Cancer-Associated Thrombosis (CAT)

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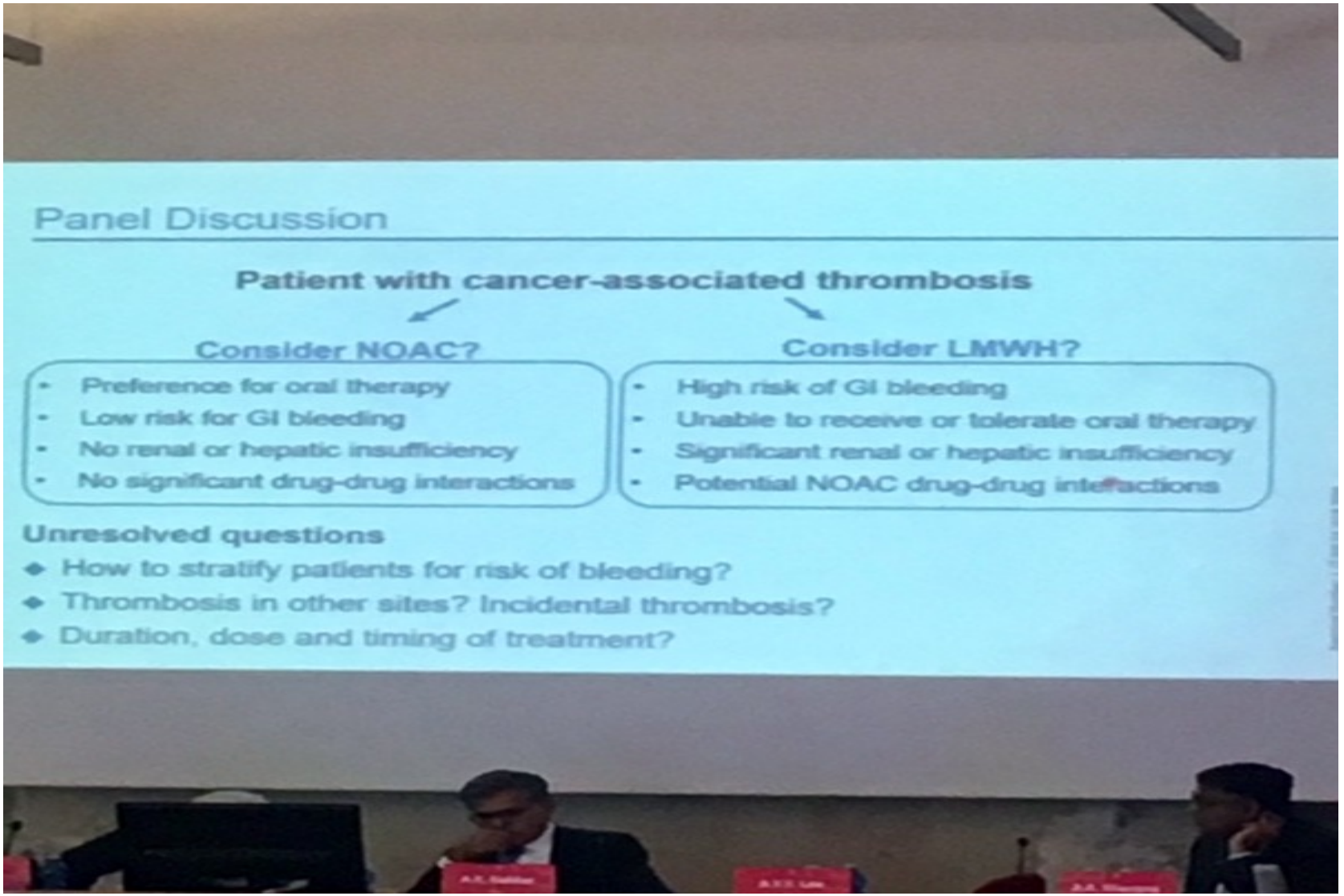
BERGAMO 2018 Thrombosis Issues in cancer



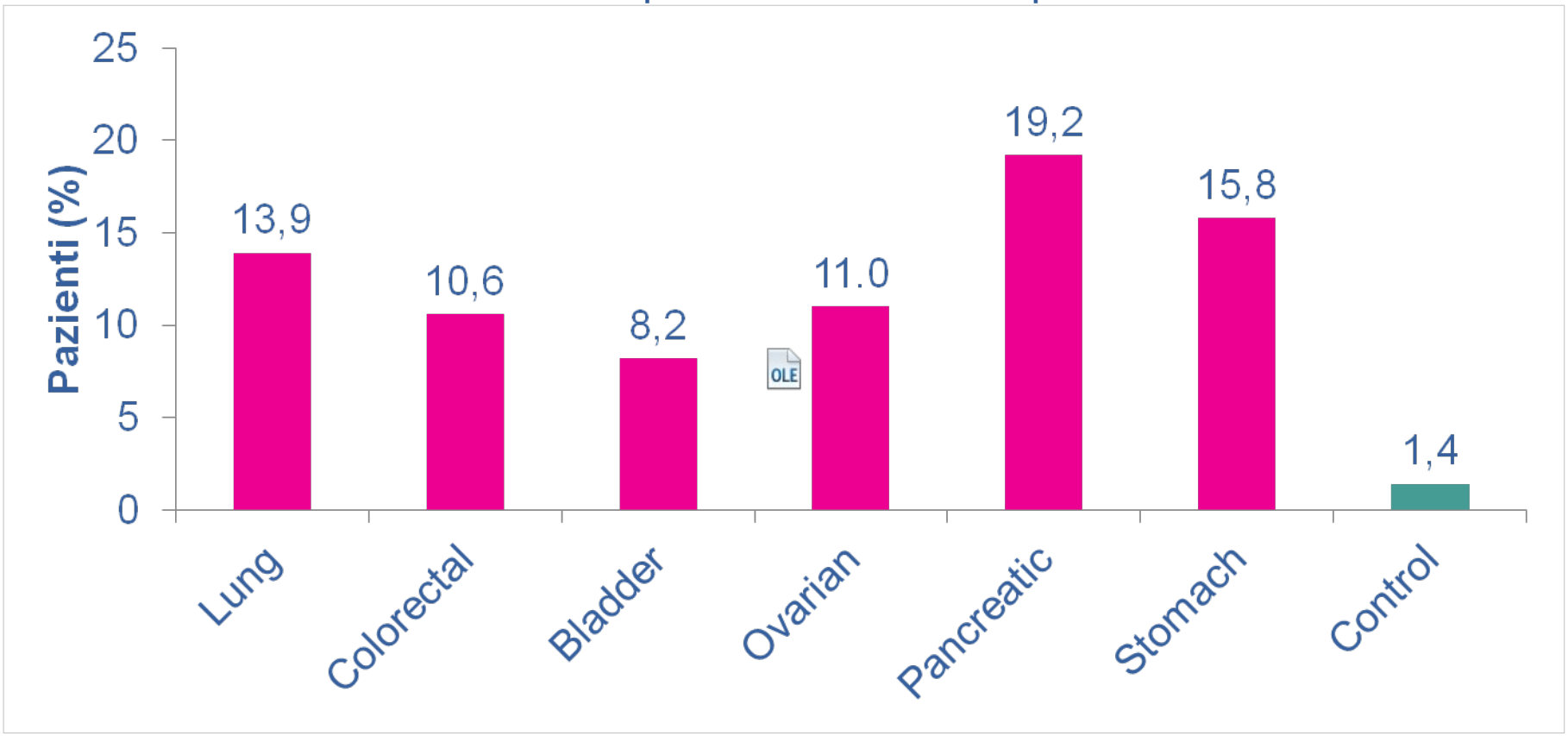
Cancer-associated Thrombosis

- Risk for VTE increased up to 4-7 fold in cancer[1]
  - 10-20% patients with cancer develop symptomatic VTE
  - 20% of all patients diagnosed with VTE have active cancer
- "Idiopathic" VTE
  - 2-4 fold increased risk of cancer diagnosis within next 12 months
- Cancer patients with VTE have shorter life expectancy
  - VTE is second leading cause of death after cancer itself
  - More likely advanced/disseminated malignancy at diagnosis than in patients without VTE
  - 3-fold lower survival than in cancer patients without VTE

[1] Barsam SJ, Patel R, Arya R. B J Haem 2013;161:764-777; [2]Laporte S et al Circulation 2008;117:1711-1716

