NAO: quando, per quanto e per quale paziente

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Acronimi degli anticoagulanti orali

DOAC (Direct Oral AntiCoagulants)

NOAC *or* **NOA** (New Oral AntiCoagulants,
Non-VKA Oral AntiCoagulants),
nella variante Italiana: **NAO**

…ulteriore proposta, da evitare: **TSOAC** (Target-Specific
Oral AntiCoagulants)

Argomenti della mia relazione

- DOAC nel VTE: vantaggi/svantaggi *vs* VKA
- Efficacia e sicurezza
- Differenti schemi e posologie
- In tutti i pazienti con VTE? (il problema dell'APS)
- E nei pazienti con CTEPH?
- Quale farmaco, in quale paziente (How I treat)

Principi generali di terapia del VTE

- Trattare un episodio trombotico e le sue complicanze (embolizzazione)
- Tutti i farmaci anticoagulanti aumentano il rischio emorragico
- Obiettivo primario: beneficio clinico netto (trombosi *vs* emorragie)
- Altri obiettivi rilevanti:
  - Trattamento domiciliare, ove possibile
  - Accettabilità (semplicità del trattamento per il paziente nelle terapie a lungo termine)
  - Costi

Comparative PK/PD of DOAC

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	IIa (thrombin)	Xa	Xa	Xa
Hours to C_{max}	1-3	2-4	3-4	1-2
Half-life, hours	12-17	5-13	12	10-14
Renal Clearance, %	80	33*	27	50
Transporters	P-gp	P-gp	P-gp	P-gp
CYP Metabolism, %	None	32	<32	<4

CYP = cytochrome P450; P-gp = P-glycoprotein

33% renally cleared; 33% excreted unchanged in urine

Advantages of DOAC

- Rapid onset of action > No need for bridging
- Specific coagulation enzyme target > Low risk of off-target adverse effects
- Low potential for food interactions > No dietary precautions
- Low potential for drug interactions > Few drug restrictions
- **Predictable anticoagulant effect > NO need for routine coagulation monitoring**

Efficacy and Safety of DOACs for the Treatment of VTE: Results From Clinical Trials

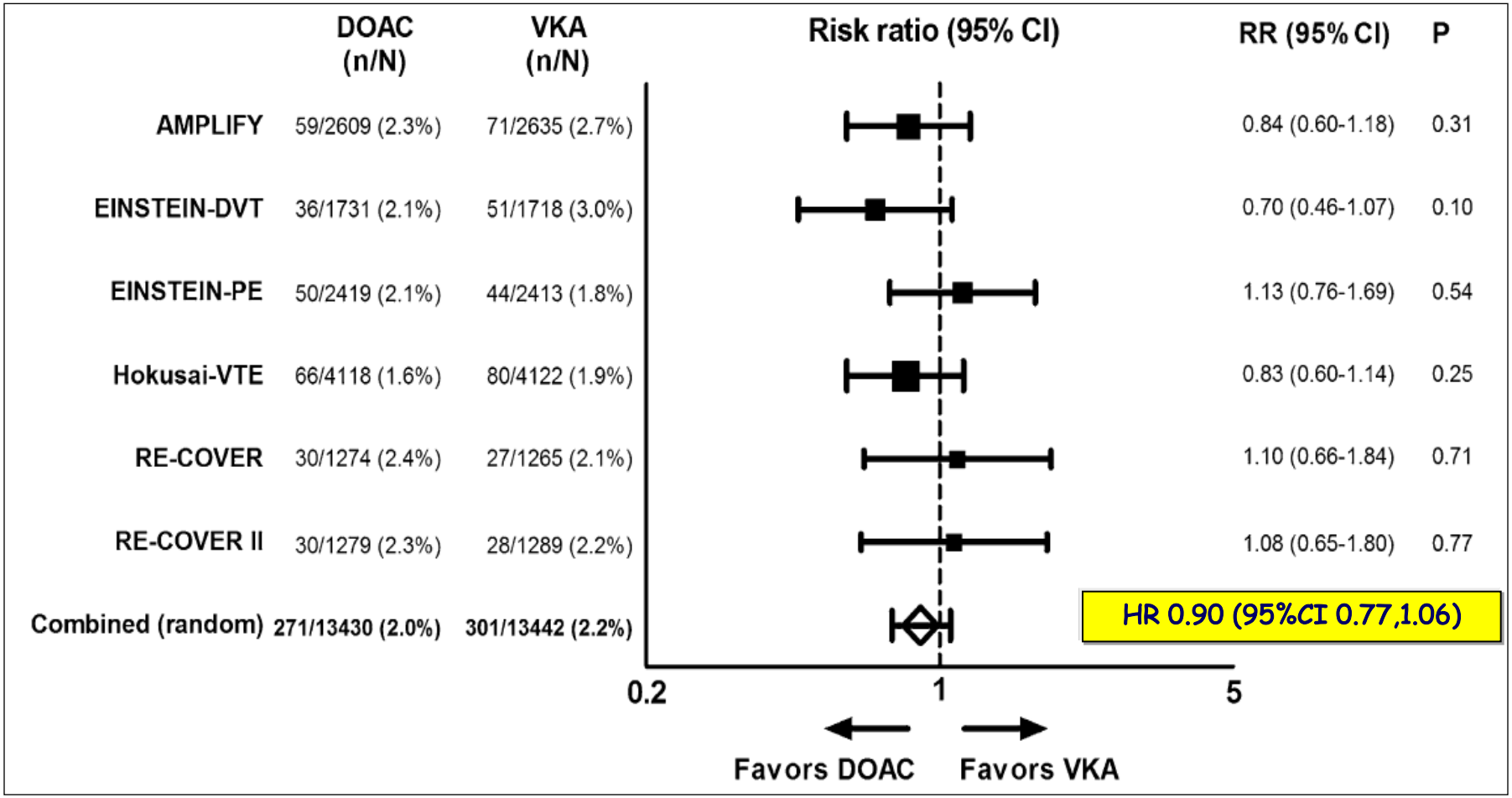
Trial Name (Ref. #)	Design	Treatments	Duration (months)	Patients	TTR (%)	Efficacy Outcome	Safety Outcome
RE-COVER, 2009 (37)	DB	Enoxa/dabigatran (150 mg bid) Enoxa/warfarin	6	2,539 acute VTE	60	Recurrent VTE or VTE-related death: 2.4% enoxa/dabigatran, 2.1% enoxa/warfarin	Major/clinically relevant nonmajor bleeding: 5.6% dabigatran, 8.8% warfarin
RE-COVER II, 2011 (38)	DB	Enoxa/dabigatran (150 mg bid) Enoxa/warfarin	6	2,539 acute VTE	57	Recurrent VTE or fatal PE: 2.3% dabigatran, 2.2% warfarin	Major/clinically relevant nonmajor bleeding: 5.0% dabigatran, 7.9% warfarin
EINSTEIN-DVT, 2010 (39)	Open-label	Rivaroxaban (15 mg bid for 3 weeks, then 20 mg od) Enoxaparin/VKA	3, 6, or 12	3,449 acute DVT	58	Recurrent VTE: 2.1% rivaroxaban, 3.0% enoxa/warfarin	Major/clinically relevant nonmajor bleeding: 8.1% rivaroxaban, 8.1% enoxa/warfarin
EINSTEIN-PE, 2012 (40)	Open-label	Rivaroxaban (15 mg bid for 3 weeks, then 20 mg od) Enoxa/VKA	3, 6, or 12	4832 acute PE	63	Recurrent VTE: 2.1% rivaroxaban, 1.8% enoxa/VKA	Major/clinically relevant nonmajor bleeding: 10.3% rivaroxaban, 11.4% enoxa/VKA
AMPLIFY, 2013 (41)	DB	Apixaban (10 mg bid for 7 days, then 5 mg bid) Enoxa/warfarin	6	5,395 acute VTE	61	Recurrent VTE or VTE-related death: 2.3% apixaban, 2.7% enoxa/VKA	Major bleeding: 0.6% apixaban, 1.8% enoxa/warfarin
Hokusai, 2013 (42)	DB	LMWH/edoxaban (60 mg od or 30 mg od) UFH or LMWH/warfarin	≤12	8,292 acute VTE	63	Recurrent VTE: 3.2% enoxa/edoxaban, 3.5% enoxa/warfarin	Major/clinically relevant nonmajor bleeding: 8.5% enoxa/edoxaban, 10.3% enoxa/warfarin

