable vena cava filters: a review

Study	Filter	No. of filters removed and placed	Mean duration between filter placement and retrieval (days)	Retrieval technical success (%)
Ponchon, 1999 [16]	Gunther Tulip	8 of 10	12; range 8–14	88
Millward *et al.*, 2001 [15]	Gunther Tulip	52 of 91	9; range 2–25	98
Offner *et al.*, 2003 [17]	Gunther Tulip	37 of 44	14; range 3–30	97
Asch, 2002 [25]	Recovery	24 of 32	53; range 5–134	100
Pieri *et al.*, 2003 [20]	ALN	7 of 18	63; range 49–192	100
Barral *et al.*, 2003 [21]	ALN	13 of 54	22; range 11–90	100
Pancione and Mecozzi 2004 [22]	ALN	28 of 96	72; range 30–120	100
Morris *et al.*, 2004 [18]	Various*	14 of 130	19; range 11–41	93
Imberti *et al.*, 2005 [23••]	ALN	14 of 30	123; range 30–345	78
Grande *et al.*, 2005 [26•]	Recovery	14 of 107	150; range 0–419	93
Oliva *et al.*, 2005 [27]	OptEase	21 of 27	11; range 5–14	100
Rosenthal *et al.*, 2005 [28]	OptEase	40 of 40	16; range 3–48	100

*The most frequently used filter was Gunther Tulip ($n = 58$).

Imberti, Curr Opin Hematol, 2009

Conclusioni

• L’impiego dei **filtri cavali definitivi** deve essere riservato a situazioni cliniche particolari (controindicazioni di tipo emorragico alla terapia antitrombotica oppure recidiva di tev nonostante adeguata anticoagulazione); rimangono ancora importanti problematiche irrisolte (impiego nei pazienti giovani, durata ottimale della tao, effetto su “hard end points” quali la mortalita’ e la sindrome post-trombotica)

• l’uso dei **filtri cavali temporanei** appare sempre meno frequente a causa delle difficoltà gestionali e della elevata frequenza di complicanze

•Particolarmente interessante sembra l’impiego dei **filtri cavali opzionali**, che uniscono al vantaggio di poter essere rimossi dopo un lungo periodo dall’impianto quello di poter essere lasciati indefinitamente in sede

TERAPIA DEL TEV: ASPETTI PARTICOLARI

- Popolazioni “speciali” (cancro, gravidanza)
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Trombosi venosa superficiale

- La trombosi venosa superficiale (TVS) non sempre è una patologia benigna ed autolimitante

- I trombi nella TVS possono estendersi al sistema venoso profondo

- Il rischio stimato che si sviluppino complicanze di TVP da una TVS,secondo dati recenti, va dal 10% al 20%

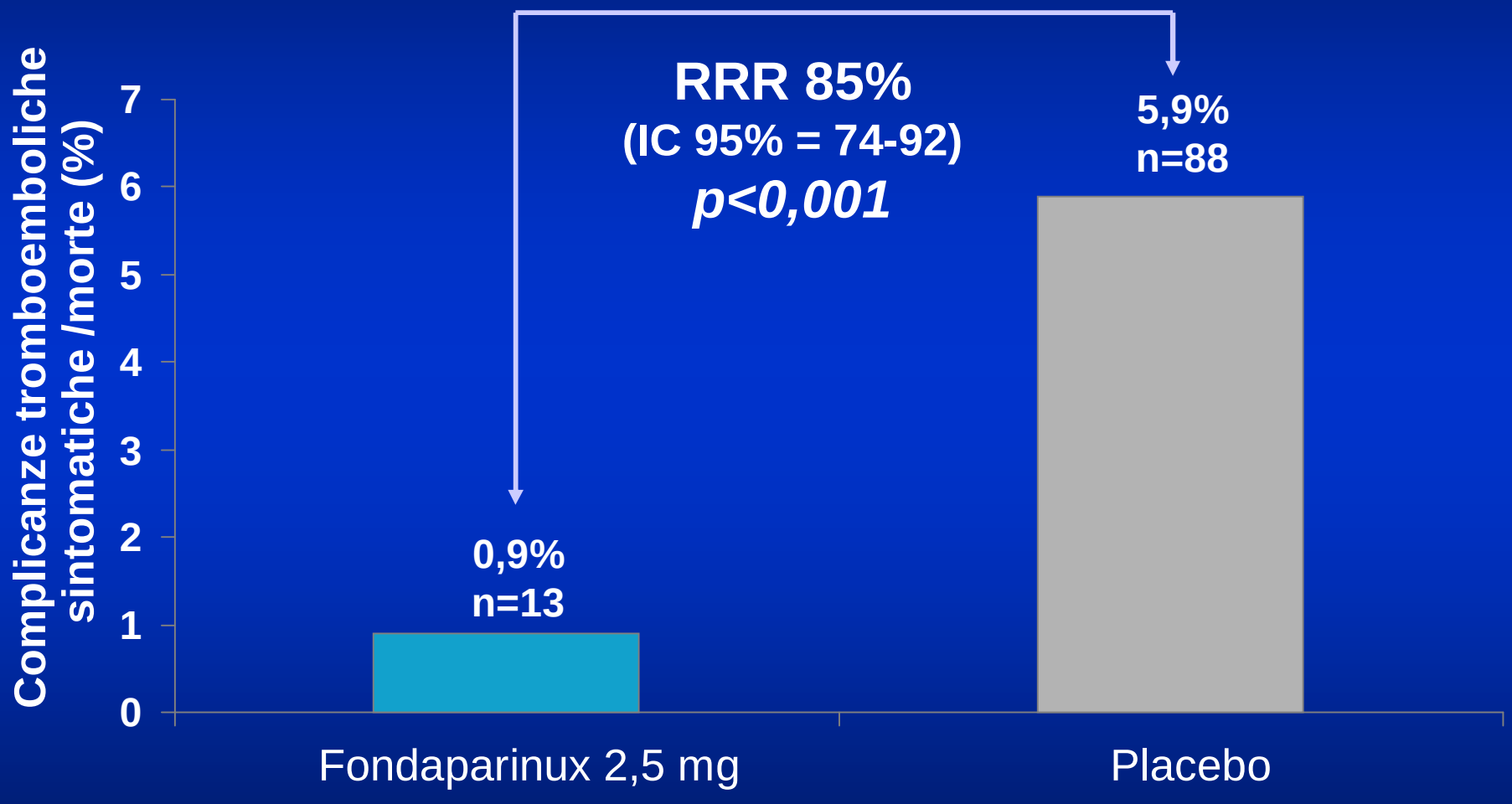
- Dati recenti hanno evidenziato un inaspettato alto tasso di EP in pazienti con tromboflebiti superficiali della coscia (fino al 33%)

Solo 6 studi hanno valutato la terapia anticoagulante nella TVS (n = 1242)

	Titon et al.[1]	Belcaro et al.[2]	Marchiori et al.[3]	Lozano e Almazan[4]	STENOX[5]	VESALIO[6]
Disegno	Randomizz in aperto **(n=117)**	Randomizz in aperto **(n=444)**	Randomizz in aperto **(n=60)**	Randomizz in aperto **(n=84)**	Randomizz doppio cieco *vs.* placebo **(n=427)**	Randomizz doppio cieco **(n=164)**
Terapia	Nadroparina *vs.* Naprossene	UFH + VKA *vs.* Nadroparina + VKA	UFH a basse dosi *vs.* UFH ad alte dosi	Enoxaparina *vs.* Intervento chirurgico	Enoxaparina (a basse o ad alte dosi) *vs.* Tenoxicam *vs.* Placebo	Nadroparina a basse dosi *vs.* Nadroparina ad alte dosi
Durata del trattamento	6 giorni	3 mesi	30 giorni	4 settimane	8-12 giorni	4 settimane
Durata del follow-up	8 settimane	3 mesi	6 mesi	6 mesi	12 settimane	12 settimane

1. *Ann Cardiol Angeiol 1994;43:160-6;* ***2***. *Angiology 1999;50:523-9;* ***3.*** *Haematologica 2002;87:523–7;*
4. *Vasc Endovasc Surg 2003;37:415-20; 5. Arch Intern Med 2003;163:1657–63;6. J Thromb Haemost 2005;3:1152-7*

Studio CALISTO
Outcome primario di efficacia (giorno 47)



Outcome primario: EP/TVP sintomatiche, estensione della TVS iniziale alla GSF, TVS recidivante, morte per tutte le cause

Decousus, N Engl J Med, 2010

Studio CALISTO
Outcomes di sicurezza (giorno 47)

	Fondaparinux N=1499	Placebo N=1488
Emorragie gravi	1 (0,1%)	1 (0,1%)
Emorragie fatali	0	0
Emorragie non gravi ma clinicamente rilevanti	5 (0,3%)	8 (0,5%)
Sanguinamenti minori	9 (0,6%)	6 (0,4%)
Sanguinamenti (totale)	15 (1,0%)	14 (0,9%)

Decousus, N Engl J Med, 2010

TERAPIA DEL TEV: ASPETTI PARTICOLARI

- Popolazioni “speciali” (cancro, gravidanza)
- Filtri cavali
- Trattamento della trombosi venosa superficiale
- Nuovi farmaci anticoagulanti

TERAPIA DEL TEV: ASPETTI PARTICOLARI

- Pazienti neoplastici
- Gravidanza
- Nuovi farmaci anticoagulanti

Targets of New Anticoagulant Agents

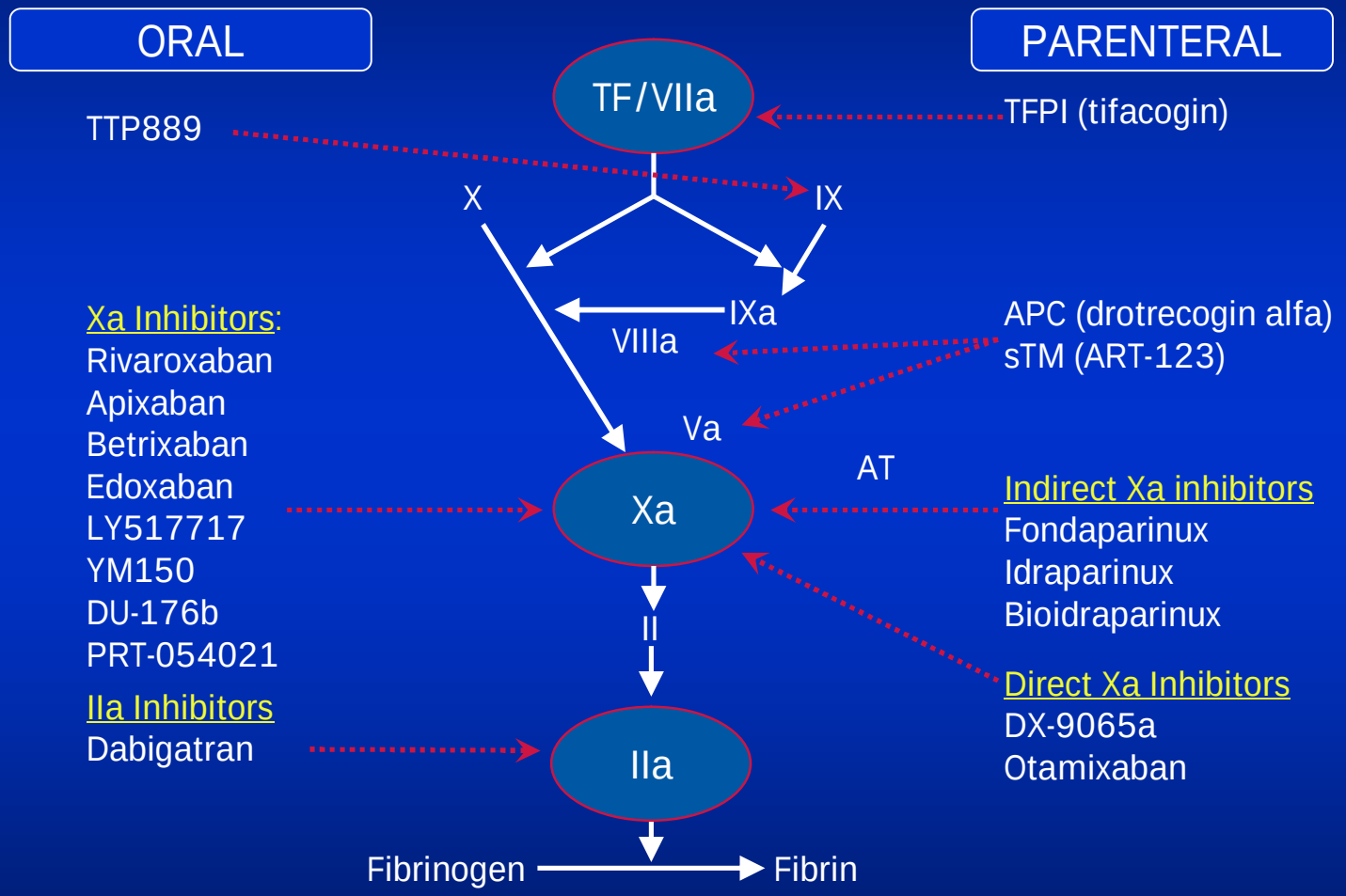


Table 1. Partial list of anticoagulants in development

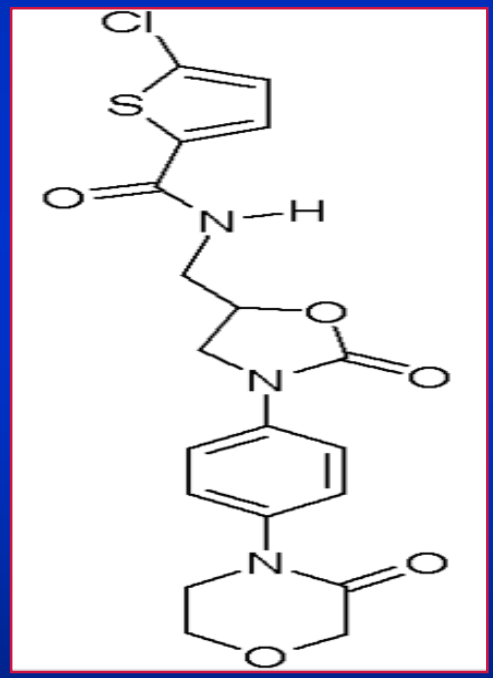
Agent	Company	Status, phase
Direct thrombin inhibitors		
Dabigatran etexilate	Boehringer Ingelheim	3
AZD0837	Astra Zeneca	2
MCC 977	Mitsubishi Pharma	2
Direct factor Xa inhibitors		
Rivaroxaban	Bayer, Ortho-McNeill	3
Apixaban	Bristol-Myers Squibb, Pfizer	3
Betrixaban	Portola	2
YM150	Astellas	2
Edoxaban (DU-176b)	Daichi Sankyo	3
TAK-442	Takeda	2
Otamixaban*	Sanofi-Aventis	2
Indirect factor Xa inhibitor		
Idraparinux*	Sanofi-Aventis	3
Idrabiotaparinux*	Sanofi-Aventis	3
Novel VKA		
ATI-5923	Aryx Therapeutics	2b

*Parenteral agent.