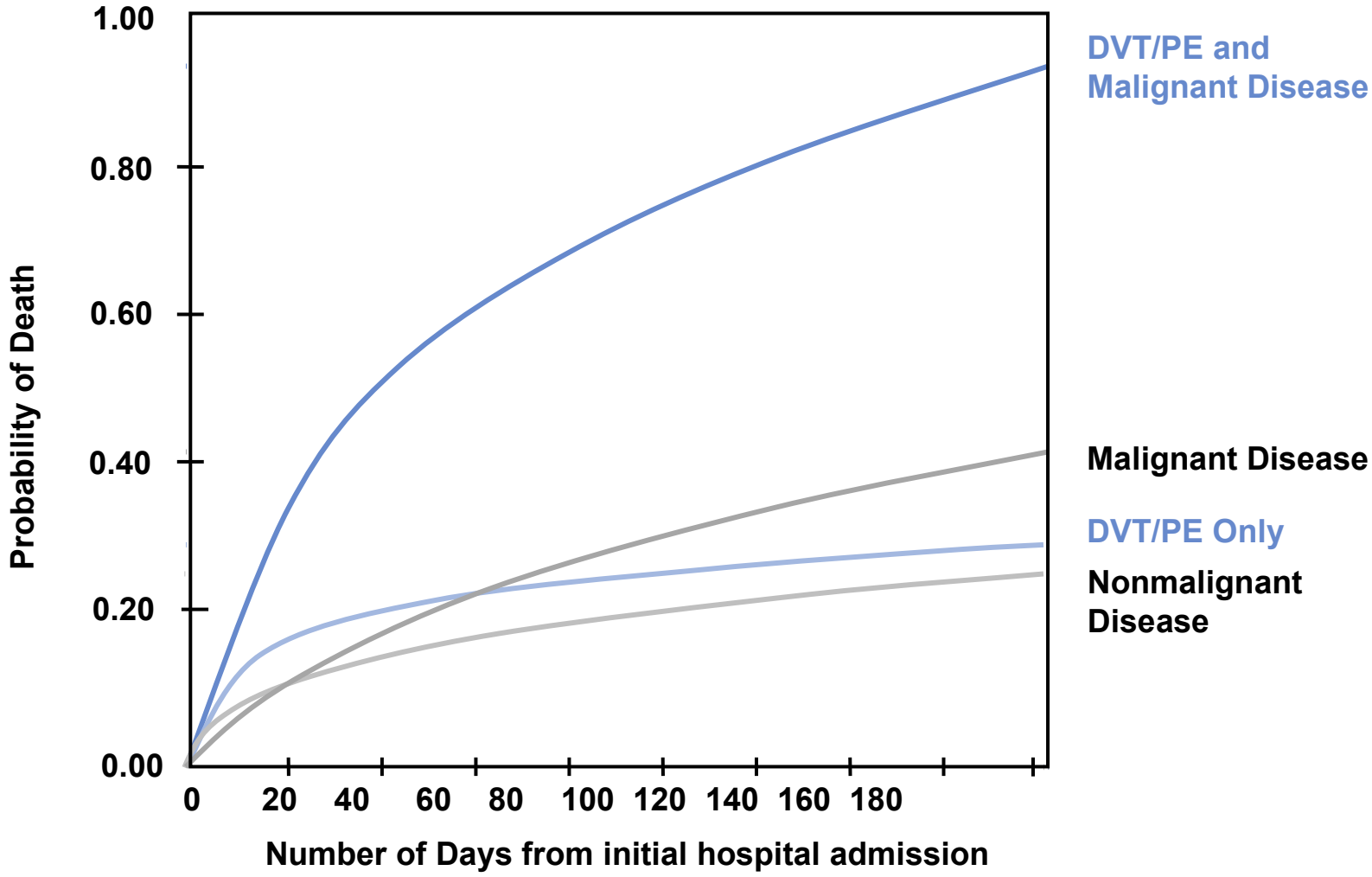
INCIDENZA

Incidenza di TEV a seconda del tipo di cancro in pazienti ambulatoriale sottoposti a chemioterapia (n=17,284)



Khorana AA, et al, Cancer 2013;119:648–55.

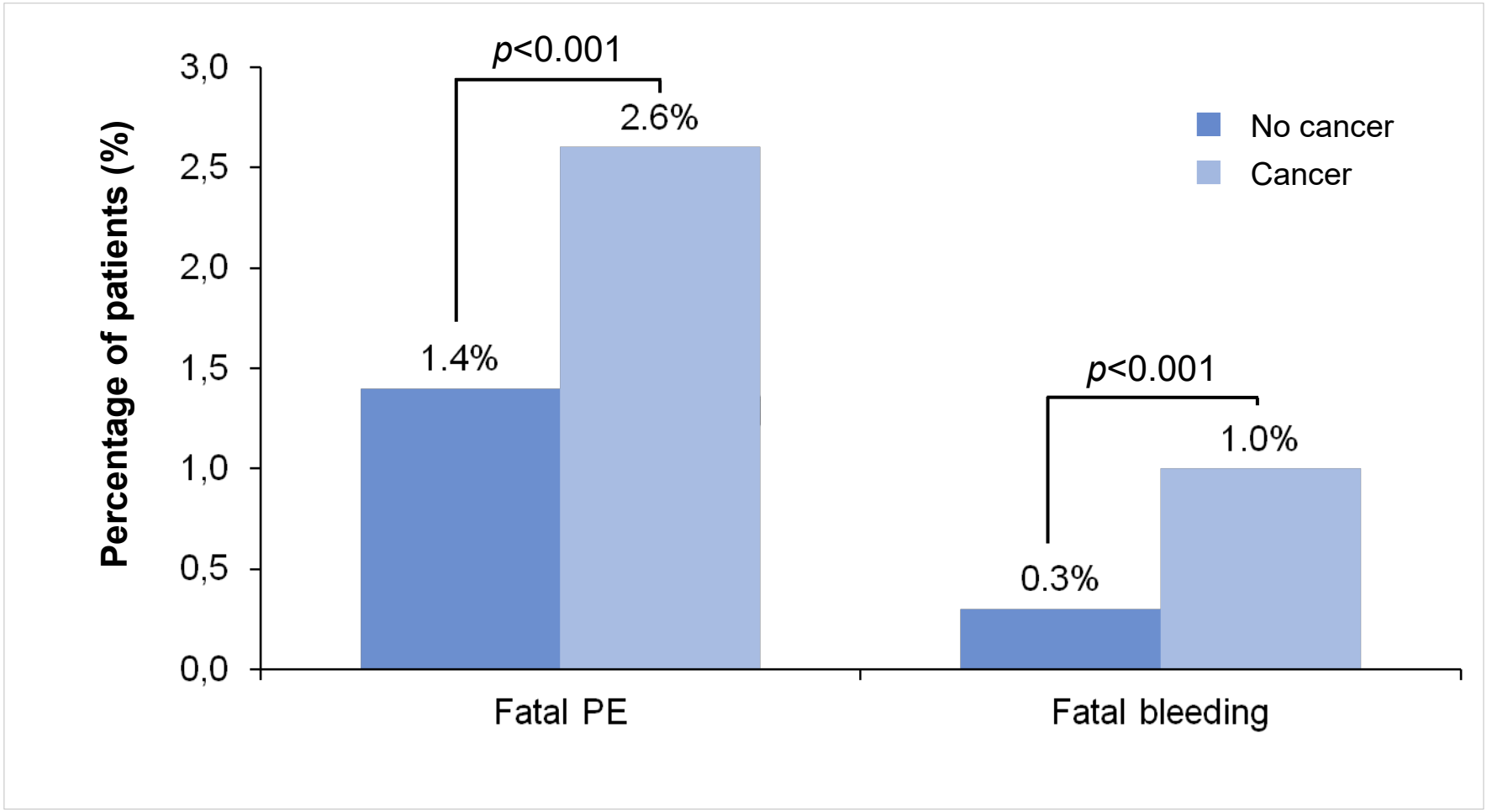
Thrombosis and Cancer increases risk of death



Adapted from Levitan N, *et al*. Medicine 1999;78:285-291.

Higher rates of fatal PE and fatal bleeding in patients with cancer: data from the RIETE registry

Risk of fatal PE or fatal bleeding in the RIETE registry[1]



1. Monreal M *et al*. *J Thromb Haemost* 2006;4:1950–1956

Venous Thromboembolism: risk of recurrence

First episode		Annual rec rate (%)	Recommended VKAs duration
Idiopathic/unprovoked		5	3 mos/indefinite
Associated with	Temporary RF	2	3 months
	Cancer	10	indefinite
	Thrombophilia	5	3 mos/indefinite
Recurrent episodes		10	indefnite

Current Guidelines

Choice of Long-Term (First 3 Months) and Extended (No Scheduled Stop Date) Anticoagulation

		ACCP recommendation	Grade of recommendation
2016 CHEST guidelines CHEST	**Proxymal DVT or PE**	Long-term (3 months)	1B
	DVT or PE *and NO CANCER*	NOACs over VKA	2B
	DVT or PE *with CANCER*	LMWH over VKA and NOACs	2C
	DVT or PE in extended therapy	No need to change the coiche of anticoagulant after the first 3 months	2C

"…In patients with VTE and cancer who are not treated with LMWH, we do not have a preference for either an NOAC or VKA…"

"…In the absence of direct comparisons between NOACs, and no convincing indirect evidence that one NOAC is superior to another, we do not have a preference for one NOAC over another NOAC…"

Adapted from Kearon C, et al. *Chest*. 2016;149:315-352

PERCHE' NO AL TRATTAMENTO DELLA TVP CON FARMACI ANTI-VK?