Over 30,000 patients, if EXT studies are included

Becattini C, JACC 2016

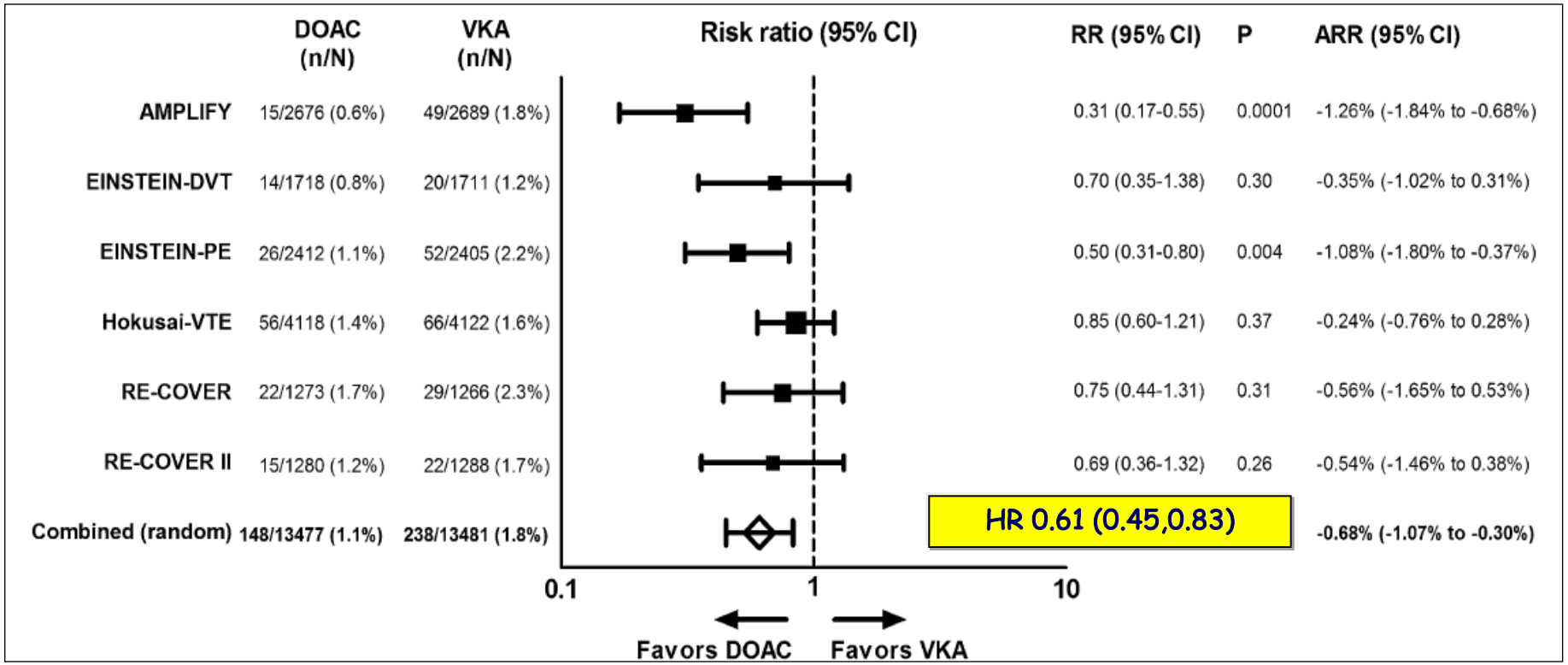
VTE recurrence

DOACs vs VKA



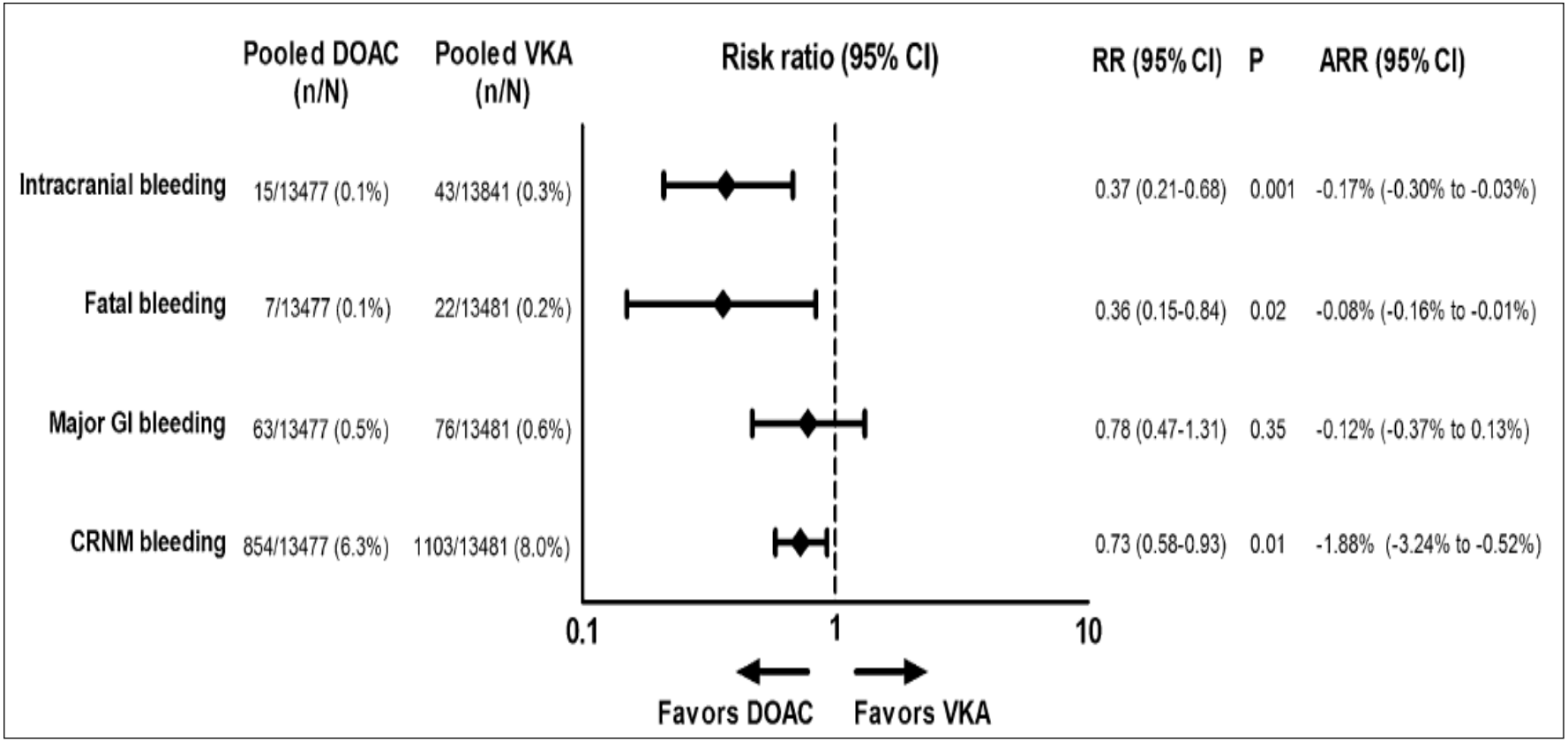
Van Es et al. Blood 2014

Major Bleeding



Van Es et al. Blood 2014

Other End Points



Van Es et al. Blood 2014

DOACs for Treatment of PE

Study	Primary endpoint	Event, % (n/N)		HR*/RR† (95%CI)
		DOAC	Warfarin	
RECOVER I & II (index PE)	**VTE/VTE-related death**	2.9 **%** **(23/795)**	3.1 **%** **(25/807)**	0.93* **(0.53–1.64)**
EINSTEIN-PE	**Recurrent VTE**	2.1% **(50/2419)**	1.8 % **(44/2413)**	1.12* **(0.75–1.68)**
AMPLIFY (Index PE)	**Recurrent VTE / VTE-related death**	2.3 % **(21/900)**	2.6 % **(23/886)**	0.90† **(0.50–1.61)**
HOKUSAI (Index PE)	**Recurrent VTE**	2.8 % **(47/1650)**	3.9 % **(65/1669)**	0.73* **(0.50–1.06)**
HOKUSAI (Severe PE) **(ProBNP ≥500 pg/mL)**	**Recurrent VTE**	3.0 % **(14/465)**	5.9 % **(30/507)**	0.50* **(0.26–0.94)**
HOKUSAI (Severe PE) **(RV/LV ≥0.9)**	**Recurrent VTE**	2.7 % **(11/414)**	4.7 % **(20/427)**	0.57* **(0.27-1.17)**
HOKUSAI (Severe PE) **(ProBNP ≥500 pg/mL and RV/LV ≥0.9)**	**Recurrent VTE**	2.1 % **4/192**	4.8 % **10/207**	0.44* **(0.14-1.36)**