Rivaroxaban

- Small molecule
- Potent reversible inhibitor
- Fast onset and offset of action
- Good oral bioavailability (60-80%)
- Fixed dose
- Oral administration without interactions with food and low probability of interference with drugs
- $T_{1/2}$ life
  - 5-9 h in younger patients
  - 11-13 h in elderly patients

- Metabolized by the liver
- Renal clearance
  - 66% excreted by kidneys
- No monitoring

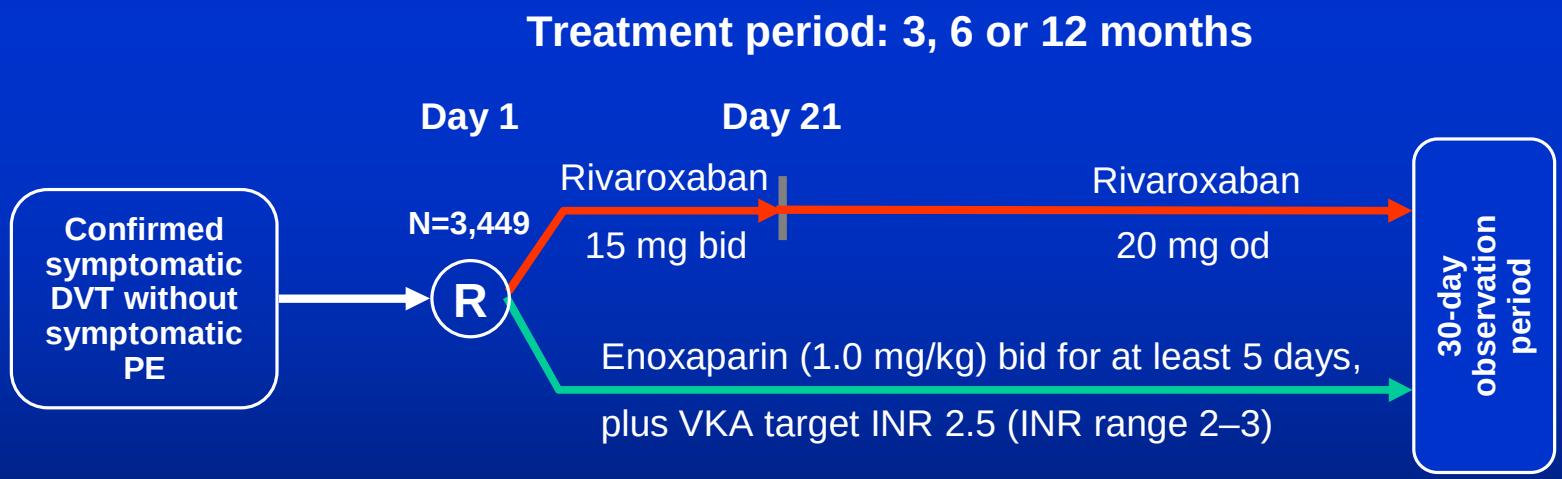


Gross, Arterioscler Thromb Vasc Biol, 2008

EINSTEIN DVT: study design

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

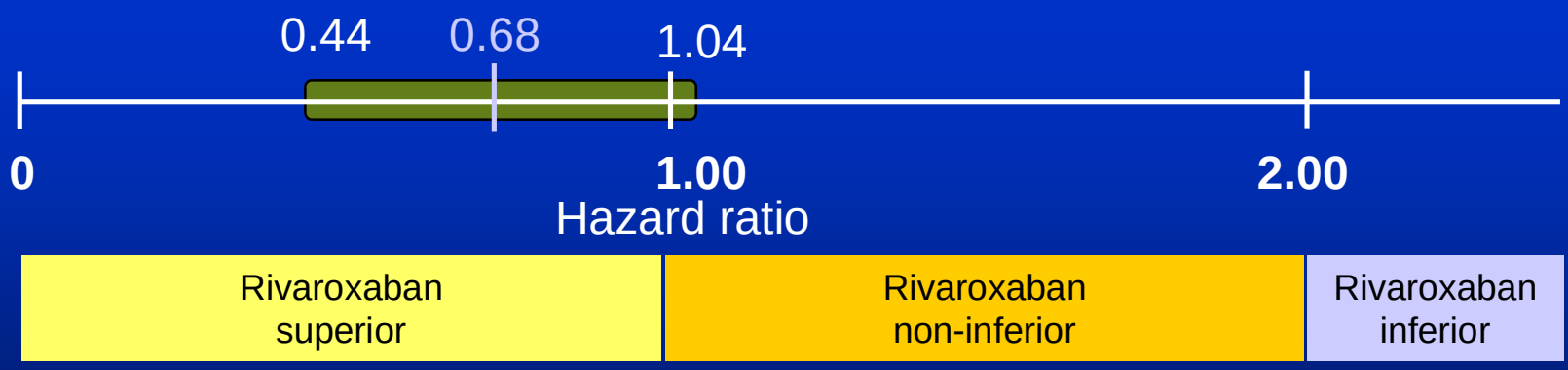
- Up to 48 hours' heparins/fondaparinux treatment permitted before
  study entry
- 88 primary efficacy outcomes needed



The EINSTEIN Investigators, N Engl J Med, 2010

Primary efficacy outcome analysis

	Rivaroxaban (n=1,731)		Enoxaparin/VKA (n=1,718)	
	n	(%)	n	(%)
First symptomatic recurrent VTE	36	(2.1)	51	(3.0)
Recurrent DVT	14	(0.8)	28	(1.6)
Recurrent DVT + PE	1	(<0.1)	0	(0)
Non-fatal PE	20	(1.2)	18	(1.0)
Fatal PE/unexplained death where PE cannot be ruled out	4	(0.2)	6	(0.3)



p=0.076 for superiority (two-sided)

p<0.001 for non-inferiority (one-sided)

ITT population

The EINSTEIN Investigators, N Engl J Med, 2010

Principal safety outcome analysis

	Rivaroxaban (n=1,718)		Enox/VKA (n=1,711)		HR (95% CI)
	n	(%)	n	(%)	*p* value
First major or clinically relevant non-major bleeding	139	(8.1)	138	(8.1)	0.97 (0.76–1.22) *p*=0.77
Major bleeding	14	(0.8)	20	(1.2)	
Contributing to death	1	(<0.1)	5	(0.3)	
In a critical site	3	(0.2)	3	(0.2)	
Associated with fall in Hb ≥2 g/dL and/or transfusion of ≥2 units	10	(0.6)	12	(0.7)	
Clinically relevant non-major bleeding	126	(7.3)	119	(7.0)	

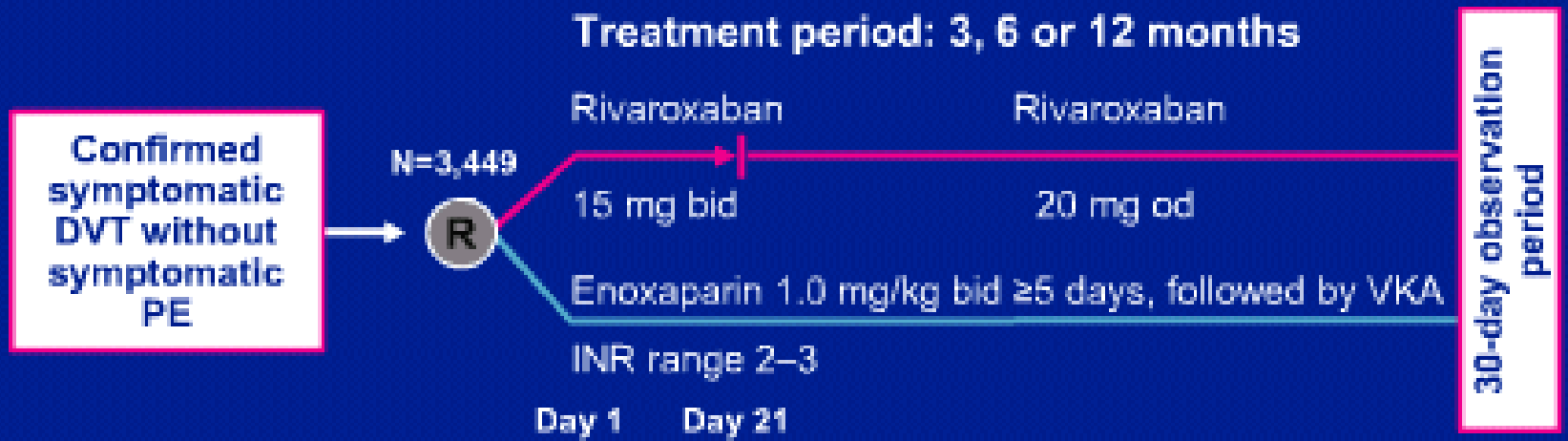
Safety population

The EINSTEIN Investigators, N Engl J Med, 2010

EINSTEIN DVT: study design

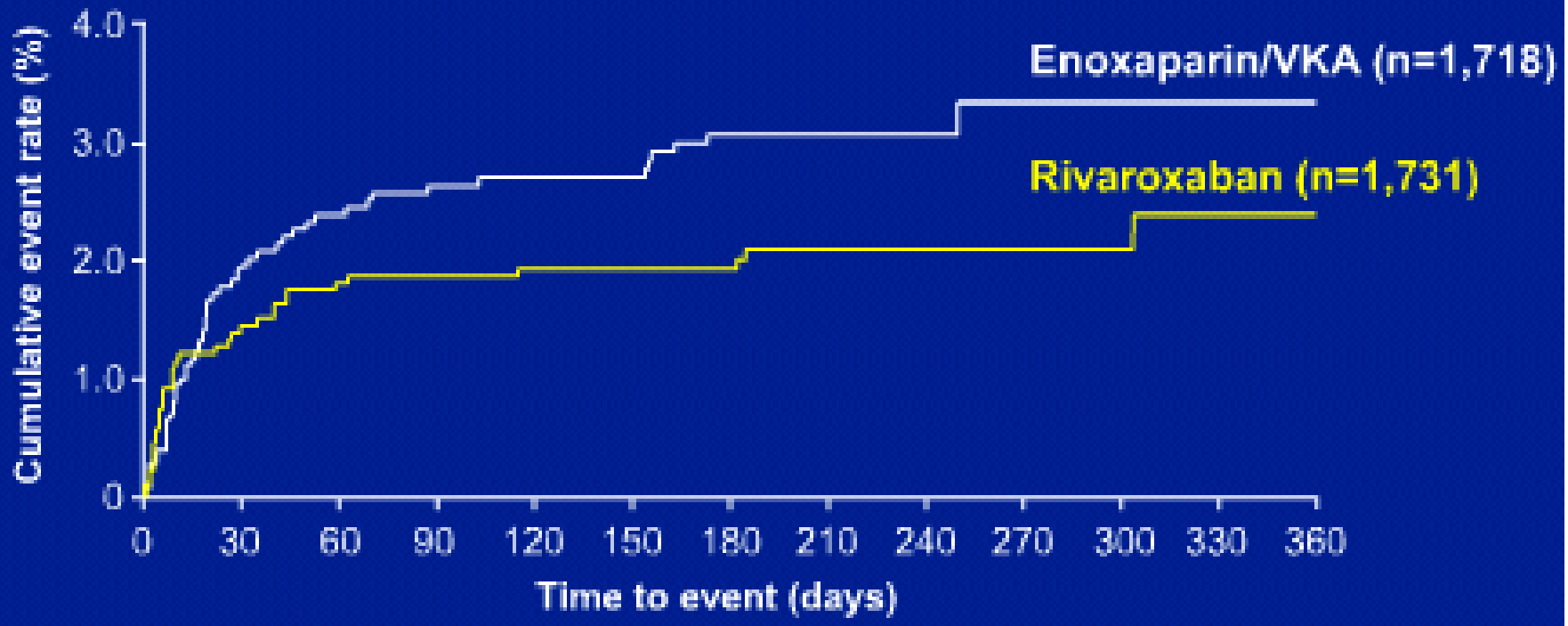
Randomized, open-label, event-driven, non-inferiority study

- Up to 48 hours' heparins/fondaparinux treatment permitted before study entry
- 88 primary efficacy outcomes needed



The EINSTEIN Investigators, N Engl J Med, 2010

Primary efficacy outcome: time to first event



Number of subjects at risk

Rivaroxaban	1,731	1,668	1,648	1,621	1,424	1,412	1,220	400	369	363	345	309	266
Enox/VKA	1,718	1,616	1,581	1,553	1,368	1,358	1,186	380	362	337	325	297	264