LIMITI TERAPIA ANTI-VK (WARFARINA)

Factors That May Inc
Warfarin in the Onc

Patient characteristics
Elderly age
Debilitation
Low body weight
Patient adherence co
Infection
Nausea, vomiting
Steatorrhea
Dietary status
Inconsistency of oral i
Low albumin levels
Malabsorption
Undernourishment
Vitamin-K deficiency

Potential Warfarin/Anticancer Drug Interactions

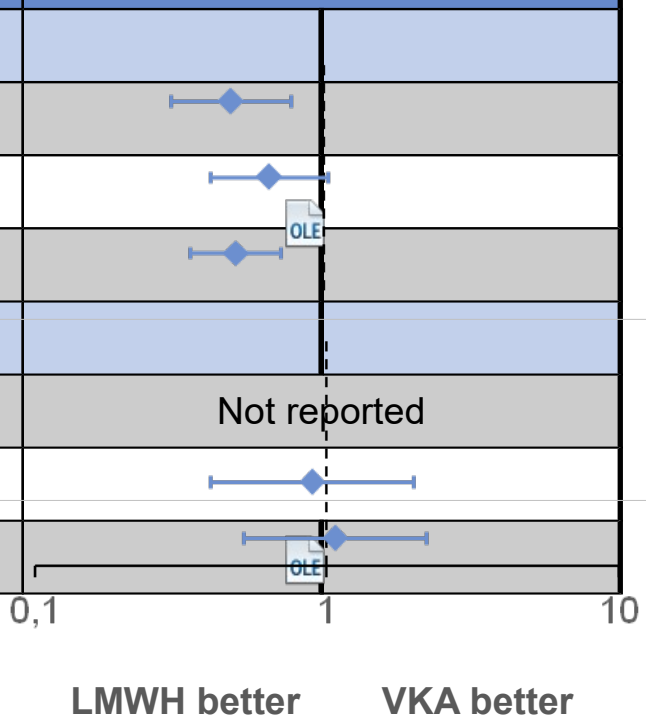
Increase INR
Adrenal steroid inhibitor
Aminoglutethimide[20]
Alkylating agent
Cyclophosphamide[a,18]
Antimetabolite
Hormone/hormone modifier
Androgen[9] (17-alkylated androgen)
Antiandrogen
Bicalutamide[27]
Flutamide[28]
Nilutamide[29]
Antiestrogen
Tamoxifen[30]
Toremifene[31]
Progestin[32]

Difficoltà a garantire il giusto range terapeutico e controllare il rischio di sanguinamento

Pangilinan et al, 2007

LMWH Versus VKA in the Treatment of CAT

	LMWH monotherapy		LMWH overlapping with VKA		HR (95% CI)
	n/N	(%)	n/N	(%)	
Recurrent VTE					
CLOT study*[1]	27/336	8.0	53/336	15.8	
CATCH study#[2]	31/449	6.9	45/451	10.0	
Meta-analysis‡[3]	**42/591**	**7.1**	**82/571**	**14.4**	
Major bleeding					
CLOT study*[1]	19/338	5.6	12/335	3.6	Not reported
CATCH study#[2]	12/449	2.9	11/451	2.4	
Meta-analysis§[3]	**37/556**	**6.7**	**32/536**	**6.0**	

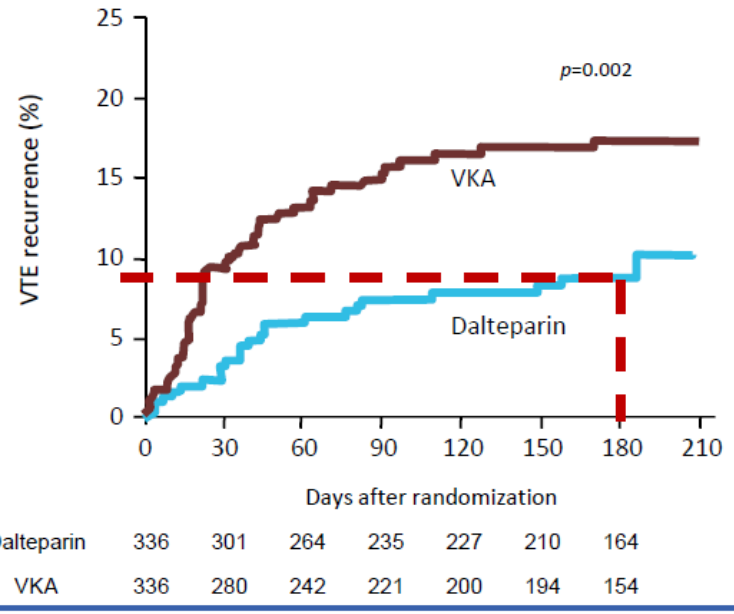


*Dalteparin versus VKA; in the VKA arm the estimated time in therapeutic range was 46% (30% below and 24% above); #tinzaparin versus warfarin; in the warfarin arm the time in therapeutic range was 47% (26% below and 27% above); ‡meta-analysis included four other small studies in addition to the CLOT study; §meta-analysis included three other small studies in addition to the CLOT study

1. Lee AYY *et al*, *New Engl J Med* 2003;349:146–153; 2. Lee AYY *et al*, *Blood* 2014:124:Abstract LBA-2; 3. Akl EA *et al*, *Cochrane Database Rev* 2014;7:CD006650

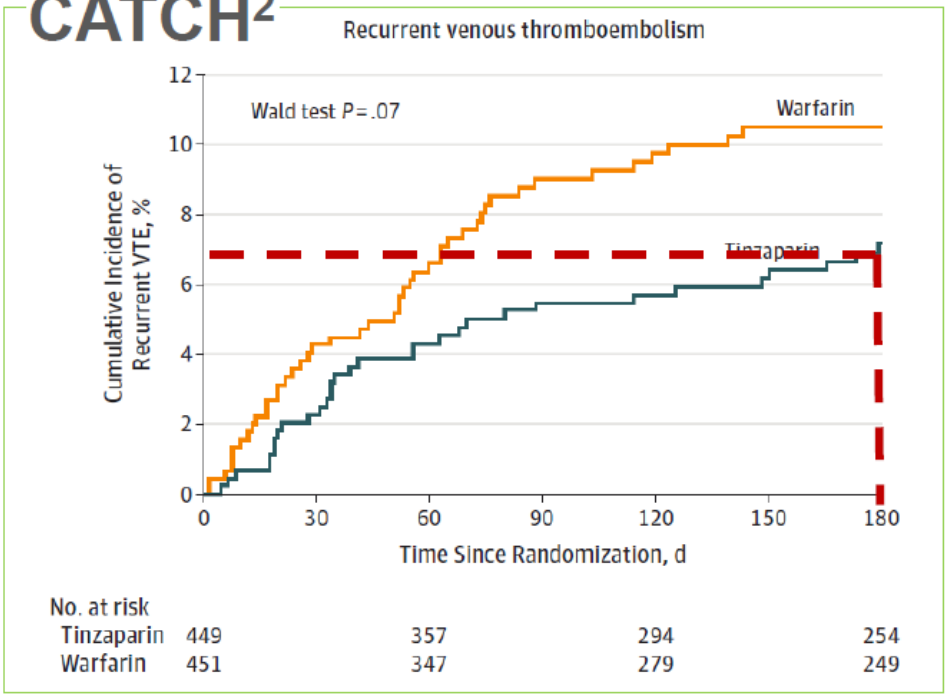
CLOT and CATCH Studies: LMWH vs VKA in CAT

CLOT[1]



Major bleeding (6% vs 4%) and mortality (39% vs 41% at 6 months)

CATCH[2]



Major bleeding similar 2.7% (LMWH) vs 2.4% (VKA) (p=0.77)