JAMA Clinical Guidelines Synopsis

Antithrombotic Therapy for Venous Thromboembolism

Christopher D. Jackson, MD; Adam S. Cifu, MD; Desirée C. Burroughs-Ray, MD, MPH

Published Online: May 16, 2022

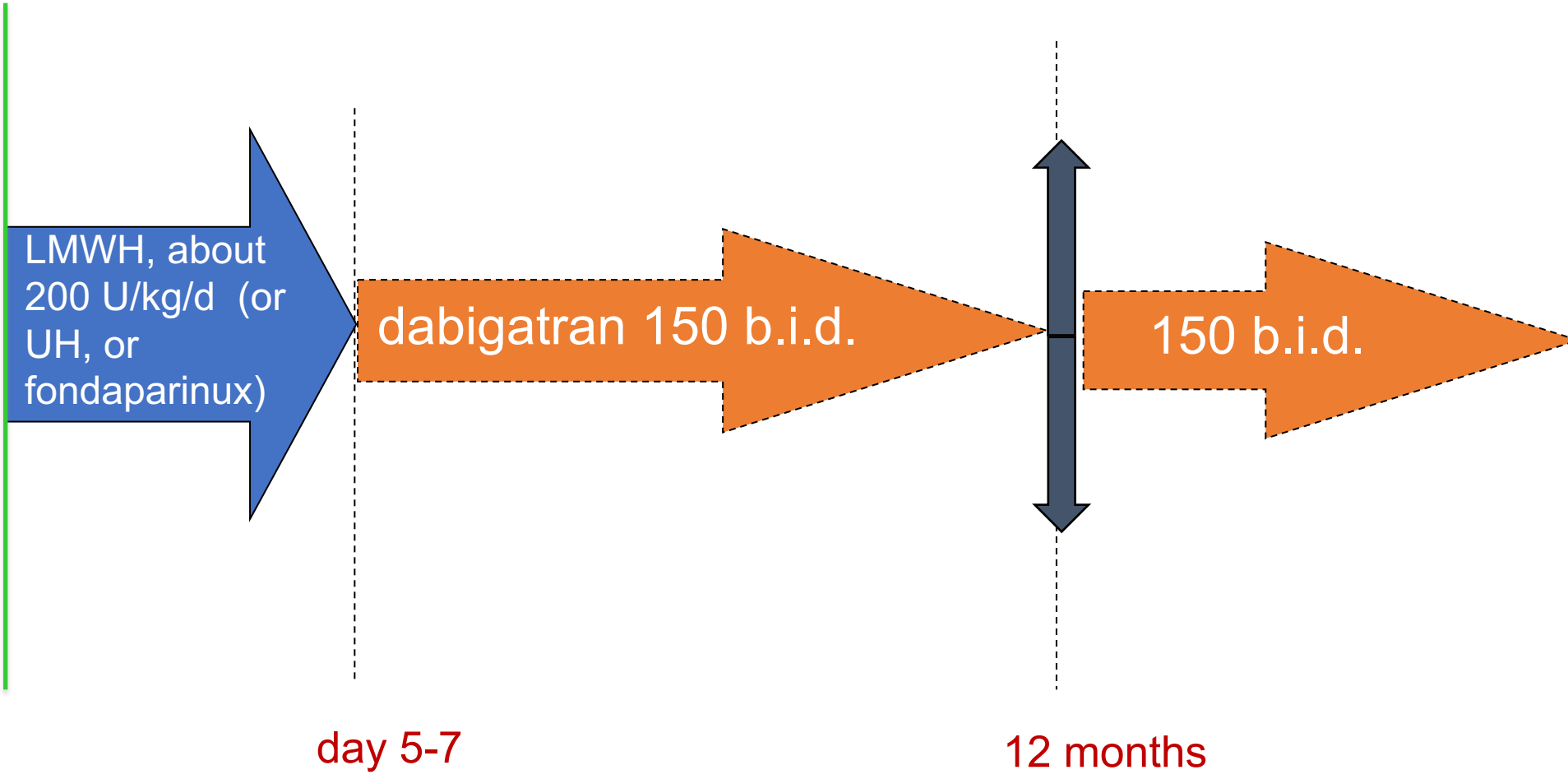
MAJOR RECOMMENDATIONS

- DOACs should be used to treat acute VTE for the 3-month treatment phase (strong recommendation, moderate evidence)
- Oral Xa inhibitors should be used to treat acute VTE in a patient with cancer for both the initial and extended treatment phases (strong recommendation, moderate evidence)
- VTE: treatment with full dose DOACs for 3 months (strong recommendation, moderate evidence) followed by reduced-dose DOACs for extended therapy if indicated (weak recommendation, moderate evidence)