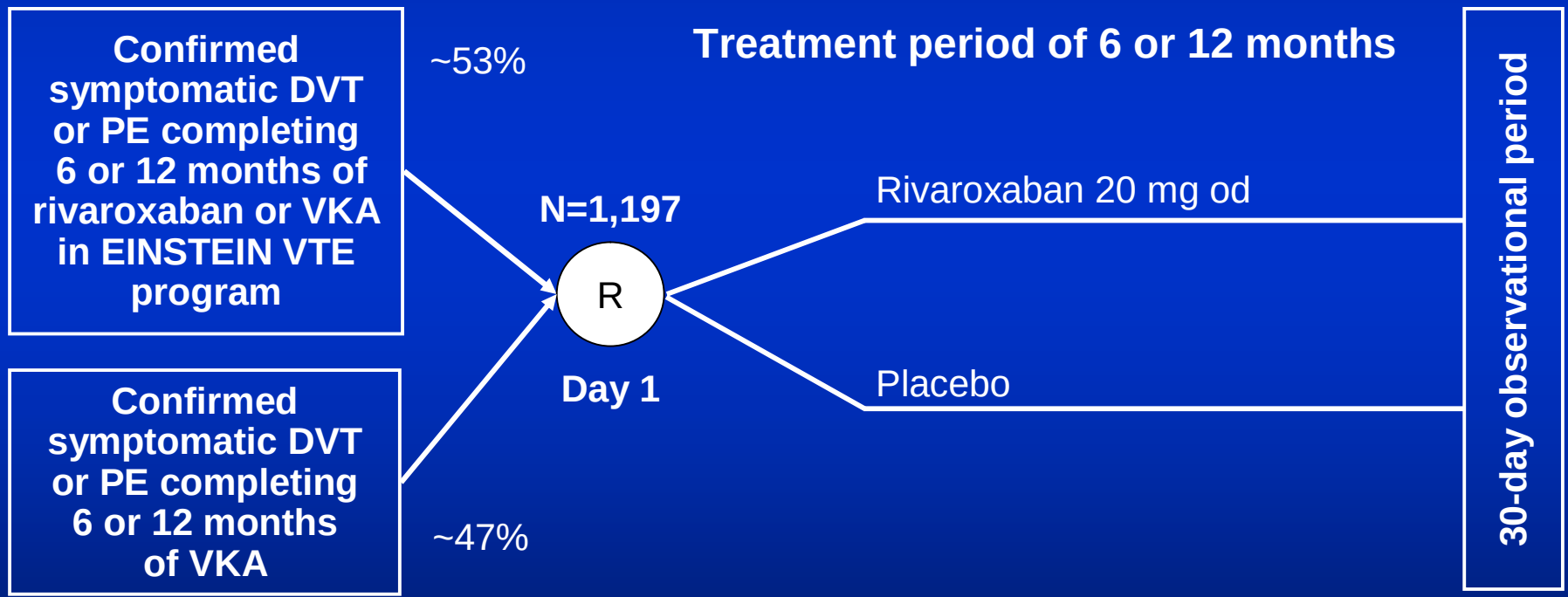
Principal safety outcome analysis

	Rivaroxaban (n=1,718)		Enox/VKA (n=1,711)		HR (95% CI)
	n	(%)	N	(%)	*p* value
First major or clinically relevant non-major bleeding	139	(8.1)	138	(8.1)	0.97 (0.76–1.22) *p*=0.77
Major bleeding	14	(0.8)	20	(1.2)	
Contributing to death	1	(<0.1)	5	(0.3)	
In a critical site	3	(0.2)	3	(0.2)	
Associated with fall in Hb ≥2 g/dl and/or transfusion of ≥2 units	10	(0.6)	12	(0.7)	
Clinically relevant non-major bleeding	129	(7.5)	122	(7.1)	

Safety population

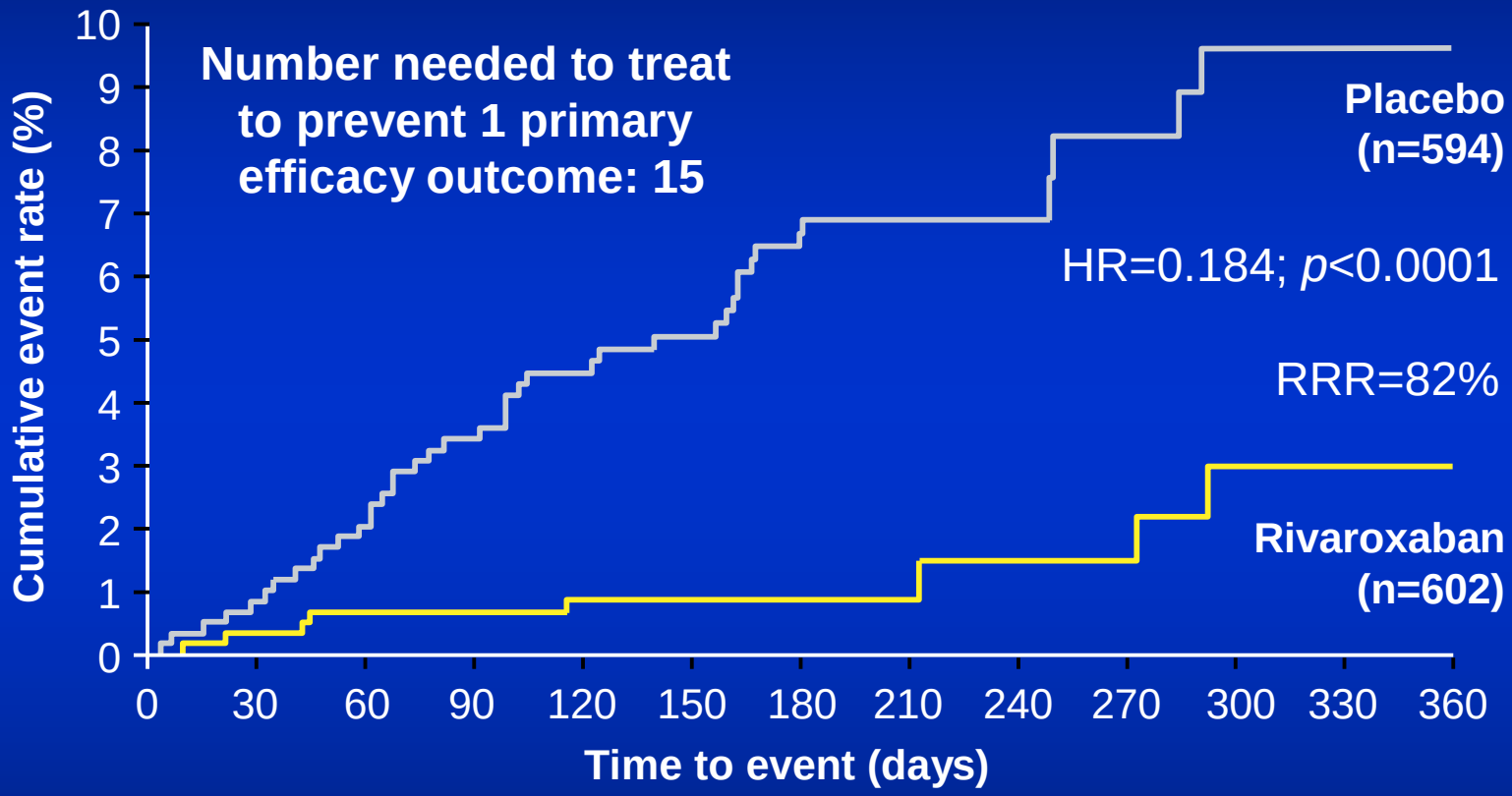
Once-daily oral rivaroxaban versus placebo in the long-term prevention of recurrent symptomatic VTE. The EINSTEIN Extension study

Randomized, double-blind, placebo-controlled, event-driven (n=30), superiority study



The EINSTEIN Investigators, N Engl J Med, 2010

Primary efficacy outcome analysis (time to first event)



Number of subjects at risk

ITT population

Rivaroxaban	602	590	583	573	552	503	482	171	138	132	114	92	81
Placebo	594	582	570	554	521	467	444	164	138	133	110	93	85

Principal safety outcome: major bleeding

	Placebo (n=590)	Rivaroxaban (n=598)
Major bleeding	**0**	**4 (0.7%)***
Bleeding contributing to death	0	0
Bleeding in a critical site	0	0
Associated with fall in hemoglobin ³2 g/dL and/or transfusion		
Gastrointestinal bleeding	0	3 (0.5%)
Menorrhagia	0	1 (0.2%)

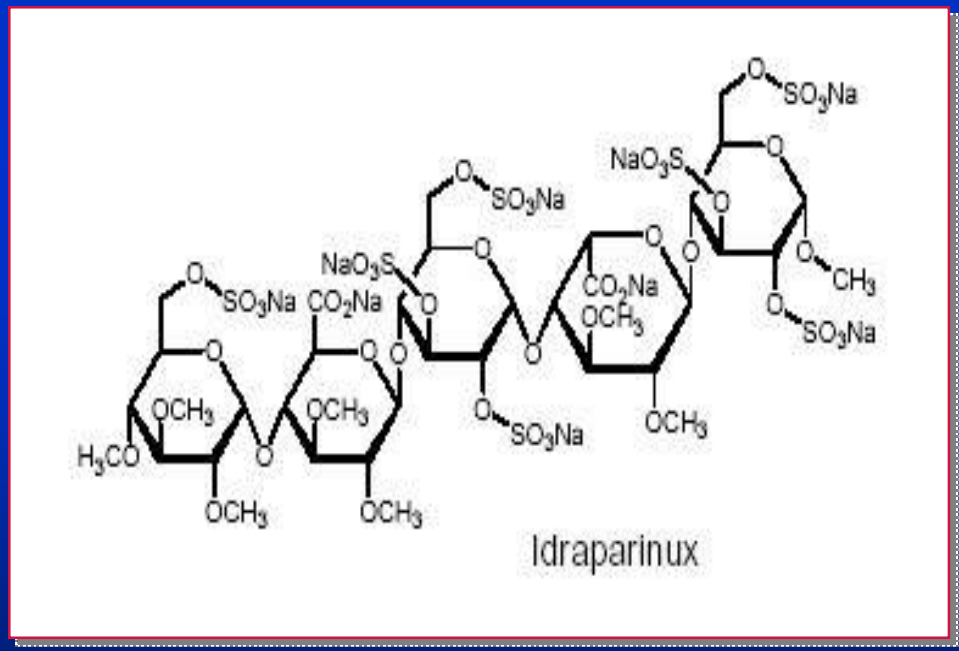
- Number needed to harm: approximately 139

*p=0.11

Safety population

Idraparinux/Idrabiotaparinux

- Novel, synthetic pentasaccharide
- Longer half-life than fondaparinux
- Administered sc once weekly
- Dosage must be reduced in patients with renal insufficiency
- Does not require monitoring
- A biotinylated version has evaluated in clinical trials