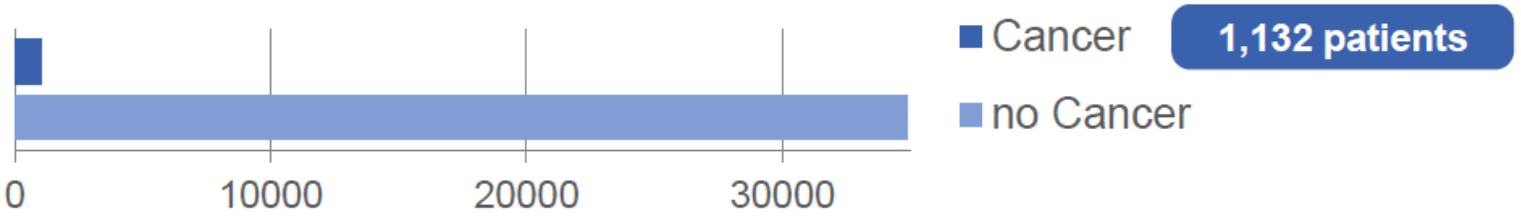
1, Lee AY et al, N Engl J Med 2033;349:146-153; 2. Lee AY et, JAMA 2015;314:677-686

Long-term VTE treatment in cancer patients
international guidelines: recommendations

	ASCO	NCCN National Comprehensive Cancer Network	AIOM ESMO		CHEST
Initial treatment	LMWH is the preferred approach for the initial 5-10 days.	LMWH, UFH or fondaparinux according to patient's characeristics and clinical situation	Weight –adjusted LMWH, If creatinine clearance < 25-30 ml/min either UFH or LMWH with antiXa monitoring	LMWH, UFH or fondaparinux for the first 10 days, if severe renal failure UFH or early VKA	LMWH for the first 3-6 months of long-term anticoagulant therapy (Grade 1A)
Long term treatment	LMWH for at least 6 months; VKA are acceptable when LMWH are not available,	LMWH is preferred	LMWH	LMWH for 3-6 months; LMWH or VKA beyond 6 months	Cancer patients with VTE are recommended to receive long-term LMWH monotherapy (grade 2B)
Optimal duration	Indefinite anticoagulation in patients with active cancer	Indefinite anticoagulation in patients with active cancer or persistent risk factors	for at least 3-6 months Long term treatment for patients with active cancer	Not specified	indefinitely or until the cancer is resolved (Grade 1C)

Treatment of VTE in cancer patients: NOACs

Phase III NOAC trials including more than 30,000 patients



Drug	Trial name	cancer patients (%)
Rivaroxaban	EINSTEIN-DVT	5,2
	EINSTEIN-PE	4.6
	EINSTEIN-extension	4.5
Dabigatran	RE-COVER	4.8
	RE-COVERII	0
	RE-MEDY	2.1
	RE-SONATE	
Apixaban	AMPLIFY	2.7
	AMPLIFY-EXT	1.7
Edoxaban	Hokusai-VTE	2.5

C.Wharin, V. Tagalakis / Blood Reviews 28 (2014) 1–8
Vedovati MC, Germini F, Agnelli G, Becattini C. Chest. 2015 Sep 11.2014/09/12.

RCP

TUTTI I NAO HANNO LA CONTROINDICAZIONE NELL'IMPIEGO IN PAZIENTI CON NEOPLASIE MALIGNE AD ALTO RISCHIO DI SANGUINAMENTO

Nel paragrafo 4.4 (Avvertenze speciali e precauzioni di impiego):

- **RIVAROXABAN**

Nessuna menzione ai pazienti con cancro.

- **APIXABAN**

L'efficacia e la sicurezza di Apixaban nei pazienti con cancro attivo nel TEV non sono state stabilite.

- **DABIGATRAN**

L'efficacia e la sicurezza di Dabigatran nei pazienti con cancro attivo nel TEV non sono state stabilite.

- **EDOXABAN**

L'efficacia e la sicurezza di Edoxaban nei pazienti con neoplasia attiva nel TEV non sono state stabilite.

I DOACs nei pazienti oncologici

Study		Event Rate, n/N (%) DOAC	VKA	HR (95% CI)
Recurrent VTE				
RE-COVER I+II[57]	Dabigatran (150 mg BID)	4/114 (3.5)	5/107 (4.7)	0.74 (0.20–2.7)
EINSTEIN DVT+PE[54]	Rivaroxaban (20 mg OD)[a]	6/258 (2.3)	8/204 (3.9)	0.62 (0.21–1.79)
AMPLIFY[55]	Apixaban (5 mg BID)[b]	3/81 (3.7)	5/78 (6.4)	0.56 (0.13–2.37)[c]
HOKUSAI-VTE[56]	Edoxaban (60 mg OD)[d]	4/109 (3.7)	7/99 (7.1)	0.55 (0.16–1.85)
Major Bleeding				
RE-COVER I+II[57]	Dabigatran (150 mg BID)	4/105 (3.8)	3/100 (3.0)	1.23 (0.28–5.5)
EINSTEIN DVT+PE[54]	Rivaroxaban (20 mg OD)[a]	5/257 (1.9)	8/202 (4.0)	0.47 (0.15–1.45)
AMPLIFY[55]	Apixaban (5 mg BID)[b]	2/87 (2.3)	4/80 (5.0)	0.45 (0.08–2.46)[c]
HOKUSAI-VTE[56]	Edoxaban (60 mg OD)[d]	5/109 (4.6)	3/99 (3.0)	1.52 (0.36–6.43)

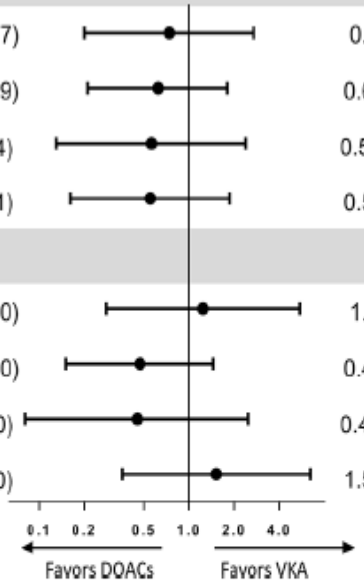
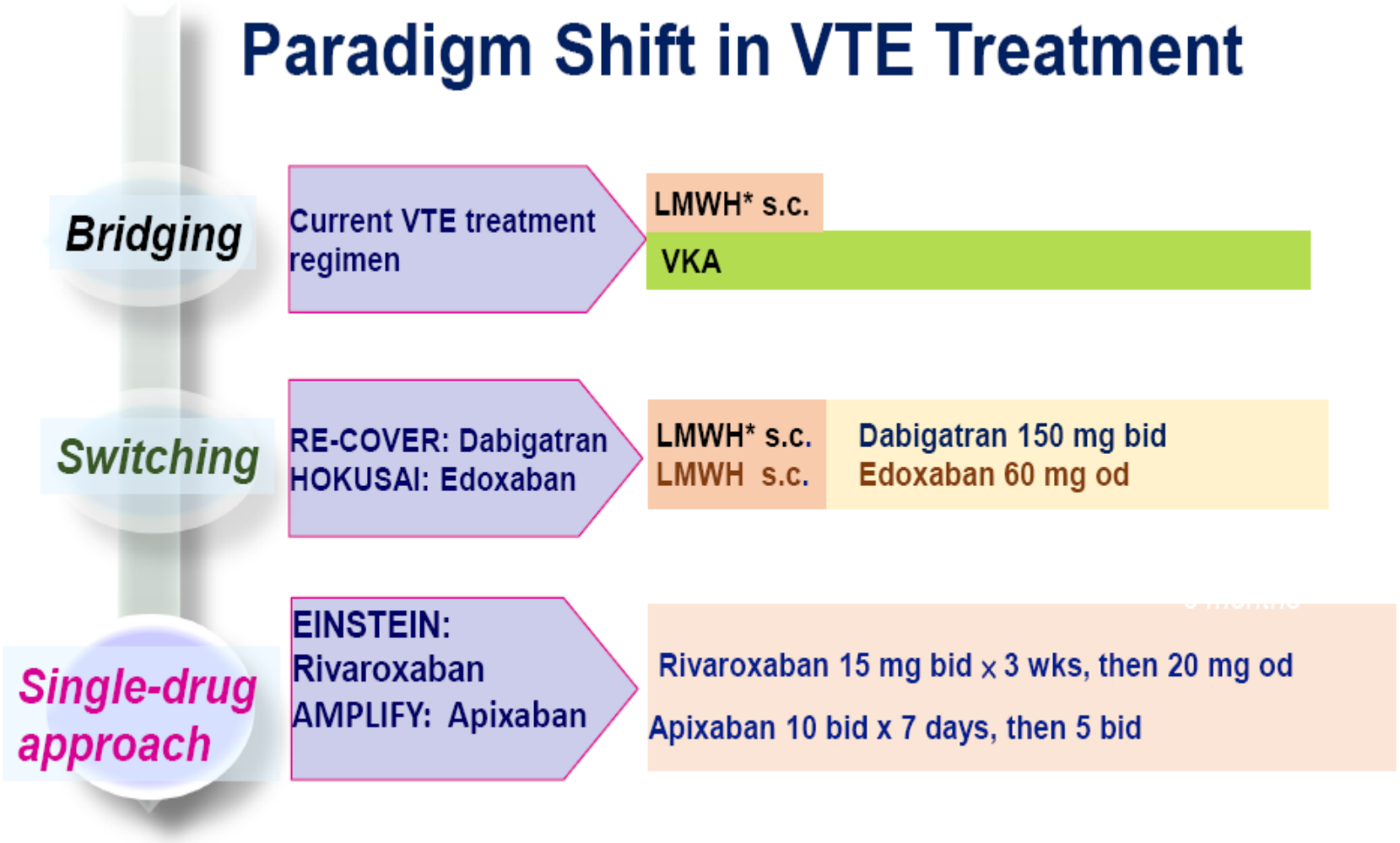