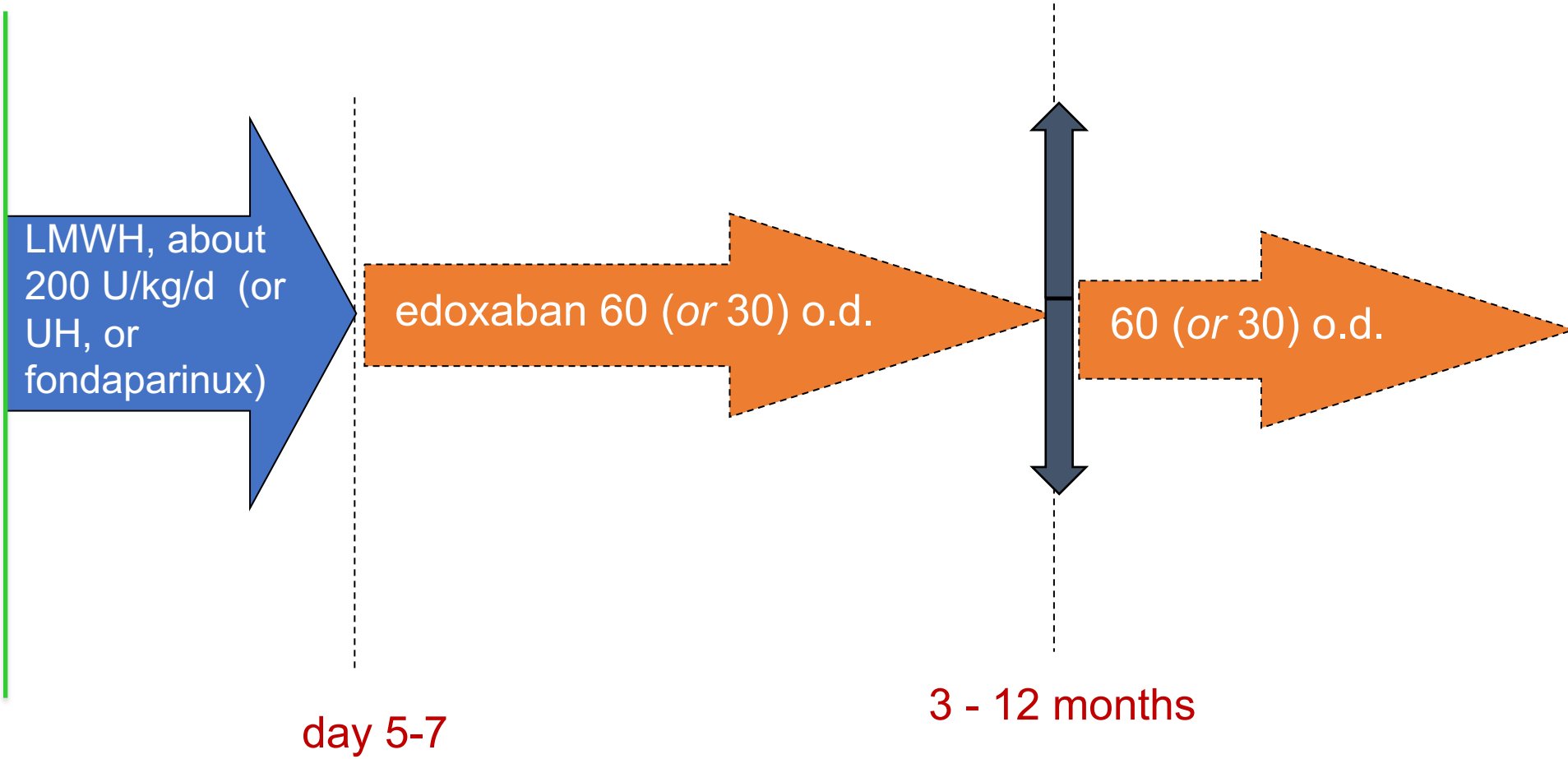
Heparin lead-in approach

dabigatran, edoxaban

Dabigatran


LMWH, about 200 U/kg/d (or UH, or fondaparinux)
dabigatran 150 b.i.d.
150 b.i.d.
day 5-7
12 months

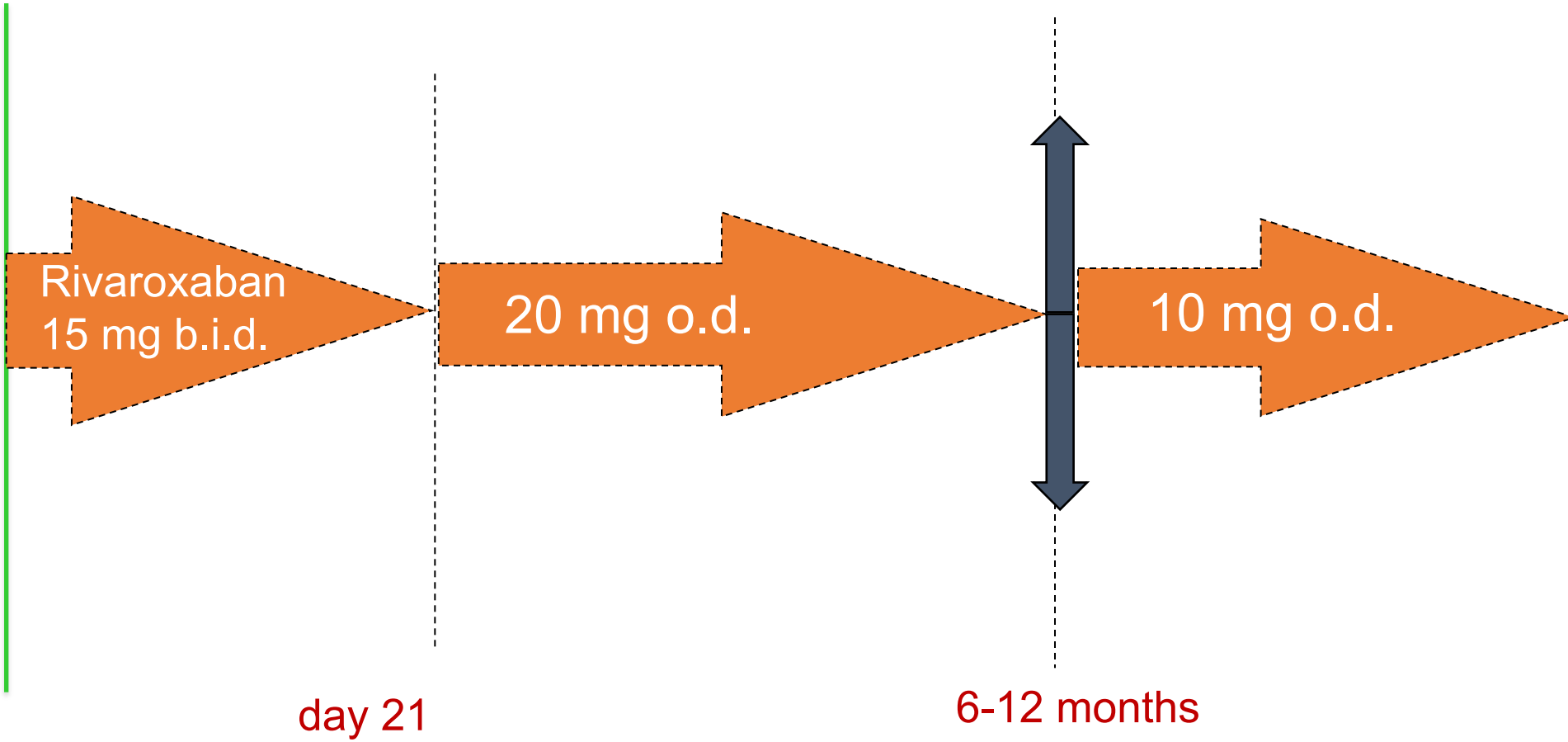
Edoxaban


LMWH, about 200 U/kg/d (or UH, or fondaparinux)
edoxaban 60 (*or* 30) o.d.
60 (*or* 30) o.d.
day 5-7
3 - 12 months