Gross, Arterioscler Thromb Vasc Biol, 2008

VAN GOGH studies: Idraparinux versus standard therapy for VTE disease

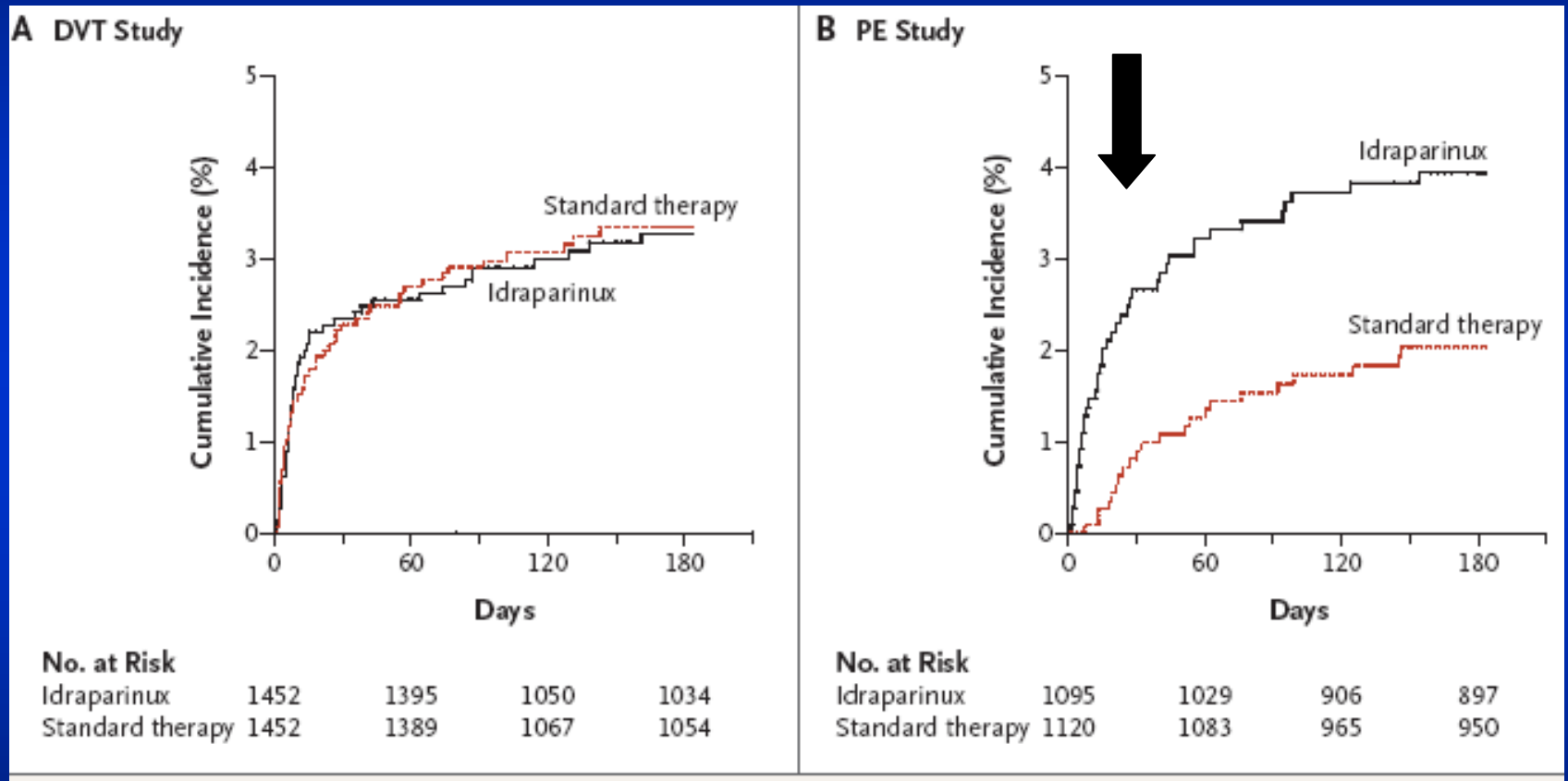
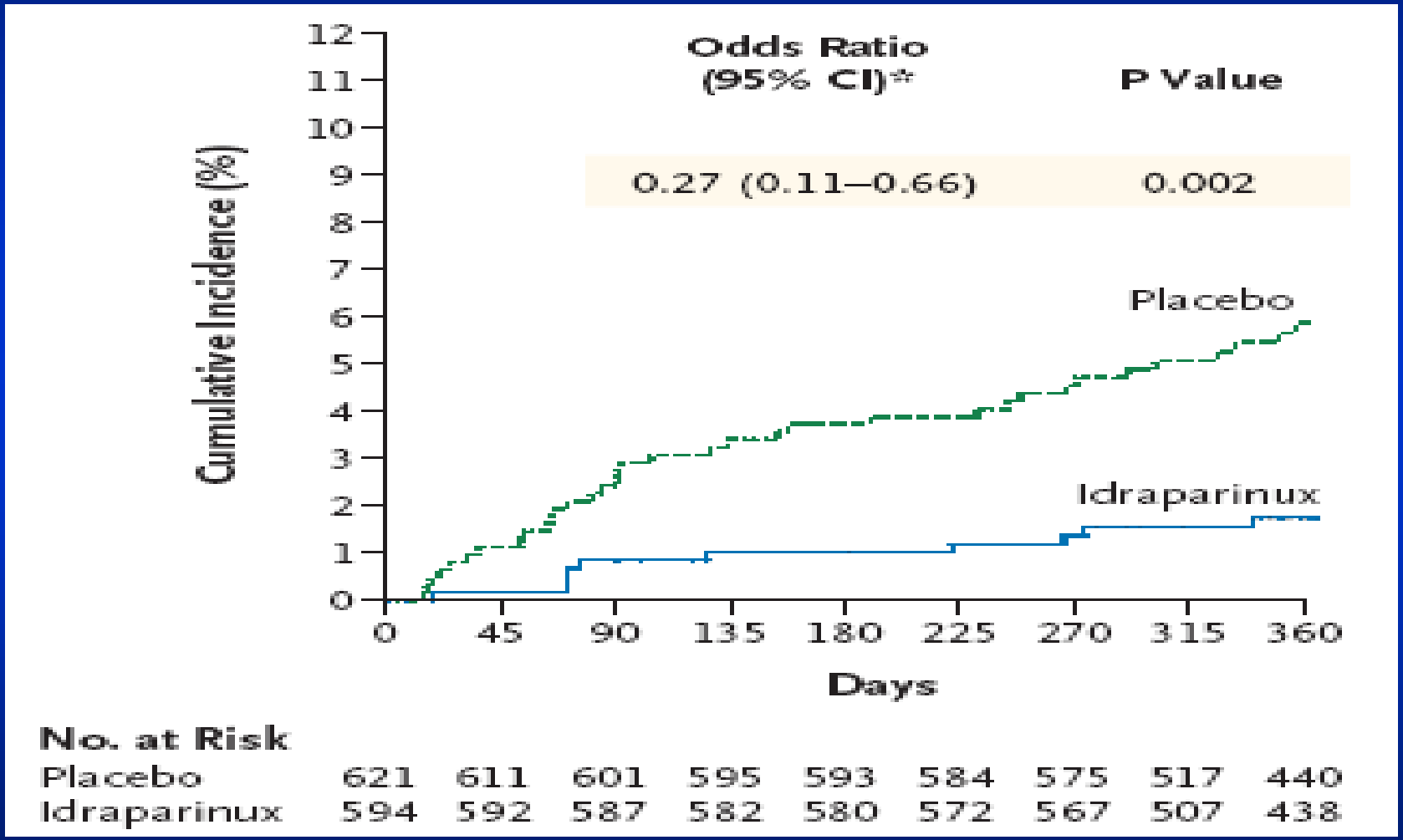


Figure 1. Cumulative Incidence of Venous Thromboembolic Events.

The graphs show comparisons between the idraparinux group and the standard-therapy group for patients with deep-vein thrombosis (the DVT Study, Panel A) and those with pulmonary embolism (the PE Study, Panel B).

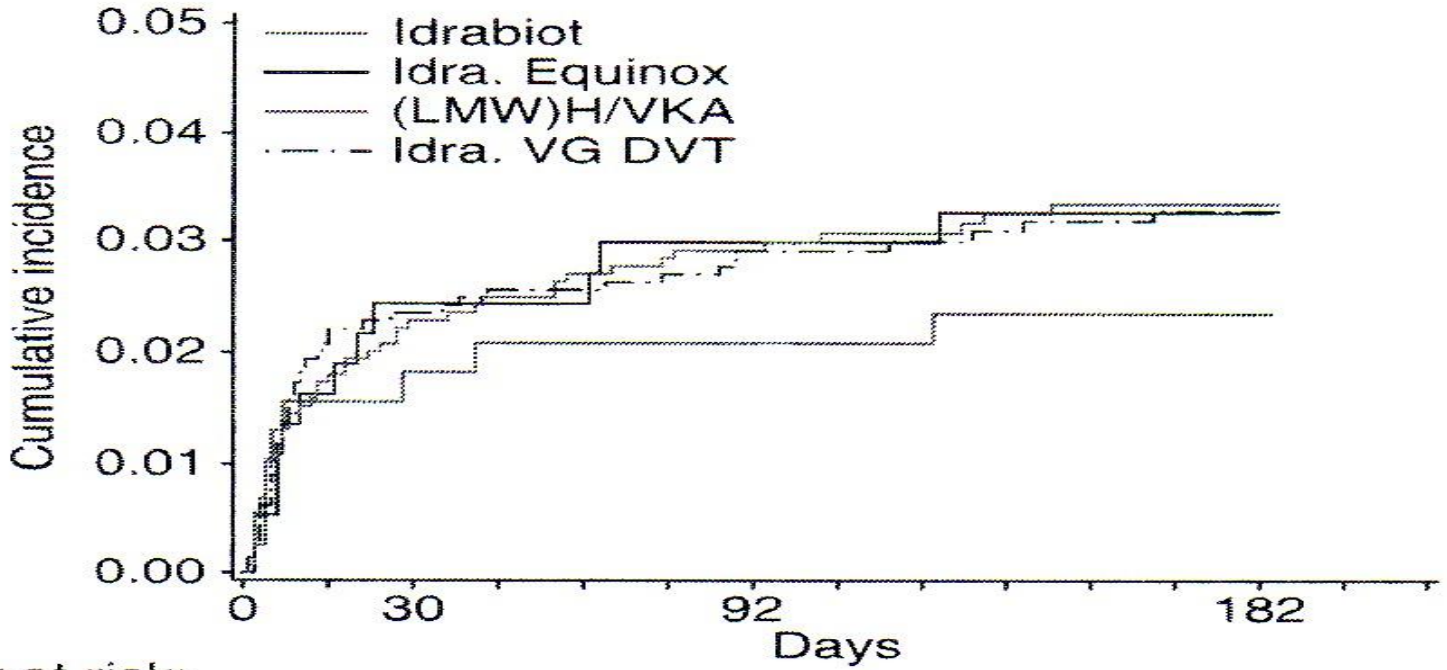
Buller, N Engl J Med, 2007

Extended prophylaxis of VTE with idraparinux



The Van Gogh Investigators, N Engl J Med, 2007

Efficacy and safety of once weekly subcutaneous idrabiotaparinux in the treatment of patients with symptomatic DVT



Number at risk:

Idrabiot.	386	377	374	367
Idra. Equinox	371	358	353	344
(LMW)H/VKA	1452	1409	1378	1053
Idra. VG DVT	1452	1408	1381	1034

The EQUINOX Investigators, J Thromb Haemost, 2011

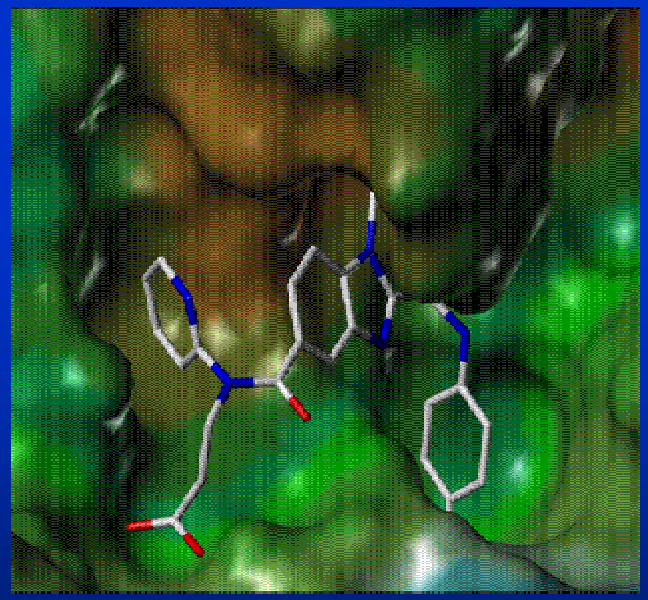
Efficacy and safety of once weekly subcutaneous idrabiotaparinux in the treatment of patients with symptomatic DVT

	Idrabiotaparinux (n = 385)	Idraparinux (n = 370)
	n (%)	n (%)
Any clinically relevant bleeding	20 (5.2%)	27 (7.3%)
Major bleeding		
Fatal		
Intracranial	—	3
Other	1	—
Non-fatal		
Intracranial	—	2
Intraperitoneal	—	2
Fall in hemoglobin ≥ 2 g dL^{-1} or leading to transfusion ≥ 2 units of red blood cells	2	7
Non-major bleeding only	17 (4.4%)	13 (3.5%)

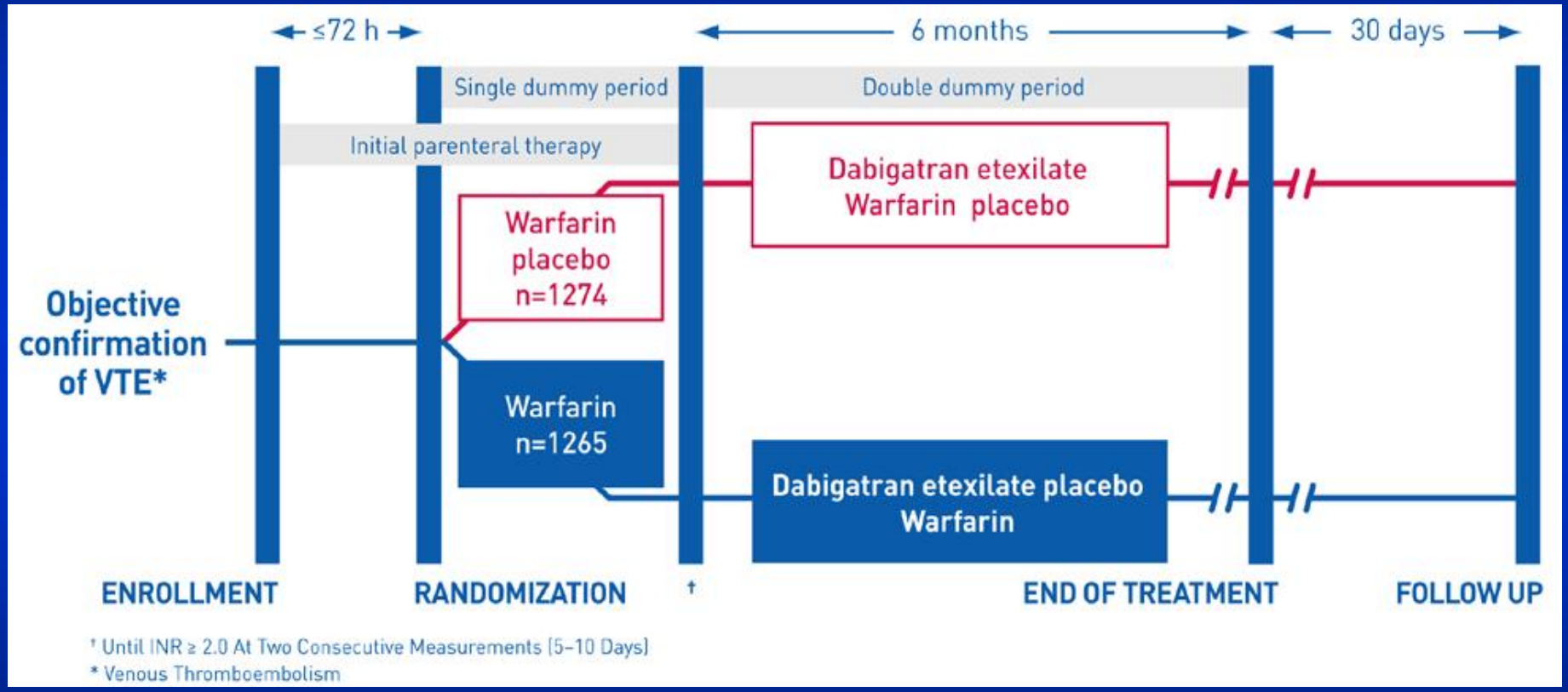
The EQUINOX Investigators, J Thromb Haemost, 2011

DABIGATRAN ETEXILATE

- Acts on clot bound and free thrombin
- Highly specific for thrombin
- Predictable and reproducible PK/PD
- Oral administration without interactions with food and drugs
- Fixed dose
- Fast onset and offset of action
- No need for coagulation and platelet monitoring
- Dabigatran can be used both in the hospital and out-patient setting