Figure 2 Forest plot of the HRs for DOACs vs warfarin for (**A**) new or recurrent VTE and (**B**) major bleeding based on the published subanalyses of the patients with active cancer at baseline included in the major DOAC phase 3 clinical trials for VTE. BID, two times per day; DOAC, direct oral anticoagulant; OD, one time per day; VKA, vitamin K antagonist; VTE, venous thromboembolism. [a]Rivaroxaban 15 mg BID for the first 21 days followed by 20 mg OD. [b]Apixaban 10 mg BID for 7 days followed by 5 mg BID. [c]Relative risk. [d]Patients with a creatinine clearance of 30 to 50 mL/min, a bodyweight of <60 kg or who were receiving concomitant treatment with select P-glycoprotein inhibitors received edoxaban 30 mg OD.

Ay C, *et al. ESMO Open* 2017;**2**:e000188. doi:10.1136/esmoopen-2017-000188

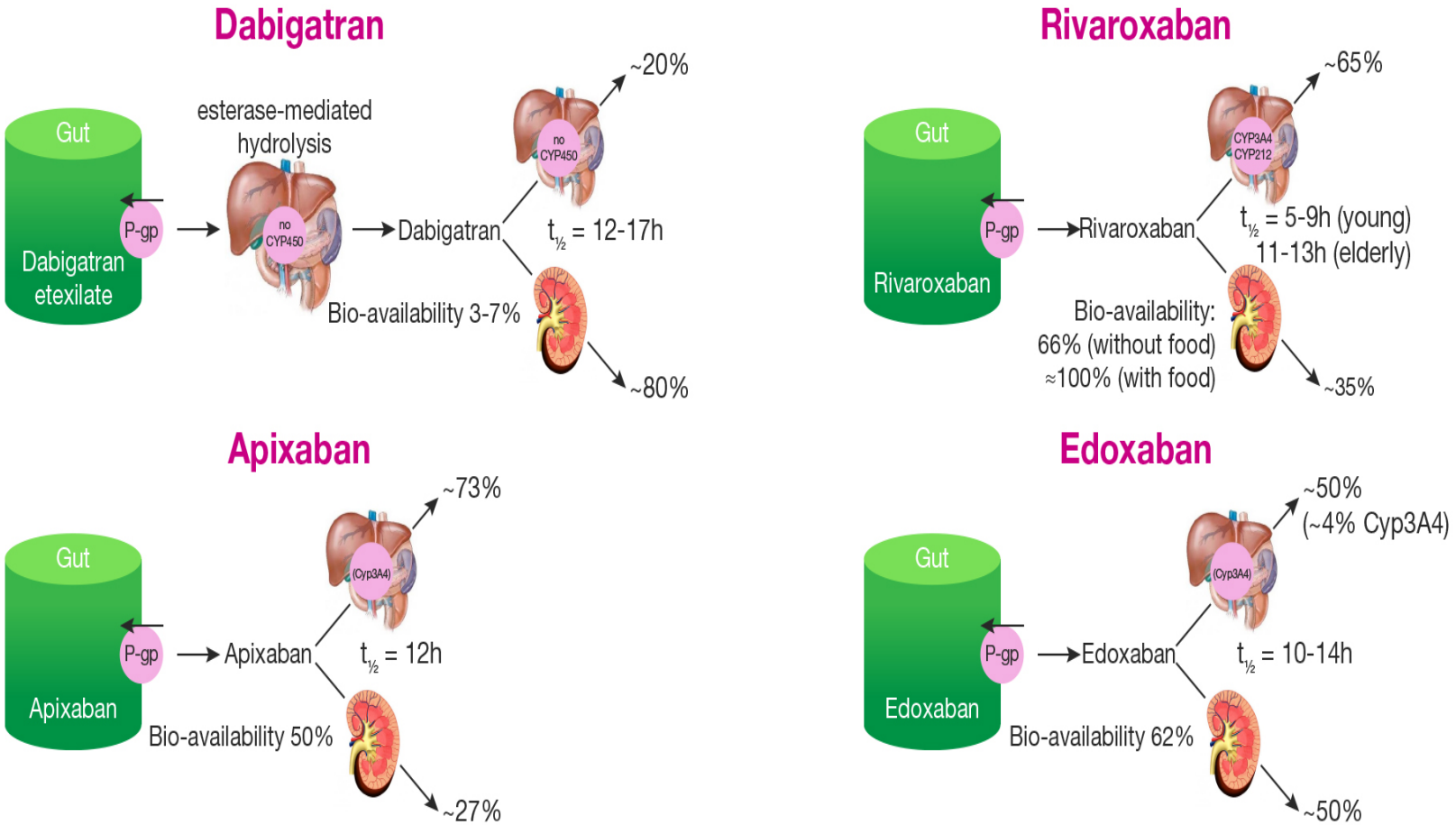
Interazioni Farmacologiche nella scelta dei DOAC

Paradigm Shift in VTE Treatment



1. Schulman S *et al. N Engl J Med* 2009;361:2342–2352; 2. RE-COVER II. Available at: http://clinicaltrials.gov. Trial ID: NCT00680186. Accessed August 2011;
3. The EINSTEIN Investigators. N Engl J Med 2010;363:2499–2510; 4. The EINSTEIN-PE Investigators. N Engl J Med 2012;366:1287–1297

Assorbimento e metabolismo dei NAO



Heidbuchel H et al. EHRA Practical Guide. Europace 2015;17(10):1467-507.

Utilizzo per diversi classi di funzionalità renale (Insufficienza renale o funzionalità superiore al normale)

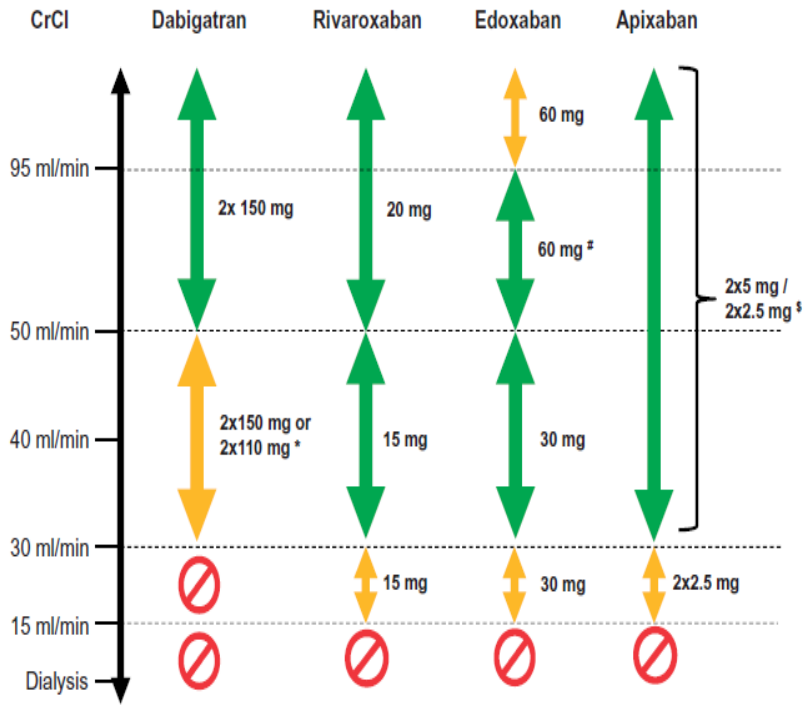


Figure 4 Use of non-vitamin K antagonist oral anticoagulants according to renal function. *2 × 110 mg in patients at high risk of bleeding (per SmPc). #Other dose reduction criteria may apply (weight ≤60 kg, concomitant potent P-Gp inhibitor therapy). $2 × 2.5 mg only if at least two out of three fulfilled: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5 mg/dL (133 µmol/L). Orange arrows indicate cautionary use (dabigatran in moderate renal insufficiency, FXa inhibitors in severe renal insufficiency, edoxaban in 'supranormal' renal function); see text for details.