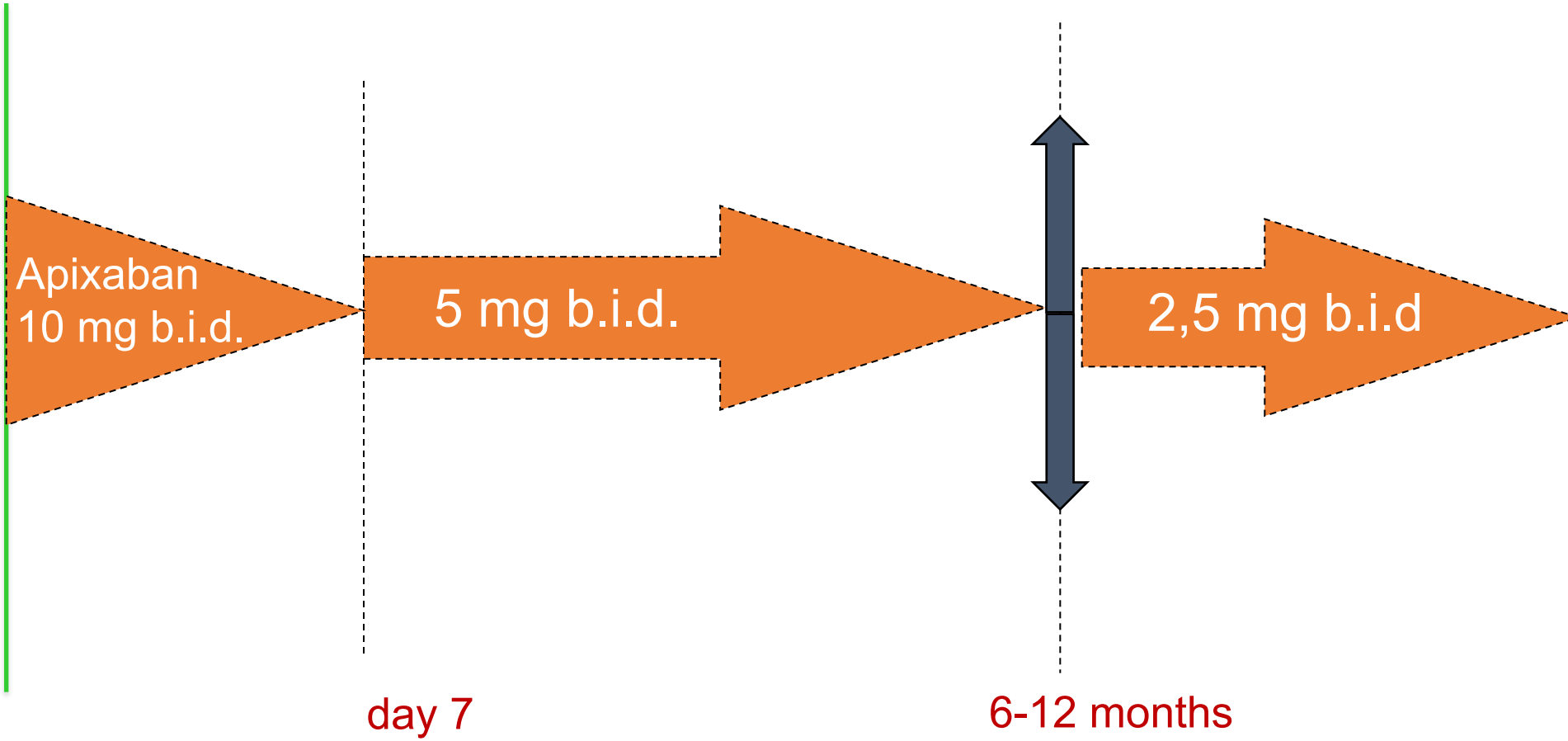
Single drug approach

rivaroxaban, apixaban

Rivaroxaban



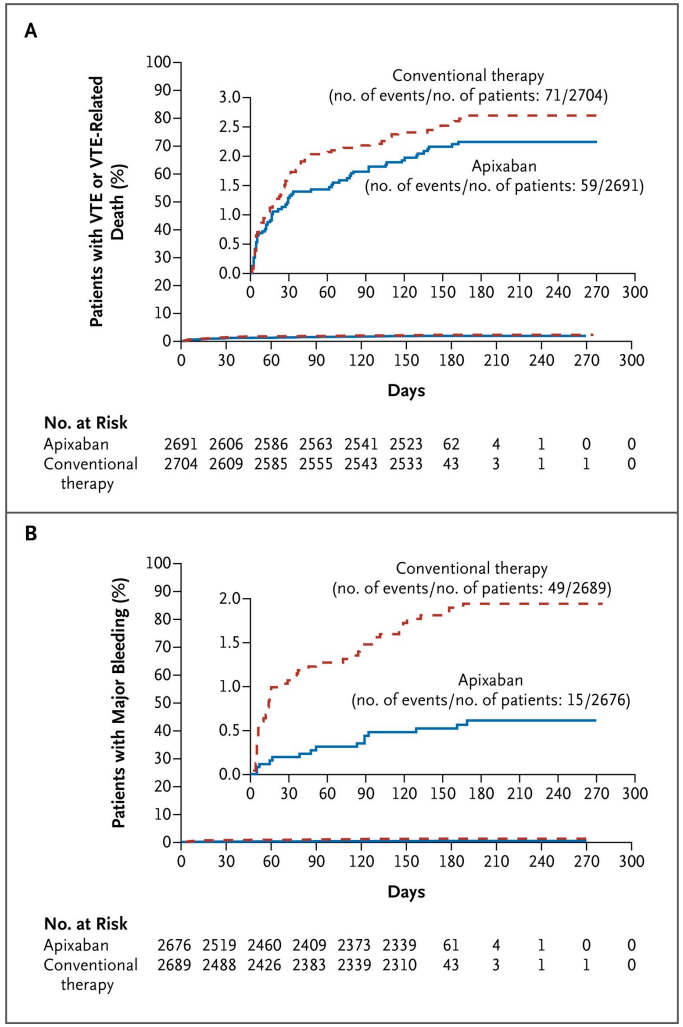
Apixaban



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 29, 2013 VOL. 369 NO. 9

Oral Apixaban for the Treatment of Acute Venous Thromboembolism

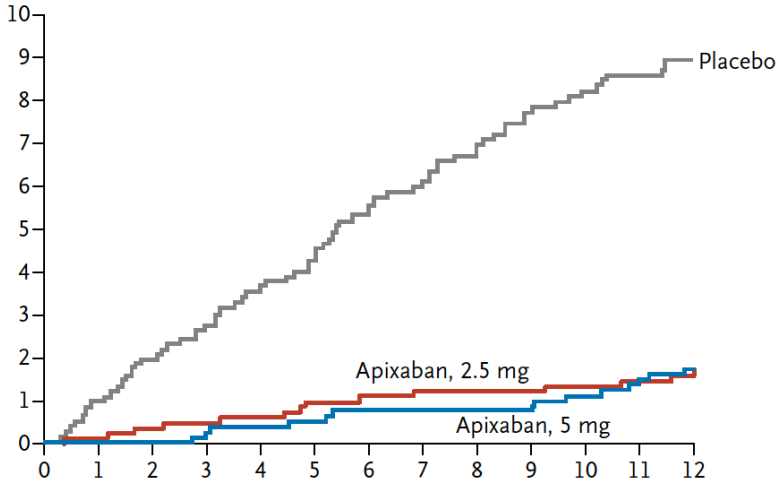


Agnelli et al, N Engl J Med 2013;369:799-808.