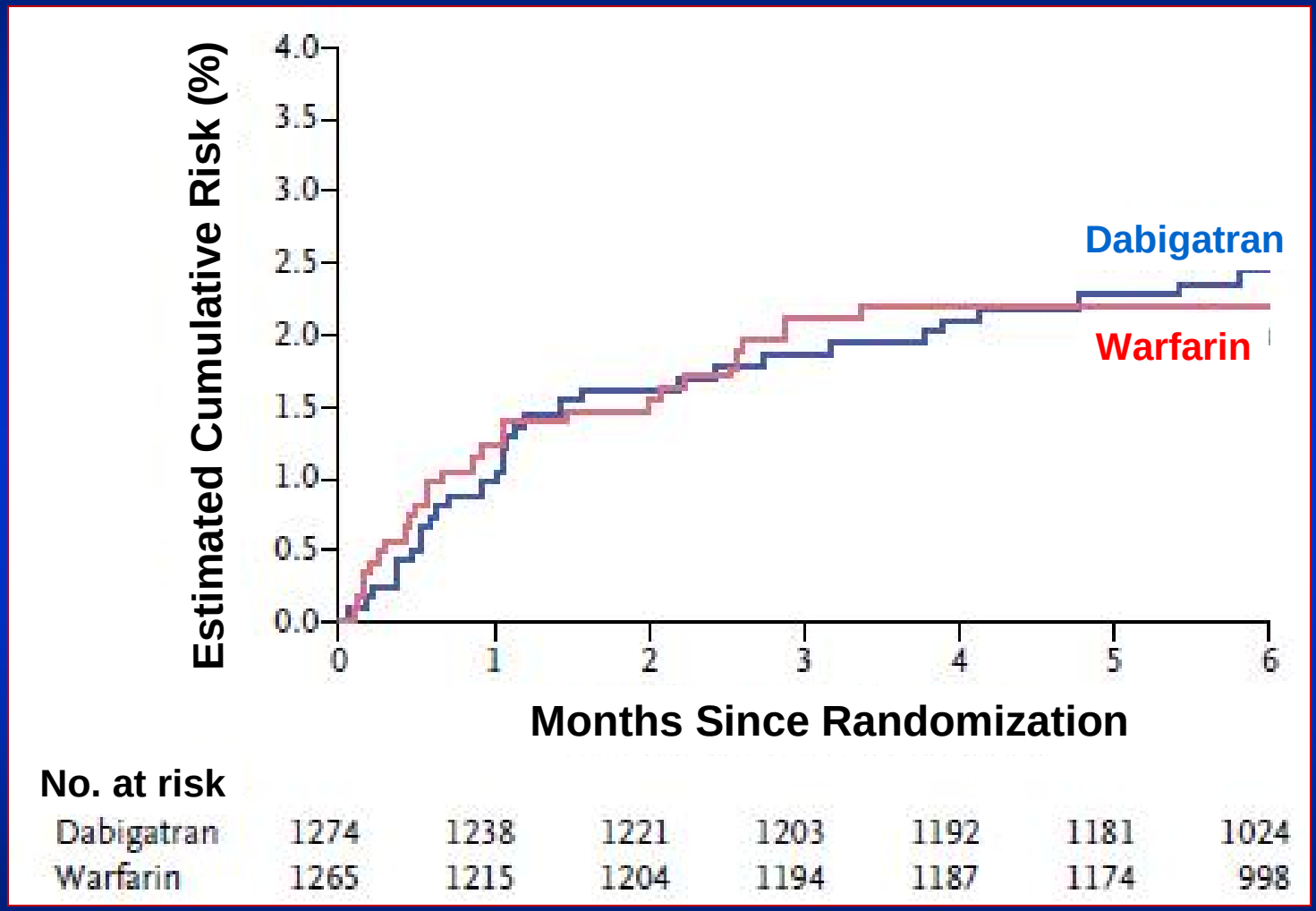


RE-COVER Trial



Schulman, N Engl J Med, 2009

Cumulative risk of recurrent VTE and related death

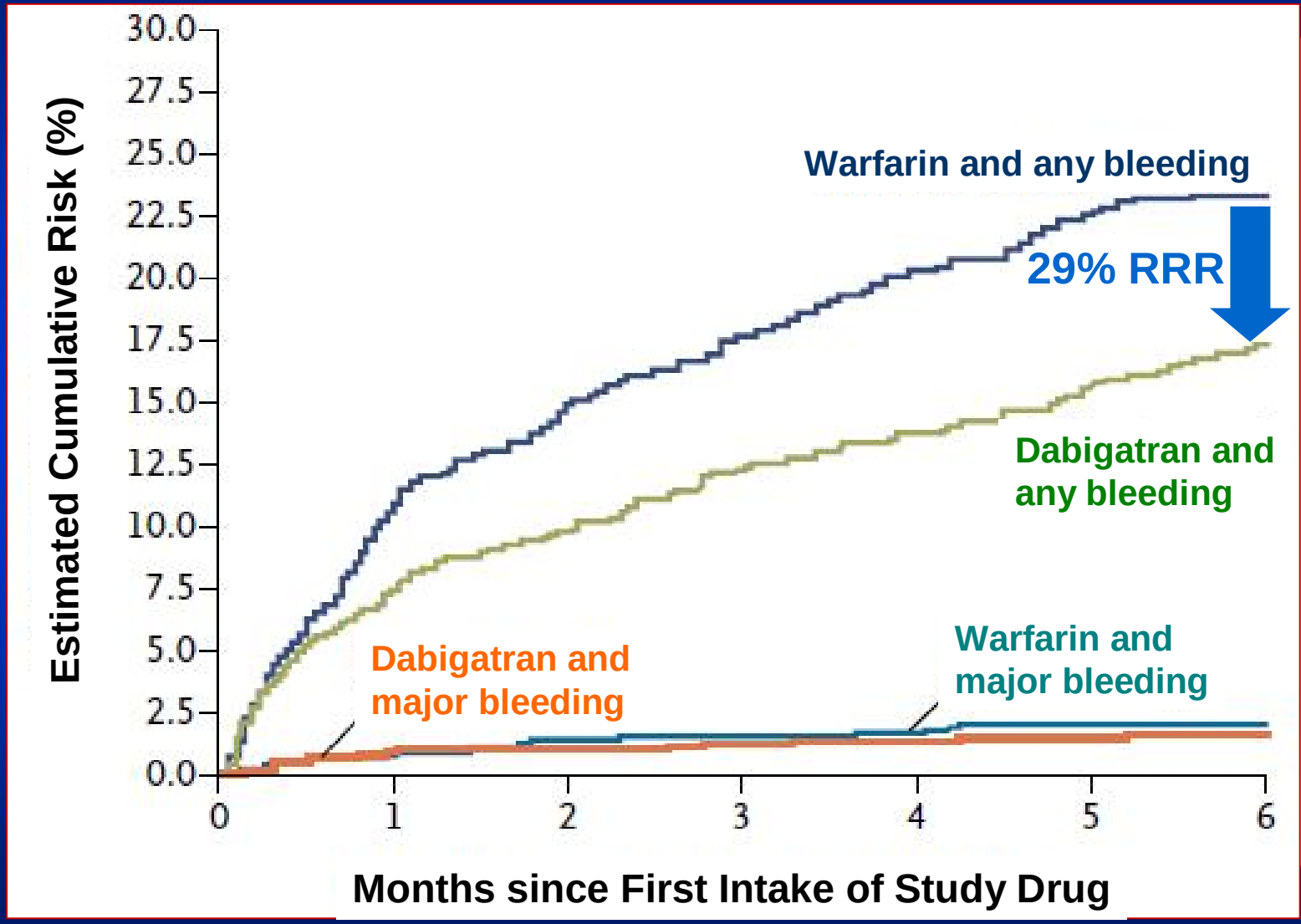


No. at risk

Dabigatran	1274	1238	1221	1203	1192	1181	1024
Warfarin	1265	1215	1204	1194	1187	1174	998

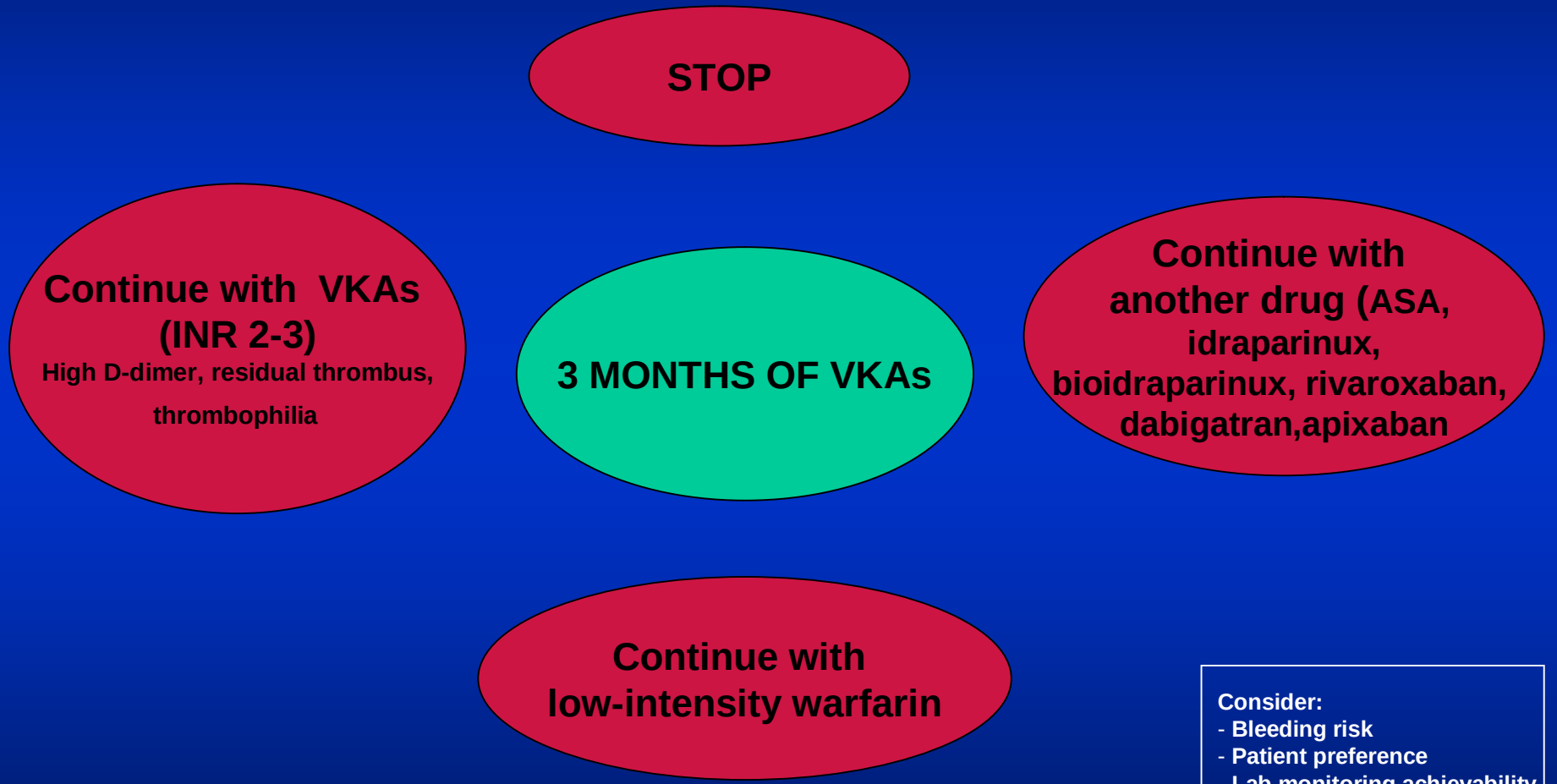
Dabigatran was non-inferior to warfarin for prevention of recurrent or fatal VTE (P<0.001 for both hazard ratio and risk difference criteria).

Cumulative risk of first event of major bleeding and of any bleeding



The hazard ratio for any bleeding at 6 months is 0.71 (95% CI, 0.59–0.85) in favor of dabigatran (P=0.0002).

First unprovoked VTE: what to do after 3 months of VKAs treatment



Valutazione dell'efficacia e sicurezza di dabigatran etexilato 150 mg due volte/die vs placebo nella prevenzione secondaria del TEV in pazienti trattati precedentemente con warfarin per 6-18 mesi

– Double-blind randomised to one of two groups:
• Oral dabigatran etexilate 150 mg b.i.d.
• Placebo
– Treatment will be continued for 6 months

– Primary outcomes:
• Efficacy – Symptomatic recurrent VTE during the treatment period
• Safety – Bleeding events during treatment period