Steffel; European Heart Journal (2018) 00, 1–64;
doi:10.1093/eurheartj/ehy136

Guida Pratica EHRA 2018: Tabelle delle interazioni farmacologiche

- Nelle tabelle 3, 4, 5 della guida pratica EHRA 2018 è presentata una panoramica dell'effetto delle interazioni di diversi farmaci comunemente utilizzati in cardiologia, oncologia e neurologia.

Steffel; European Heart Journal (2018) 00, 1–64;
doi:10.1093/eurheartj/ehy136

Effetto delle interazioni farmacologiche e dei fattori clinici sui livelli plasmatici dei NOAC (AUC)

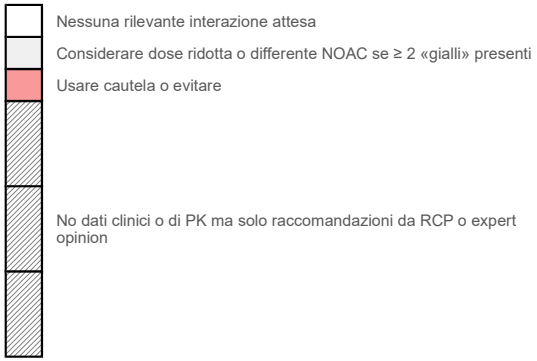
	Via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		yes	yes	yes	yes
CYP3A4 substrate		No	Yes (≈25%)	**No (<4%)**	Yes ≈18%
Antiarrhythmic drugs					
Dronedarone	P-gp competition and CYP3A4 inhibition	**+ 70 to 100%**	**No PK or PD data: caution**	**+ 85%**	**Moderate effect, should be avoided**
Antibiotics					
Rifampicin	P-gp/BCRP and CYP3A4/CYP2J2 inducers	**Minus 66%**	**Minus 54%**	**Minus 35%, but with compensatory increase of active metabolites**	**Up to minus 50%**
Fungostatics					
Itraconazole; Ketoconazole; Voriconazole	Potent P-gp and BCRP competition; CYP3A4 inhibition	**+140 to 150%**	**+100%**	**+87 to 95% (reduce NOAC dose by 50%)**	**Up to +160%**
Posaconazole	Mild to moderate P-gp inhibition		**SmPC**		**SmPC**
Others					
Naproxen	P-gp competition; pharmacodinamically increased bleeding time	**No data yet**	**+55%**	**No effect**	**No data yet**
H2B; PPI; Al-Mg-hydroxide	GI absorption	**Minus 12–30%**	**No effect**	**No effect**	**No effect**

	Nessuna rilevante interazione attesa
	Controindicato/non raccomandato
	Considerare dose ridotta o differente NOAC se ≥ 2 «gialli» presenti
	Considerare riduzione dosaggio o differente NOAC
	Controindicazione per riduzione dei livelli plasmatici del NOAC
	Cautela o evitare se possibile
	No dati clinici o di PK ma solo raccomandazioni da RCP o expert opinion

Estratto da Steffel; European Heart Journal (2018) 00, 1–64;
doi:10.1093/eurheartj/ehy136

Effetti attesi dei farmaci antineoplastici sui livelli plasmatici dei NOAC

	Via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		yes	yes	yes	yes
CYP3A4 substrate		No	Yes (≈25%)	**No(<4%)**	Yes ≈18%
Antimitotic agents					
Paclitaxel	Moderate CYP3A4 induction; CYP3A4/P-gp competition				
Docetaxel, Vincristine	Mild CYP3A4 induction; CYP3A4/P-gp competition				
Vinorelbine	Mild CYP3A4 induction; CYP3A4/P-gp competition				
Topoisomerase inhibitors					
Etoposide	Mild CYP3A4 induction; CYP3A4/P-gp competition				
Anthracyclines/Anthracenediones					
idarubicin	Mild CYP3A4 inhibition; CYP3A4 competition				
Alkylating agents					
Ifosfamide	Mild CYP3A4 inhibition; CYP3A4 competition				
Ciclophosphamide	Mild CYP3A4 inhibition; CYP3A4 competition				
Lomustine	Mild CYP3A4 inhibition				



Estratto da Steffel; European Heart Journal (2018) 00, 1–64; doi:10.1093/eurheartj/ehy136

Effetti attesi dei farmaci antineoplastici sui livelli plasmatici dei NOAC

	Via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		yes	yes	yes	yes
CYP3A4 substrate		No	Yes (≈25%)	**No(<4%)**	Yes ≈18%
Tyrosine kinase inhibitors					
Vemurafenib	Moderate CYP3A4 induction; CYP3A4/P-gp competition				
Dasatinib	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Hormonal Agents					
Bicalutamide	Moderate CYP3A4 inhibition				
Anastrozole	Mild CYP3A4 inhibition				
Immune-modulating agents					
Cyclosporine	Strong to moderate P-gp inhibition, moderate CYP3A4 inhibition; CYP3A4/P-gp competition	SmPC	SmPC	+73%	
Tacrolimus	Strong to moderate P-gp inhibition, mild CYP3A4 inhibition; CYP3A4/P-gp competition	SmPC			
Prendisone	Moderate CYP3A4 induction; CYP3A4 competition				
Temsirolimus, Sirolimus	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				

	Nessuna rilevante interazione attesa
	Considerare dose ridotta o differente NOAC se ≥ 2 «gialli» presenti
	Cautela se politerapia o in presenza di ≥ 2 fattori di rischio per sanguinamento
	Controindicato/non raccomandato
	Considerare riduzione dosaggio o differente NOAC
	Usare cautela o evitare
	No dati clinici o di PK ma solo raccomandazioni da RCP o expert opinion

Estratto da Steffel; European Heart Journal (2018) 00, 1–64;

Edoxaban non presenta cautele, mentre apixaban e rivaroxaban presentano cautele o consigli di evtare i seguenti farmaci:

1. Paclitaxel
2. Docetaxel, vincristina;
3. Vinorelbina
4. Etoposide
5. Idarubicina
6. Ifosfamide
7. Ciclofosfamide

Steffel; European Heart Journal (2018) 00, 1–64;
doi:10.1093/eurheartj/ehy136

8. Lomustina

Farmaci Antiepilettici

Apixaban perde la controindicazione presente nelle vecchie linee guida su:

- Carbamazepina,
- fenobarbital
- fenitoina.

Edoxaban non ha cautele, a differenze di apixaban e rivaroxaban con:

- Oxcarbazepina
- Topiramato

	Via[142,145,146]	Dabigatran etexilate	Apixaban[130]	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Drug					
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	SmPC	−50%[SmPC]	−35%[SmPC]	SmPC, Ref.[147]
Ethosuximide	CYP3A4 competition; No relevant interaction known/assumed				
Gabapentin	No relevant interaction known/assumed				
Lamotrigine	P-gp competition; No relevant interaction known/assumed				
Levetiracetam	P-gp induction; P-gp competition				
Oxcarbazepine	CYP3A4 induction; P-gp competition				
Phenobarbital	Strong CYP3A4/P-gp induction; P-gp competition		SmPC	SmPC	SmPC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	SmPC, Ref.[148]	SmPC	SmPC	SmPC
Pregabalin	No relevant interaction known/assumed				
Topiramate	CYP3A4 induction; CYP3A4 competition				
Valproic acid	CYP3A4/P-gp induction				Ref.[149]
Zonisamide	CYP3A4 competition; No relevant interaction known/assumed				

Nessuna rilevante interazione attesa

Controindicazione per riduzione dei livelli plasmatici del NOAC

Usare cautela o evitare

No dati clinici o di PK ma solo raccomandazioni da RCP o expert opinion

Steffel; European Heart Journal (2018) 00, 1–64;

Conclusioni

1. La nuova guida EHRA 2018 riconosce all'edoxaban un profilo migliore in termini di interazioni farmacologiche per via della quasi assenza delle interazioni sul CYP 3A4;

2. Anche il Dabigatran non ha interazioni sul CYP ma possiede una bassa biodisponibilità, la sua cinetica è influenzata anche dal Ph gastrico e non ha dati specifici nel paziente oncologico;