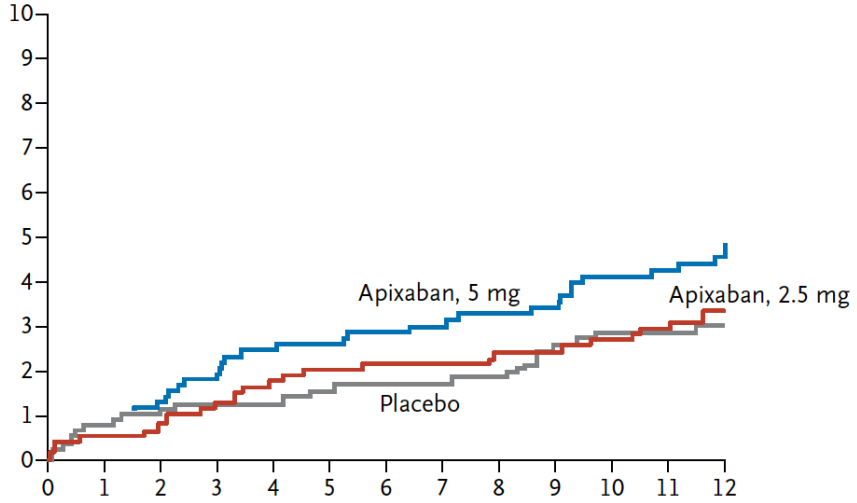
ORIGINAL ARTICLE

Apixaban for Extended Treatment of Venous Thromboembolism

Symptomatic Recurrent VTE
Or VTE-RelatedDeath



Major or Clinically Relevant
Non major Bleeding



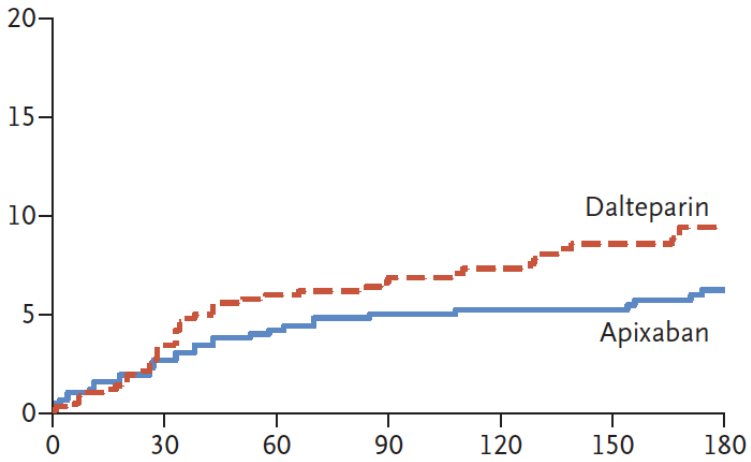
Agnelli et al, N Engl J Med 2012

The NEW ENGLAND JOURNAL of MEDICINE

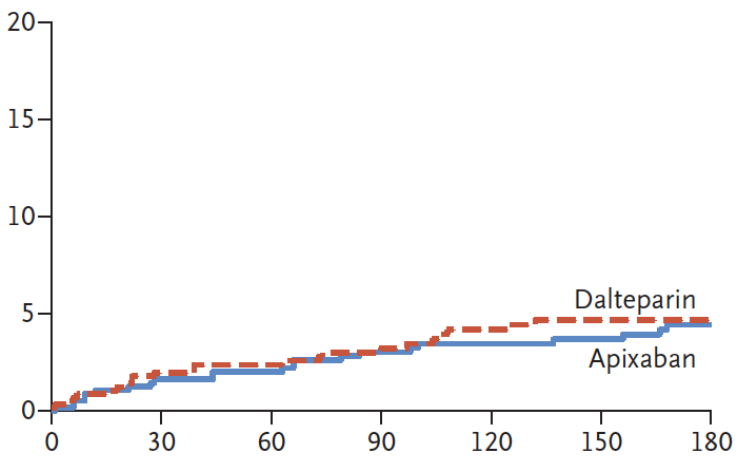
ORIGINAL ARTICLE

Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer

Recurrent VTE



MajorBleeding



Agnelli G at el, N Engl J Med 2020;382:1599-607

CLINICAL TRIALS AND OBSERVATIONS

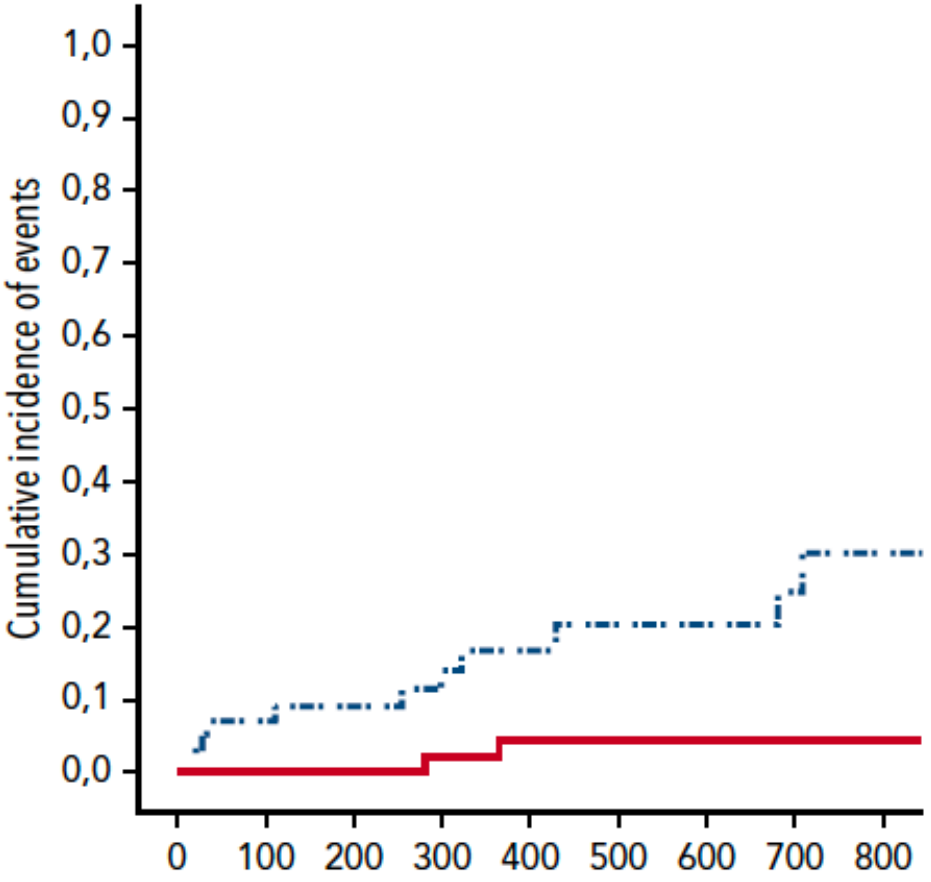
Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome

Pengo V et al, Blood 2018;132(13):1365-1371

- Efficacy and safety of rivaroxaban compared with warfarin in high-risk patients with thrombotic APS
- Positive for all 3 aPL tests in the last blood sampling (triple positivity), and had a history of thrombosis (objectively proven arterial, venous, and/or biopsy proven microthrombosis)
- The use of rivaroxaban in high-risk patients with APS was associated with an increased rate of events compared with warfarin, thus showing no benefit and excess risk

Cumulative incidence of events (death, thromboembolic events, and major bleeding)

Pengo V et al, Blood. 2018;132:1365-1371



Number at risk									
Warfarin	61	58	55	48	41	37	34	30	24
Rivaroxaban	59	50	45	38	31	26	26	20	15

Adverse events with Rivaroxaban

Patient	Sex	Age, y	BMI, kg/m²	Arm	History of events	Event	Description	Days from randomization
1	F	44	49.6	R	A+V+O	Bleeding	Metrorrhagia causing acute Hb fall	21
2	M	39	25.2	R	V	Thrombosis	Acute myocardial infarction	709
3	F	47	35.6	R	A+O	Bleeding	Rectorrhagia requiring transfusion	429
4	M	59	24.5	R	A+O	Thrombosis	Ischemic Stroke	322
5	F	35	32.8	R	A	Thrombosis	Ischemic Stroke	36
6	F	57	26.1	R	V	Thrombosis	Ischemic Stroke	299
7	F	55	24.7	R	A	Thrombosis	Acute myocardial infarction	253
8	M	52	19.8	R	A	Bleeding	Gastrointestinal bleeding causing acute Hb fall	681
9	F	58	24.2	R	A+V	Thrombosis	Ischemic Stroke	110
10	M	47	29.6	R	V	Thrombosis	Acute myocardial infarction	20
11	F	43	19.1	R	V	Bleeding	Hb fall	28
12	F	51	20.5	W	A+V	Bleeding	Provoked Hb fall	365
13	F	36	21.3	W	A+V	Bleeding	Metrorrhagia requiring intervention	280
Additional end points considered in ITT analysis								
14	M	47	22.5	R	V	Thrombosis	Bilateral DVT in the lower limbs	175
15	M	55	27.4	R	A	Death	Cardiovascular death	475

Use of direct oral anticoagulants in Chronic ThromboEmbolic Pulmonary Hypertension (CTEPH): a systematic review

Sheldom R et al, J Thromb Thrombolysis *2022;*53:51-57

- We systematically searched MEDLINE and Google Scholar databases from January 2010 to January 2021 for studies of DOACs in CTEPH
- Three observational studies, 2 abstracts and one case series met our inclusion criteria
- Similar or even less rates of major bleeding in patients receiving DOACs compared to VKA, but there were concerns about the possibility of increased risk of VTE recurrence

ORIGINAL ARTICLE

A multicenter study of anticoagulation in operable chronic thromboembolic pulmonary hypertension

Bunclark K et al, J Thromb Haemost 2020;18(1):114-122

- Retrospective analysis on 1,000 consecutive CTEPH patients undergoing PEA between 2007 and 2018
- 794 VKA, 206 DOACs (155 rivaroxaban)
- Post-PEA functional and hemodynamic outcomes appear unaffected by anticoagulant choice
- Bleeding events were similar, but recurrent VTE rates significantly higher in those receiving DOACs
- Recurrences in DOAC: n=10 (4 in subtherapeutic doses)

ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

BRIEF COMMUNICATION

Oral anticoagulants (NOAC and VKA) in chronic thromboembolic pulmonary hypertension

Marc Humbert, MD, PhD,[a] Gérald Simonneau, MD,[a] David Pittrow, MD, PhD,[b] Marion Delcroix, MD, PhD,[c] Joanna Pepke-Zaba, PhD, FRCP,[d] David Langleben, MD,[e] Lisa M. Mielniczuk, MD,[f] Pilar Escribano Subias, MD, PhD,[g] Repke J. Snijder, MD,[h] Joan A. Barberà, MD, PhD,[i] Jens Klotsche, MD,[j] Christian Meier, MD, PhD,[k] and Marius M. Hoeper, MD, PhD[l]

2022

- Prospective, uncontrolled, non-interventional cohort study in patients with pulmonary hypertension treated with riociguat
- VKA n = 683 ; NOAC n = 198 (164 rivaroxaban)
- Exposure-adjusted hemorrhagic event rates were similar in the two groups, while exposure-adjusted embolic and/or thrombotic event rates were higher in the NOAC group, although the numbers of events were small

“How I treat” VTE

- Apixaban (10x2 > 5x2 > 2,5x2)
- In alternativa: rivaroxaban (15x2 > 20x1 > 10x1)
- < 60 kg: fondaparinux (5,0 mg x 7 gg) > edoxaban (30x1)
- 30 < CrCl < 50: LMWH x 7 gg > edoxaban (30x1)
- CrCl < 30: LMWH dosi 50% + edoxaban 30x1 o VKA
- APS con “tripla positività”: fondaparinux + VKA
- CTEPH: apixaban o VKA

È men male l'agitarsi nel dubbio che il riposar nell'errore.

Alessandro Manzoni,
Storia della colonna infame, 1840