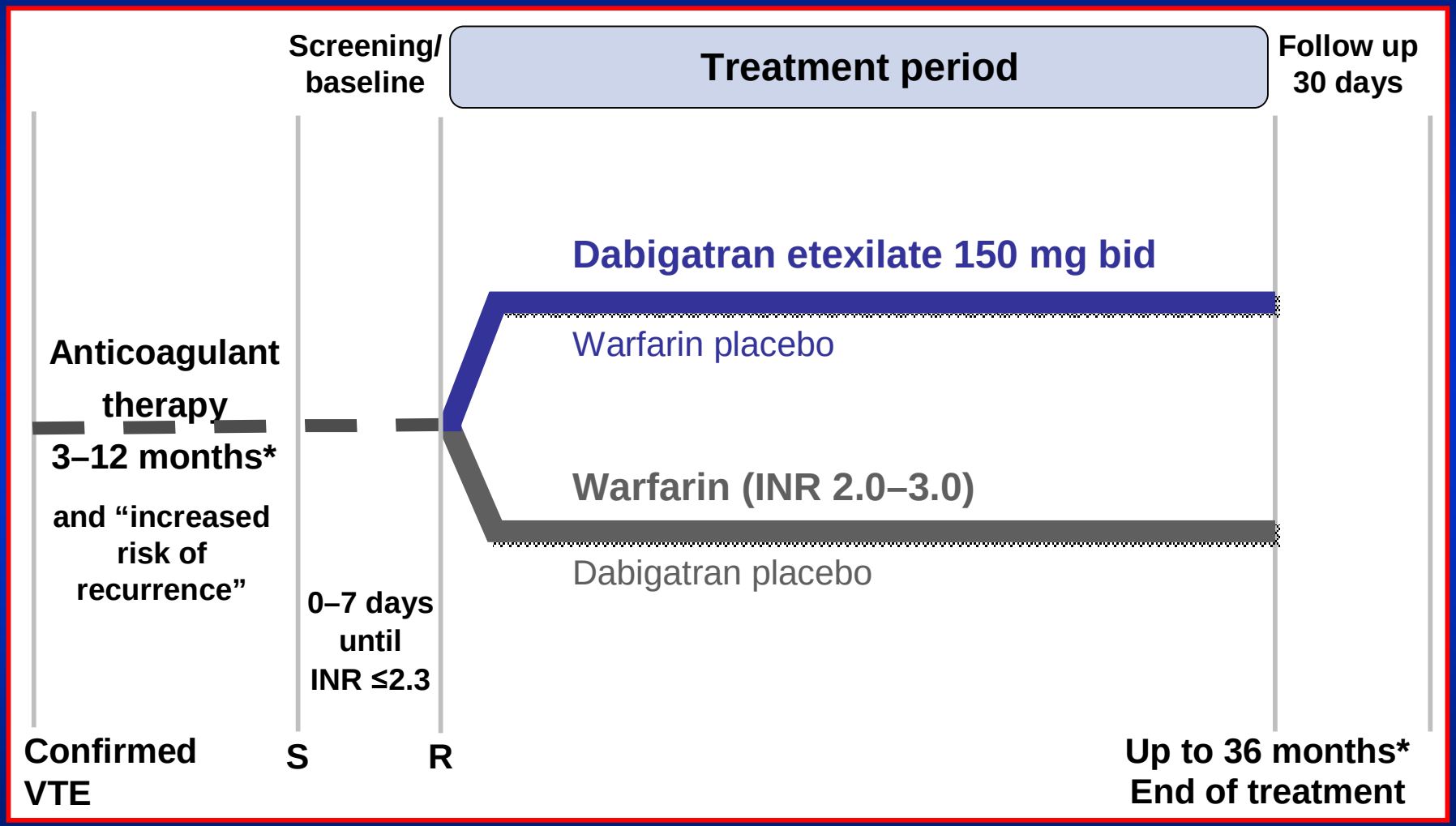
Valutazione dell'efficacia e sicurezza di dabigatran etexilato 150 mg due volte/die vs warfarin nella prevenzione secondaria del tromboembolismo venoso (TEV) in pazienti trattati precedentemente con warfarin per 3-6 mesi

– Double-blind randomised to one of two groups:
• Oral dabigatran etexilate 150 mg b.i.d.
• Warfarin (INR 2.0-3.0)

– Treatment will be continued for 18 months

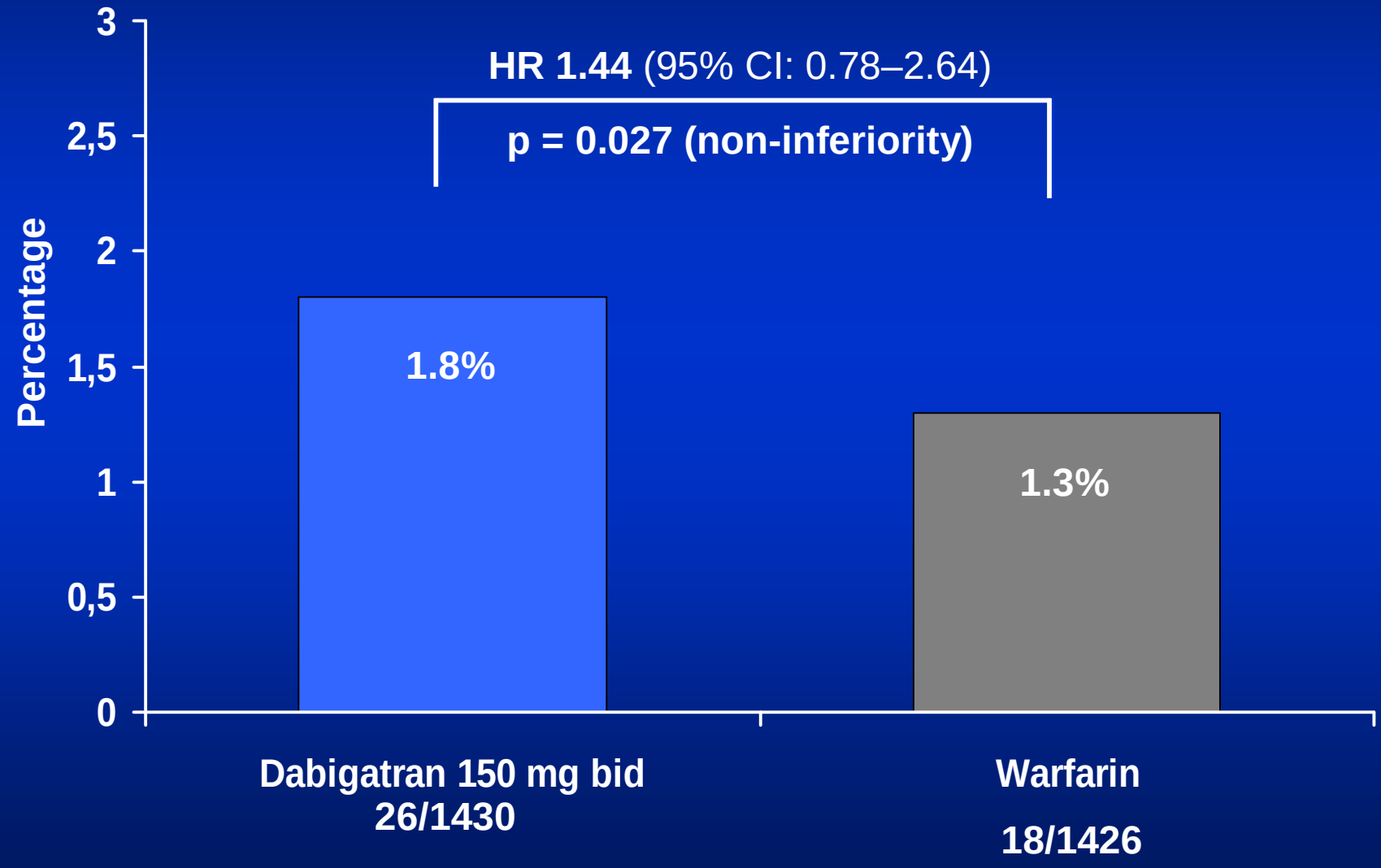
– Primary outcomes:
• Efficacy – Symptomatic recurrent VTE, VTE related death (verified by definitive diagnostic evaluation)
• Safety – Bleeding events and 6 day wash out phase

RE-MEDY™ study design



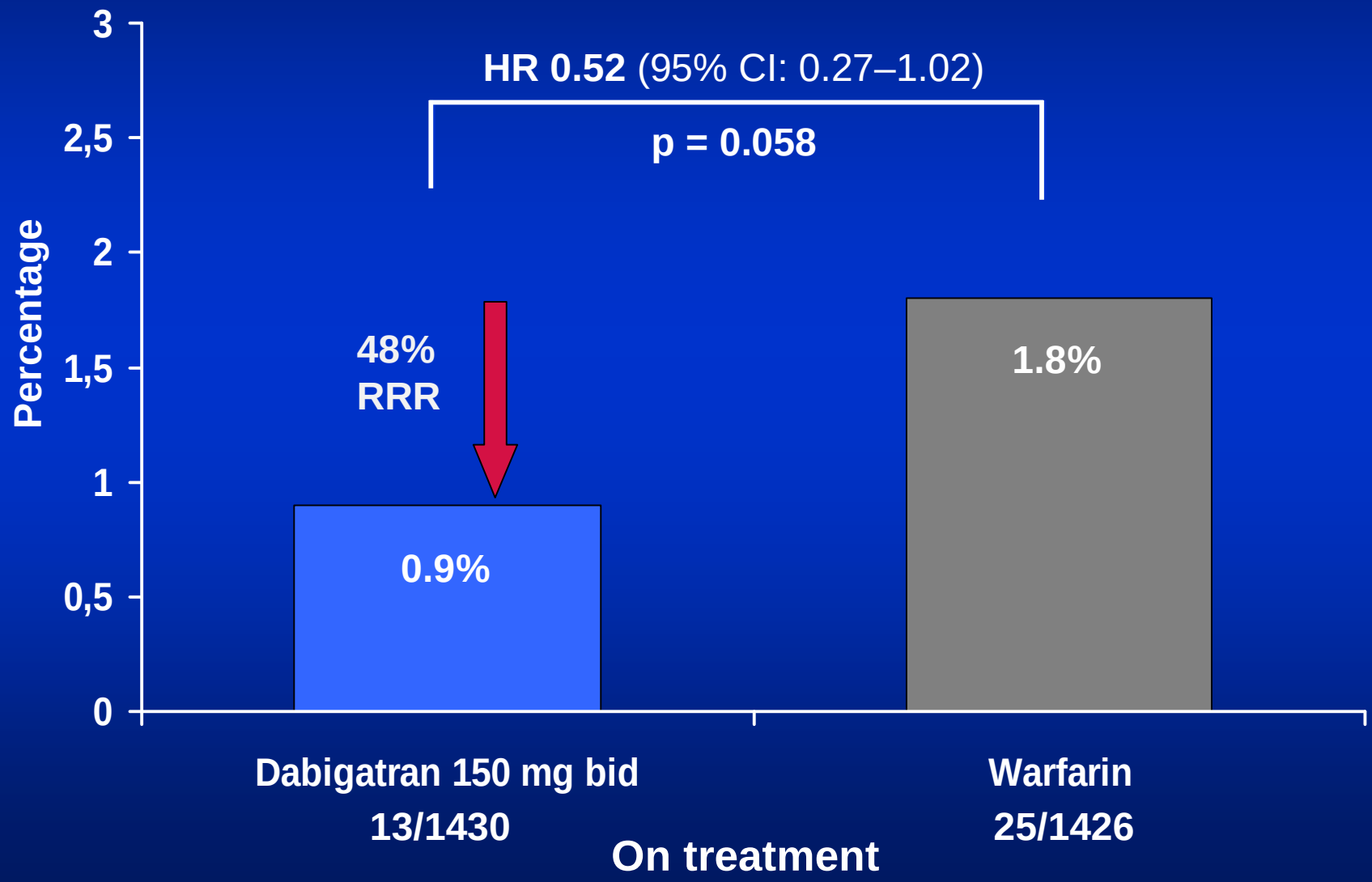
Schulman,J Thromb Haemost 2011;9 (suppl 2): O-MO- 039

Non-inferior for recurrent symptomatic VTE and VTE-related deaths



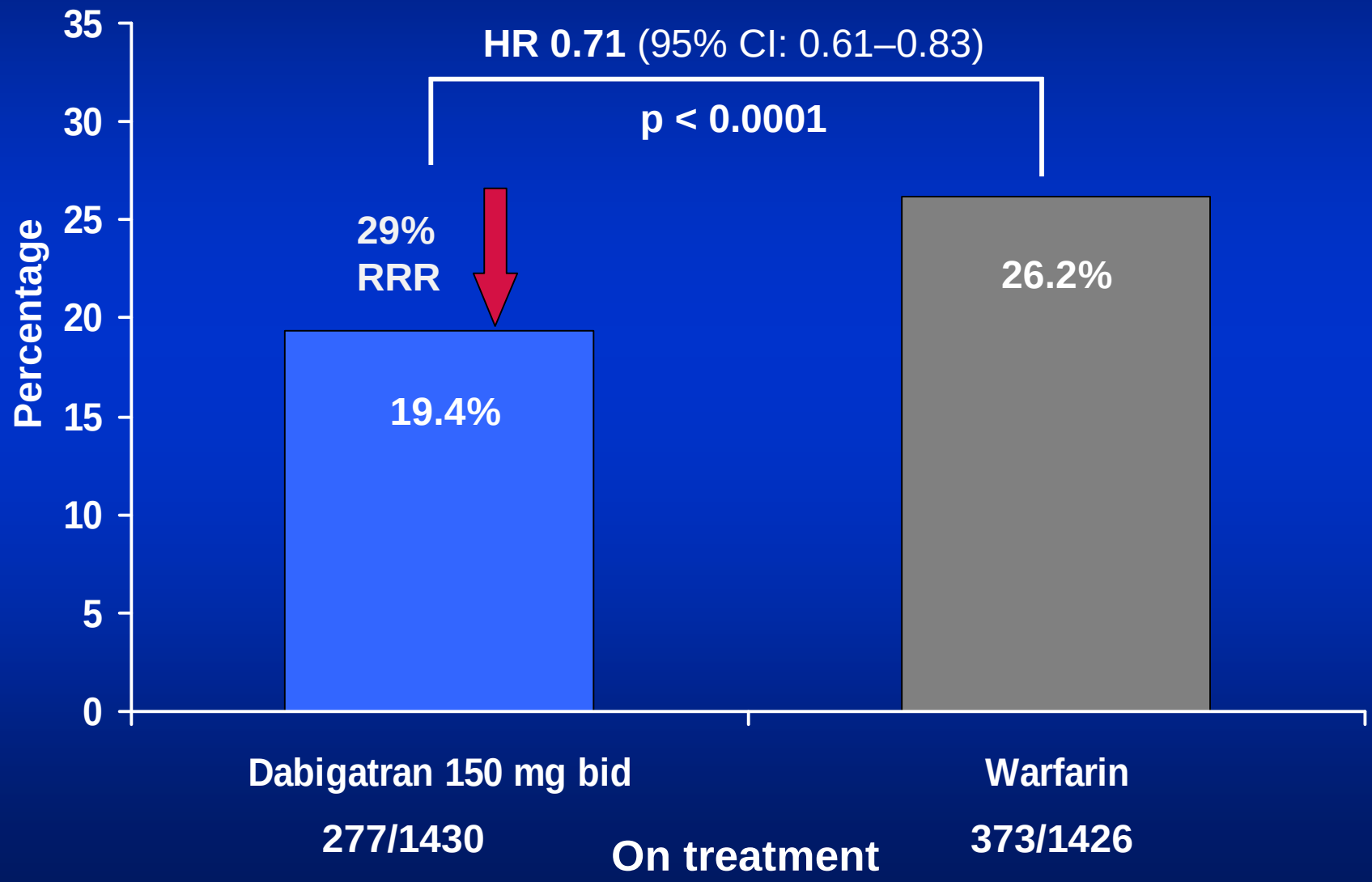
Risk difference 0.38 (95% CI: -0.50–1.25); p < 0.0001 (non-inferiority).