3. Edoxaban è il primo NOAC che porta evidenze cliniche favorevoli circa l'associazione con i farmaci antineoplastici e con quelli che inibiscono le P-gp nei pazienti con cancro;

4. Nella scelta del DOAC, un fattore determinante è costituito dalle interazioni farmacologiche ed edoxaban è il NOAC che ne possiede meno;

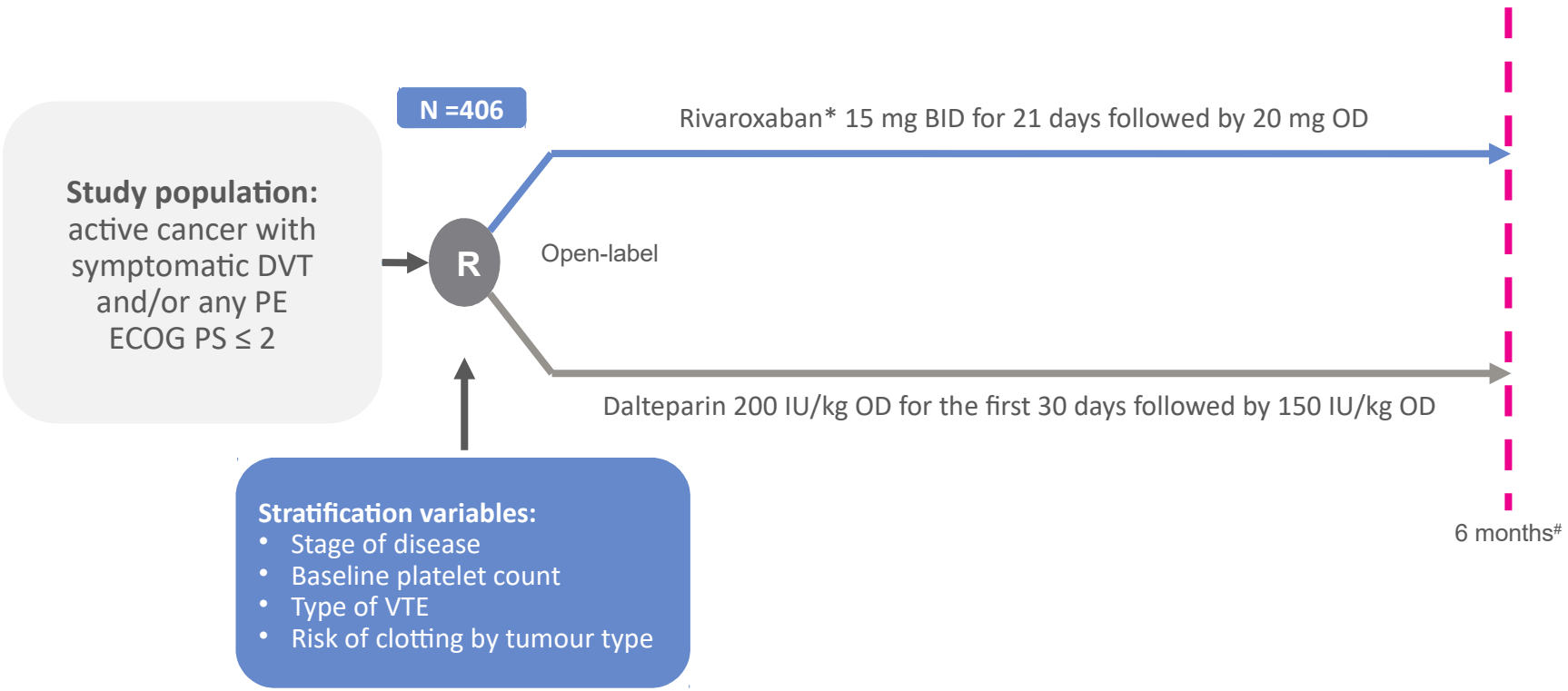
5. Viene indicato che Edoxaban è l'unico NOAC che presenta uno studio RCT che studia nello specifico i pazienti con cancro e TEV.

Anticoagulation Therapy in Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism: Results of the Select-D Pilot Trial

Oral presentation Young A et al, ASH 2017: Abstract 625;
Available at: http://www.clinicaltrialresults.org/

select-D: Phase III Study Comparing Rivaroxaban versus Dalteparin for the Treatment of Cancer Associated Thrombosis

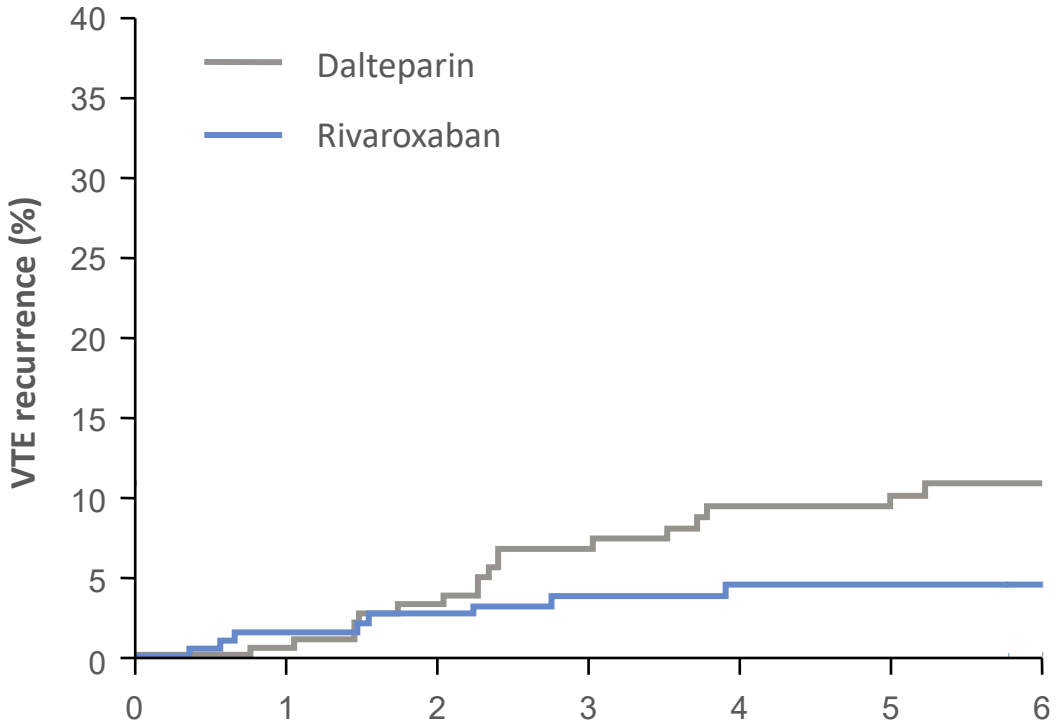
Study design: Prospective, randomized, open-label, multicentre pilot phase III study



*For patients with CrCl 30–49 ml/min dosing recommendations as in rivaroxaban SmPC; #The second randomization phase for extended treatment of VTE from 6 to 12 months for patients with PE as an index event or patients with Residual DVT at 5 month assessment was closed due to low recruitment. Sample size reduced from 530 to 400 patients for main trial comparison (95% CI for VTE recurrence +/-4.5%)

Young A et al, Thromb Res 2016;140:S172–S173; EudraCT number: 2012-005589-37; Bach M et al, Thromb Haemost 2016;116:S24–S32; Data on File

Lower Incidence of VTE Recurrence Events with Rivaroxaban Versus Dalteparin



Outcome at 6 months	Rivaroxaban (n=203)	Dalteparin (n=203)
VTE recurrence, % (95% CI)	4 (2–9)	11 (7–16)

Young A et al, ASH 2017: Abstract 625; Available at: http://www.clinicaltrialresults.org/

Bleeding - number of patients (%)

Category	Dalteparin (n=203)	Rivaroxaban (n=203)
Major*	6 (3%)	11 (5%)
Clinically relevant non-major	6 (3%)	25 (12%)
Total	12 (6%)	36 (17%)

*1 fatal bleeding event in each arm

Most major bleeding events were gastrointestinal bleeding; no CNS bleeds

Most CRNMBs were gastrointestinal or urological

Summary

- Lo studio Select-d è uno studio prospettico randomizzato, in aperto, multicentrico che ha confrontato dalteparina con rivaroxaban in 406 pazienti con tromboembolismo venoso e cancro.
- Il trattamento con rivaroxaban ha mostrato un tasso di ricorrenza di TEV a 6 mesi più basso (4%) rispetto a dalteparina (11%), un tasso simile di sanguinamenti maggiori.