Major bleeding



RRR, relative risk reduction.

Any bleeding



Adverse events during treatment

	Dabigatran n (%)	Warfarin n (%)
Treated set	1430 (100)	1426 (100)
Any adverse event	1029 (72.0)	1010 (70.8)
Severe adverse event	143 (10.0)	151 (10.6)
Investigator-defined drug-related adverse event	229 (16.0)	280 (19.6)
Adverse event leading to discontinuation of study drug	145 (10.1)	126 (8.8)
Serious adverse event	227 (15.9)	224 (15.7)
Death during treatment period	12 (0.8)	18 (1.3)

Confirmed cardiovascular events

	Dabigatran n (%)	Warfarin n (%)
Treated set	1430 (100)	1426 (100)
Patients with definite acute coronary syndrome (ACS) events, as randomized, on treatment	12 (0.8)	2 (0.1)
Events of definite ACS events, as randomized, on treatment	12	2
Definite myocardial infarction	9	1
Definite ischemia	3	1
Cardiac death	0	0
Definite and likely ACS events in patients, including post-treatment period (6 days)	13 (0.9)*	3 (0.2)

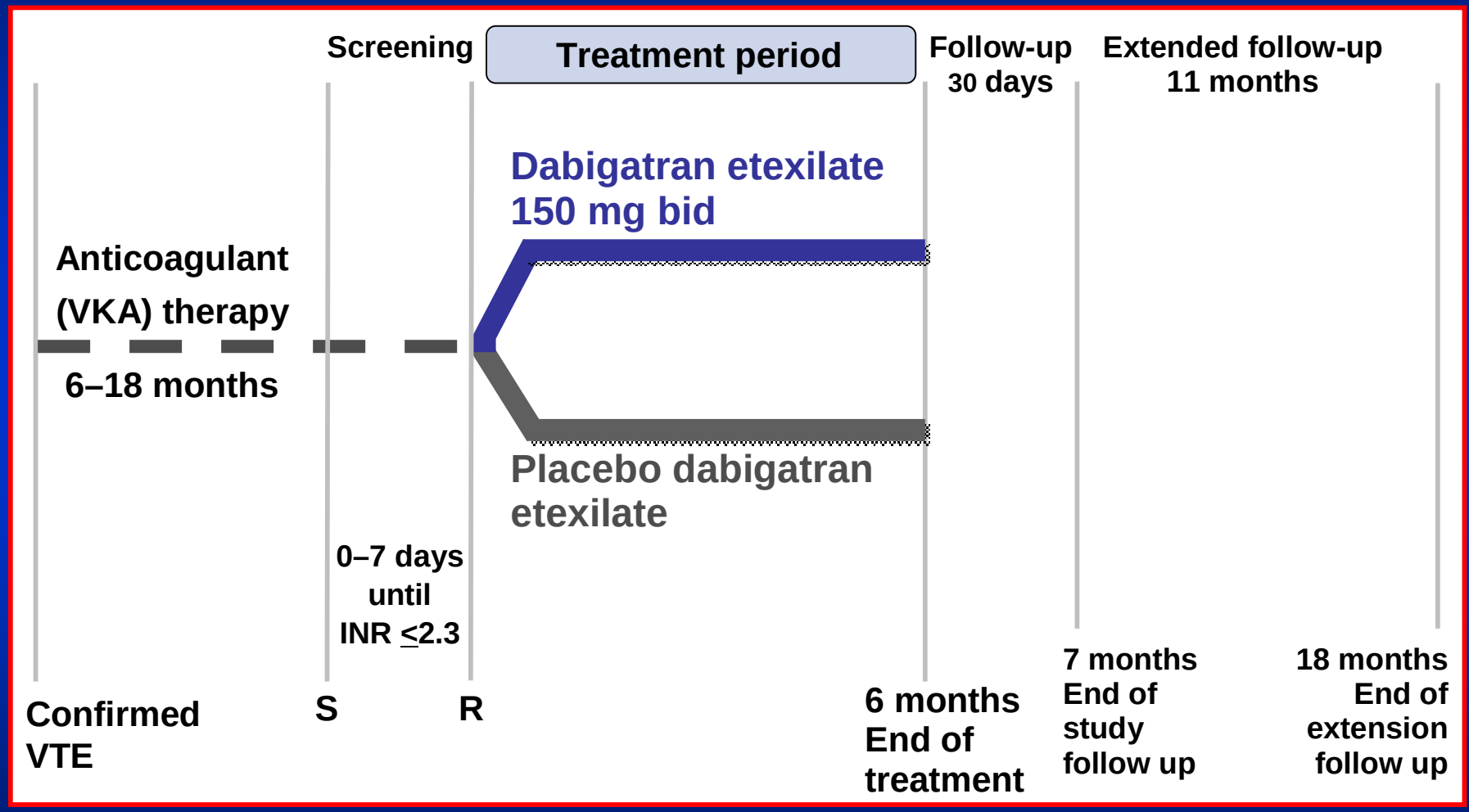
*p = 0.02 versus warfarin.

Imbalance in risk factors at baseline

	Dabigatran n (%)	Warfarin n (%)	Total n (%)
Coronary artery disease	120 (8.4)*	87 (6.1)*	**207 (7.2)**
Heart failure	57 (4.0)	42 (2.9)	**99 (3.5)**
Diabetes	150 (10.5)†	108 (7.6)†	**258 (9.0)**
Hypertension	582 (40.7)‡	520 (36.5)‡	**1102 (38.6)**

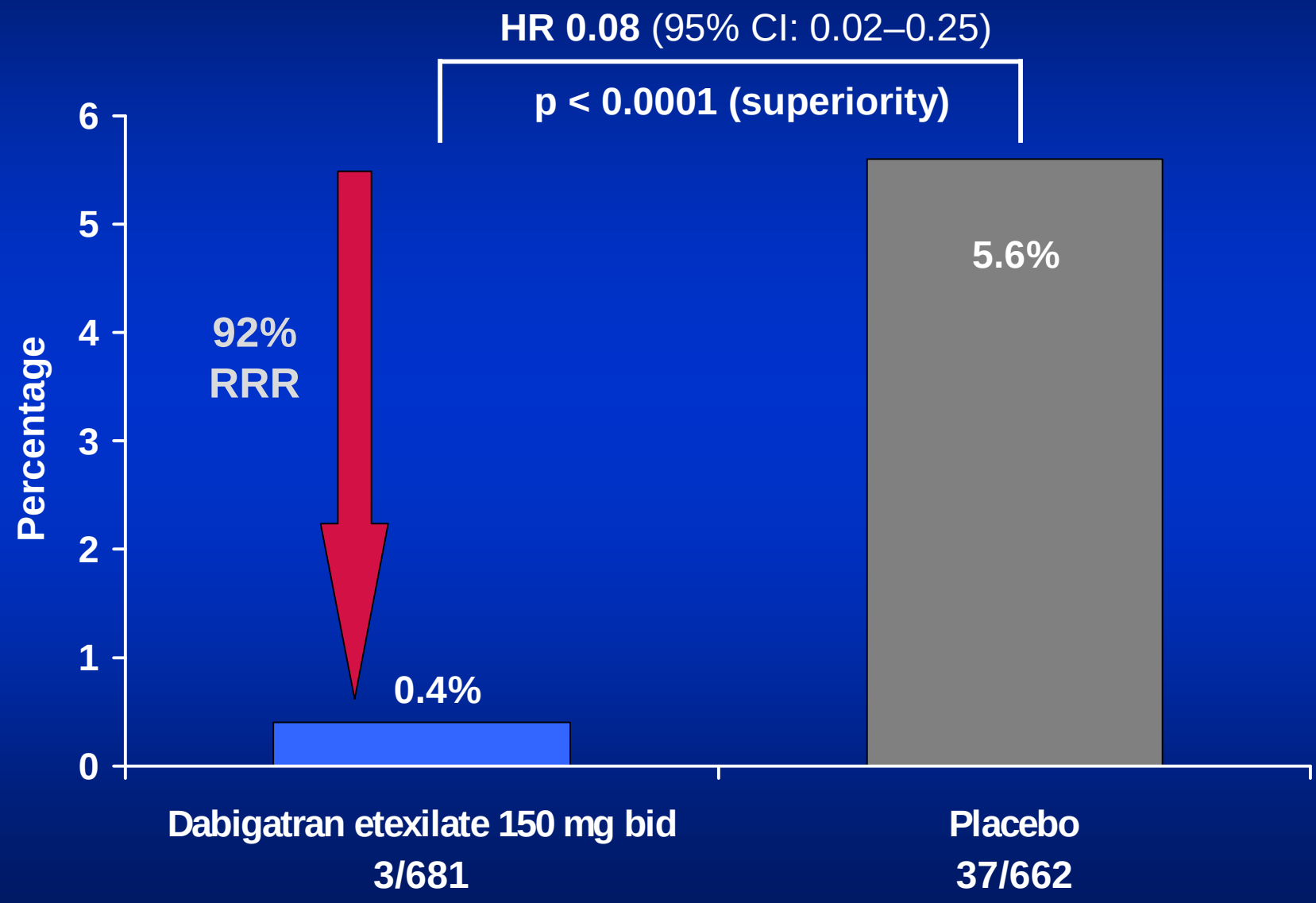
*p = 0.02; †p = 0.007; ‡p = 0.02.

RE-SONATE™ study design



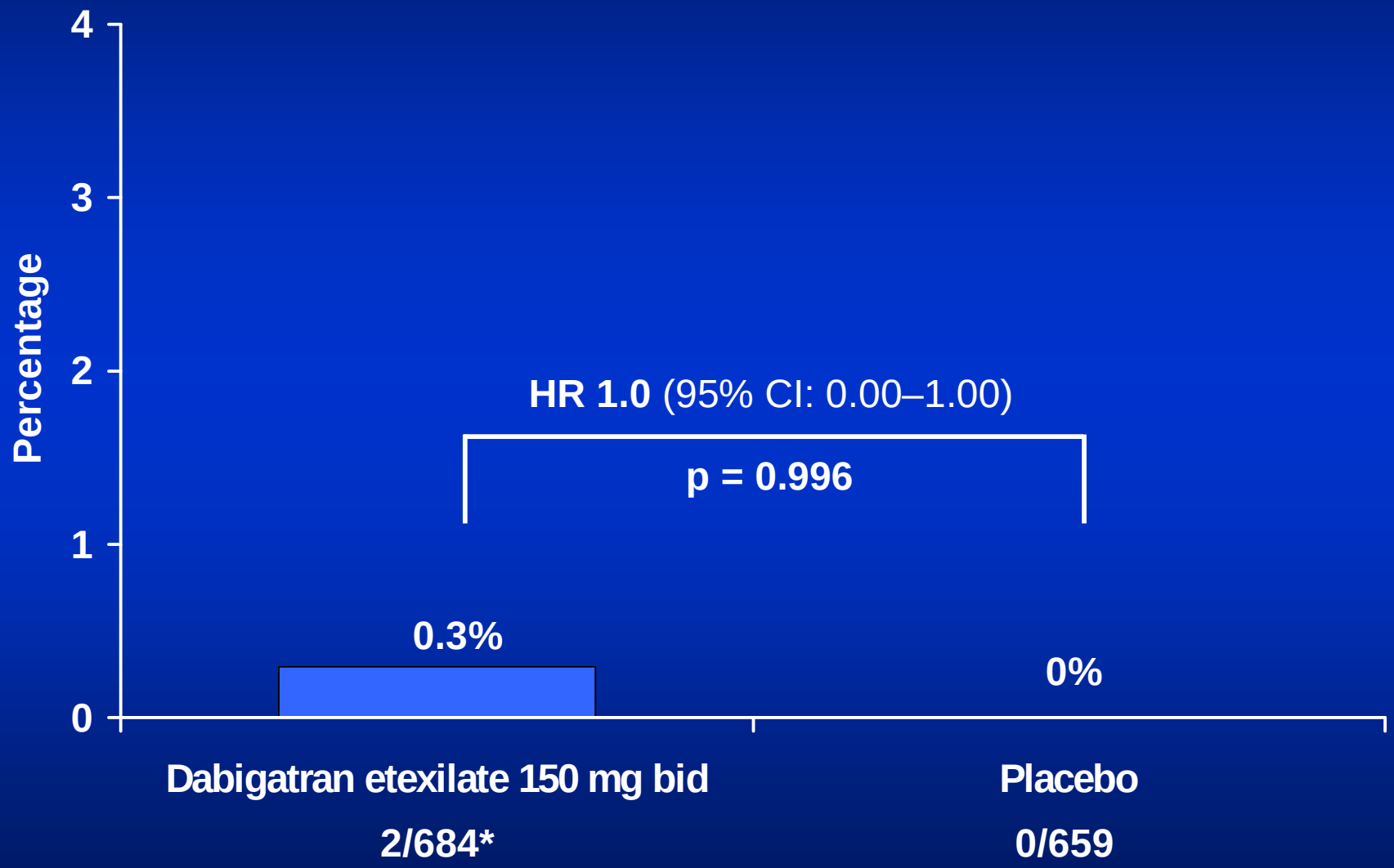
Schulman,J Thromb Haemost 2011;9 (suppl 2): O-MO- 037

Primary endpoint: symptomatic recurrent VTE



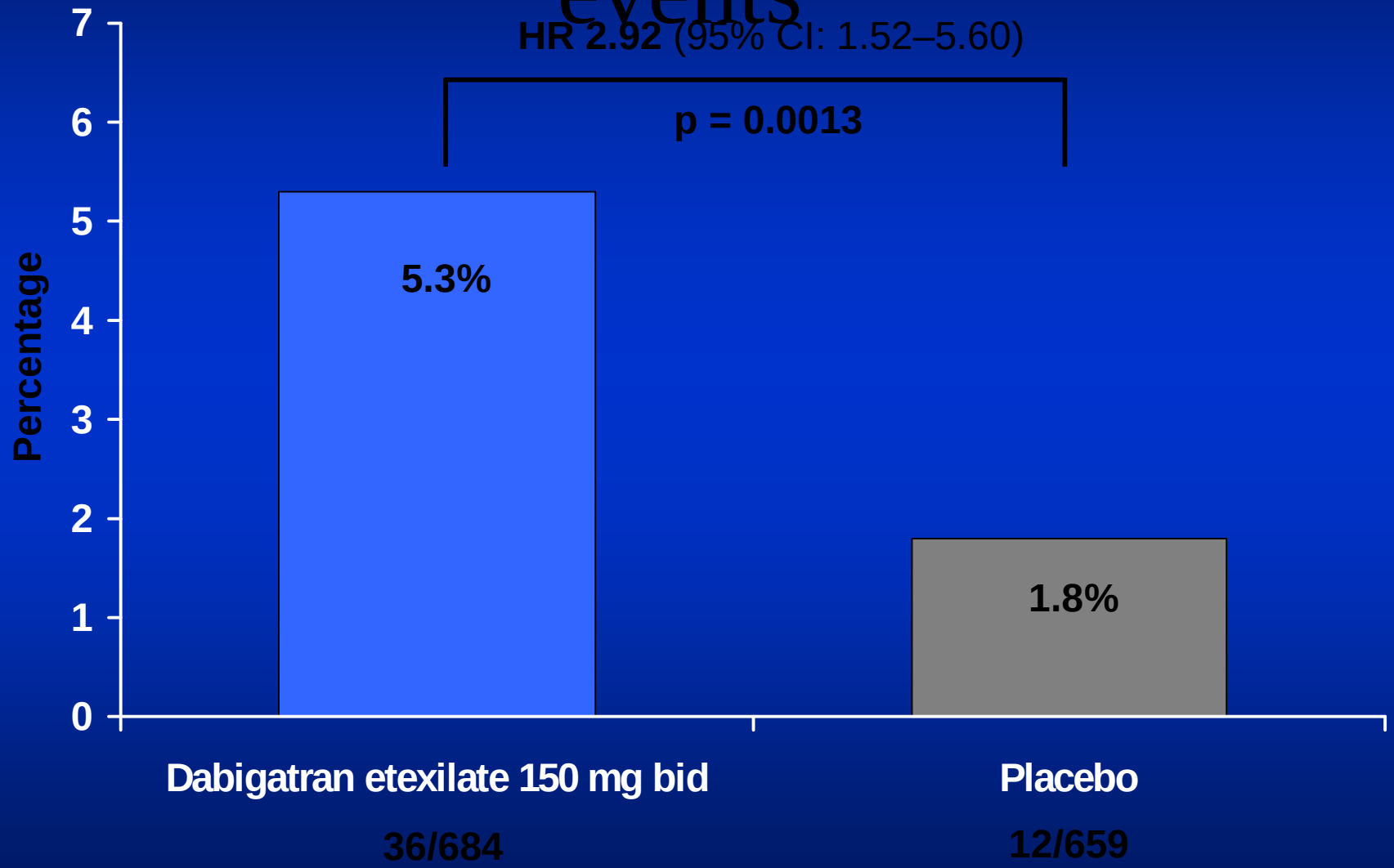
RRR, relative risk reduction.

Major bleeding



*Both MBEs were gastrointestinal with transfusions ≥ 2 units.

Clinically relevant bleeding events*



*Includes MBEs and other CRBEs.

Secondary bleeding endpoints

	Dabigatran n (%)	Placebo n (%)	HR (95% CI)
Treated	684 (100)	659 (100)	
Clinically relevant bleeding*	36 (5.3)	12 (1.8)	2.92 (1.52–5.60) p < 0.0013
Any bleeding	72 (10.5)	39 (5.9)	1.82 (1.23–2.68) p < 0.0027

*Includes major bleeding events and other clinically relevant bleeding events.

Confirmed cardiovascular events

	Dabigatran n (%)	Placebo n (%)
Full analysis set	684 (100)	659 (100)
Any cardiovascular event	3 (0.4)	2 (0.3)
NSTEMI	0	1 (0.2)
STEMI	1 (0.1)	0
Unstable angina	0	0
Transient ischaemic attack	2 (0.3)	0
Ischaemic stroke	0	1 (0.2)
Non-CNS systemic embolism	0	0

No difference in acute coronary syndrome events

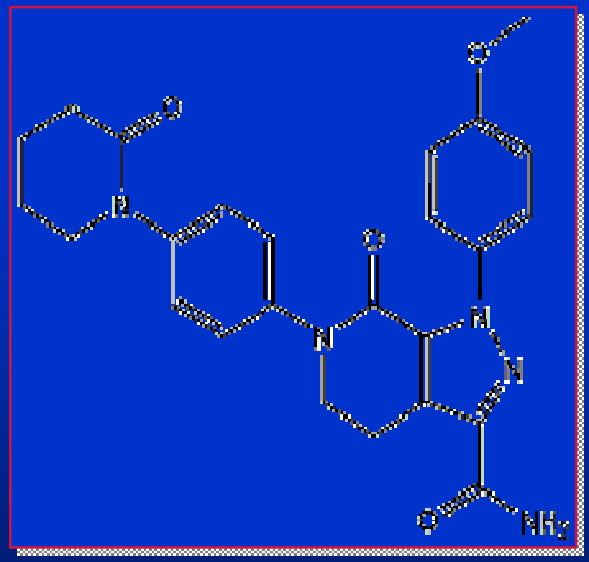
CNS, cenral nervous system; NSTEMI, non-ST-segment–elevation myocardial infarction; STEMI, ST-segment–elevation myocardial infarction.

Apixaban

- Small molecule
- Potent reversible inhibitor
  - Inhibits both prothrombinase-bound and free factor Xa
- Good oral bioavailability (50-85%)
- No food effects observed
- Multiple routes of elimination

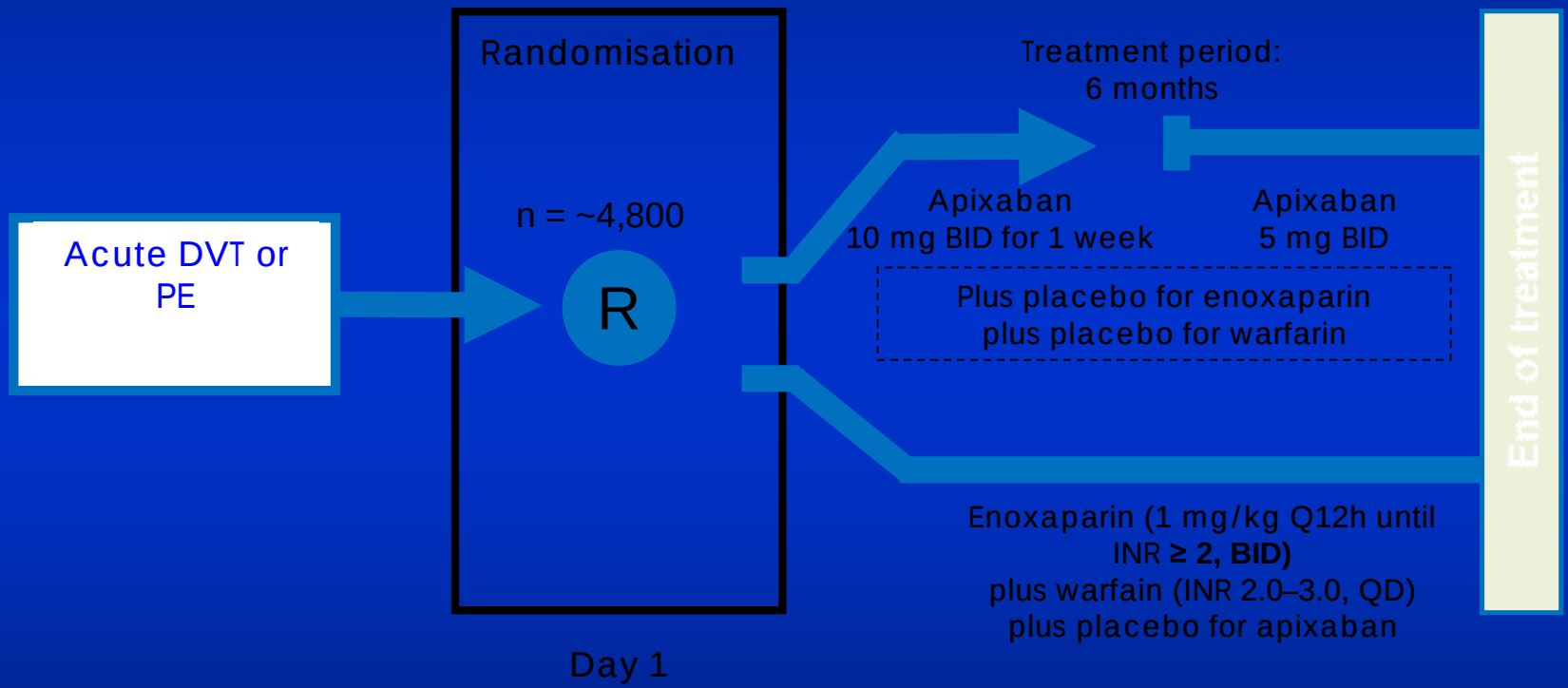
(25% renal)

- $T_{1/2}$ approximately 9 to 14 hours
- No monitoring



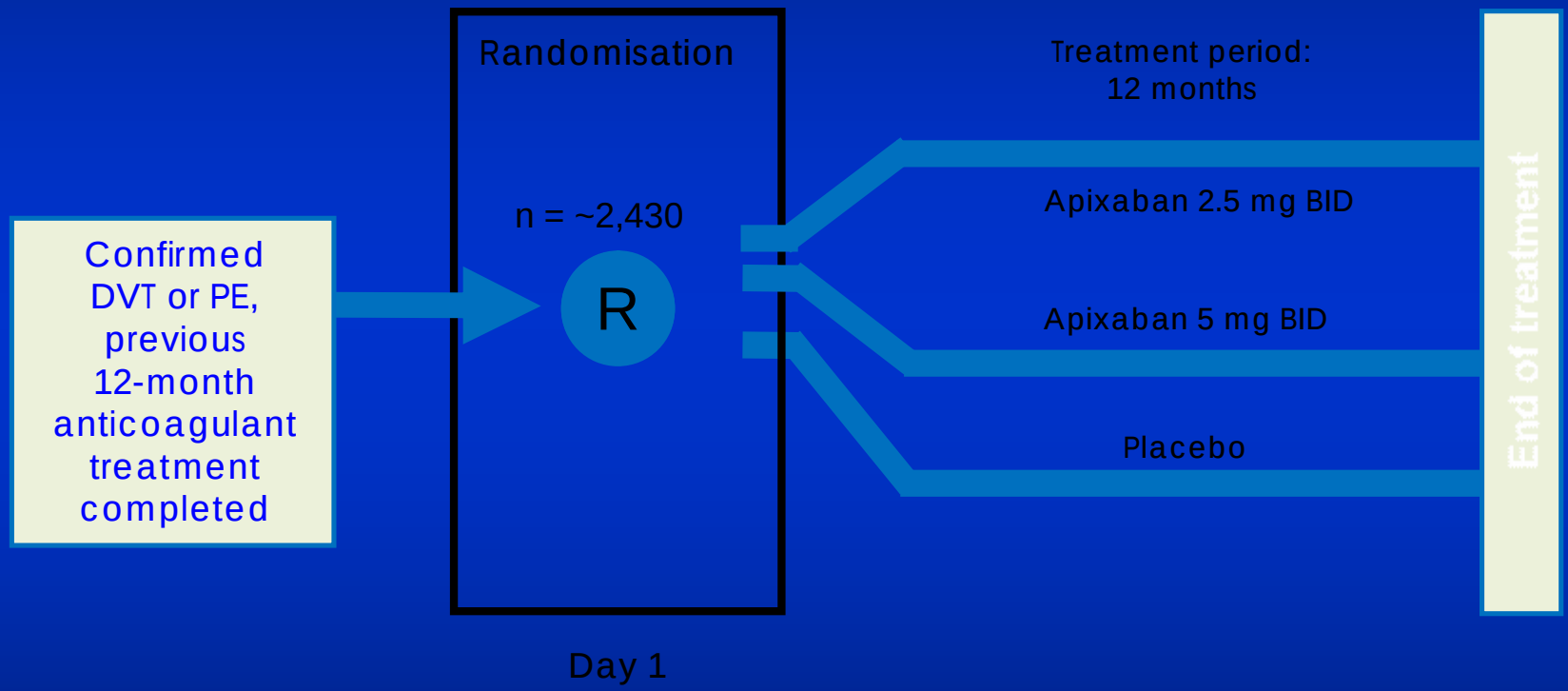
Gross, *Arterioscler Thromb Vasc Biol,* 2008

The AMPLIFY trial:



DVT, deep vein thrombosis; PE, pulmonary embolism; INR, international normalised ratio

The AMPLIFY-EXTENSION trial:



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ClinicalTrials.gov
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Comparative Investigation of Low Molecular Weight (LMW) Heparin/Edoxaban Tosylate (DU176b) Versus (LMW) Heparin/Warfarin in the Treatment of Symptomatic Deep-Vein Blood Clots and/or Lung Blood Clots. (The Edoxaban Hokusai-VTE Study).

This study is currently recruiting participants.
Verified by Daiichi Sankyo Inc., January 2011

First Received: September 25, 2009 Last Updated: January 11, 2011 History of Changes

Sponsor:	Daiichi Sankyo Inc.
Information provided by:	Daiichi Sankyo Inc.
ClinicalTrials.gov Identifier:	NCT00986154

VTE treatment
Phase III studies

AMPLIFY	**APIXABAN** **Phase III VTE treatment**
AMPLIFY EXTENSION	**APIXABAN** **Phase III VTE long-term secondary prevention**
HOKUSAI	**EDOXABAN** **Phase III VTE treatment**