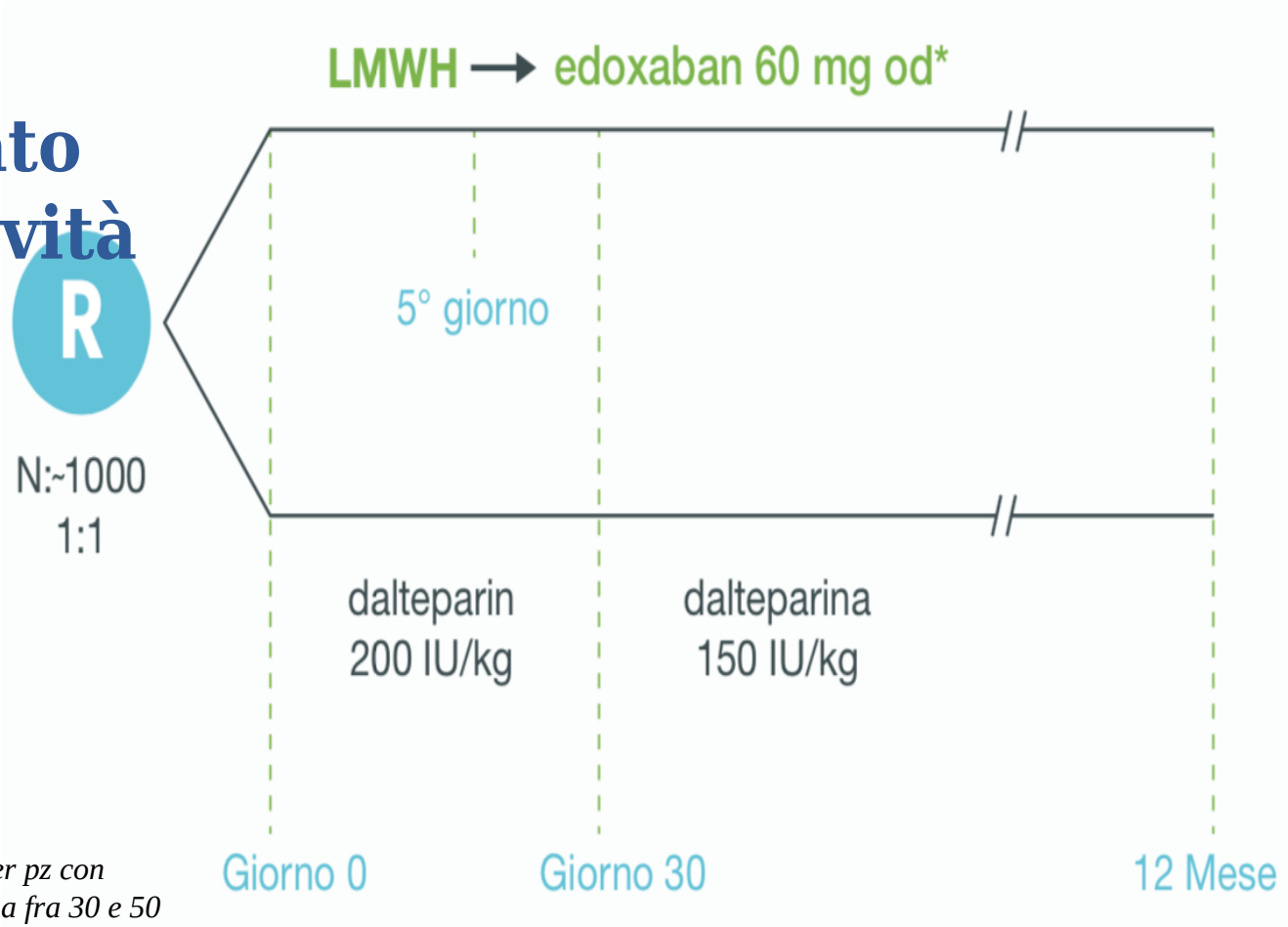
Hokusai VTE CANCER

EDOXABAN NEL PAZIENTE CON CANCRO E TEV

DISEGNO DELLO STUDIO

TEV Confermato

1050 pz
randomizzati e stratificati per rischio di sanguinamento e necessità di riduzione del dosaggio*



** Aggiustamento a 30 mg per pz con peso < 60 kg, ClCr compresa fra 30 e 50 mL/min, e uso concomitante di potenti inibitori della p-Gp*

Hokusai VTE CANCER

Raskob G.E. et al., NEJM, 20

CARATTERISTICHE UNICHE DEL DISEGNO

- End point primario COMPOSITO (recidiva di TEV e Sanguinamenti Maggiori)
- Durata dello studio 12 mesi (minimo 6 mesi di trattamento)
- Arruolati pz con cancro attivo o diagnosticato entro 2 anni
- Arruolati pz con trombosi sintomatiche ed incidentali

Van ES et al., Thrombosis and Haemostasis, 2015

CRITERI DI INCLUSIONE

- Pazienti adulti con TEV acuta confermata dall'imaging:
  - TVP prossimale, sintomatica o incidentale,
  - EP simptomatica,
  - EP incidentale di un segmento o di un'arteria polmonare maggiore;
- Qualsiasi tipo di tumore ad esclusione dei tumori della pelle basocelluari o squamocellulari;
- Cancro attivo, o diagnosticato entro 2 anni dall'arruolamento;
  - Definizione di Cancro attivo:
    - Diagnosi o trattamento negli ultimi 6 mesi
    - Recidiva, cancro localmente avanzato o metastatico
    - Neoplasia ematologica non in remissione completa
- Trattamento con LMWH previsto per almeno 6 mesi

Hokusai VTE CANCER

Raskob G.E. et al., NEJM, 2017

CARATTERISTICHE PAZIENTI

Age, y – mean (SD)	64.3 (11.0)	63.7 (11.7)
Male sex – n (%)	277 (53.1)	263 (50.2)
Platelet 50000–100000/µL – n (%)	32 (6.1)	23 (4.4)
Met criteria to receive lower dose of edoxaban – n (%)	122 (23.4)	117 (22.3)
Creatinine clearance of 30–50 mL/min – n (%)	38 (7.3)	34 (6.5)
≤60 kg – n (%)	83 (15.9)	78 (14.9)
PE with or without DVT	328 (62.8)	329 (62.8)
DVT only	194 (37.2)	195 (37.2)
Symptomatic DVT or PE	355 (68.0)	351 (67.0)
Incidental DVT or PE	167 (32.0)	173 (33.0)
Active cancer – n (%)	513 (98.3)	511 (97.5)
Metastatic disease – n (%)	274 (52.5)	280 (53.4)
Cancer treatment within previous 4 weaks n (%)	374 (71.6)	383 (73.1%)

Raskob G.E. et al., NEJM, 2017

LOCALIZZAZIONE NEOPLASIA

	Edoxaban (N=522)	Dalteparin (N=524)
Solid tumor – no. (%)	**465 (89.1)**	**467 (89.1)**
Colorectal	83 (15.9)	79 (15.1)
Lung	77 (14.8)	75 (14.3)
Genitourinary	65 (12.5)	71 (13.5)
Breast	64 (12.3)	60 (11.5)
Pancreatic or hepatobiliary	49 (9.4)	40 (7.6)
Gynecological	47 (9.0)	63 (12.0)
Upper gastrointestinal	33 (6.3)	21 (4.0)
Other	48 (9.2)	60 (11.5)
Hematological malignancy – no. (%)	56 (10.7)	55 (10.5)

Hokusai VTE CANCER

Raskob G.E. et al., NEJM, 2017

ANTITUMORALI

		Edoxaban	Dalteparin
Antimetabolites	Methotrexate,,Pemetrexed, Citarabina Fluorouracile,Gemcitabina Capecitabina	124 (23.8)	118 (22.5)
Platinum-based chemotherapy	Cisplatino,carboplatino, oxaliplatino	105 (20.1)	107 (20.4)
Monoclonal antibodies	Rituximab,trastuzumab, trastuzumab emtansine, cetuximab, panitumumab, ipilimumab, pertuzumab, nivolumab	42 (8.0)	54 (10.3)
Bevacizumab		13 (2.5)	17 (3.2)
Taxanes	Paclitaxel, docetaxel	40 (7.7)	47 (9.0)
Hormonal therapy	Megestrol,buserelina,tamoxifen,anastrazolo, letrozolo,esamestane	41 (7.9)	37 (7.1)
Topoisomerase inhibitors	Camptotecina, topotecan, irinotecan	30 (5.7)	48 (9.2)
Alkylating agents	mostarde azotate, aziridine, fosfamidi, nitroso-uree, sulfoni, non convenzionali (dibromodulcitolo, pipobroman, anaxirone, piperazinedione, procarbazina, dacarbazina)	30 (5.7)	38 (7.3)

Hokusai VTE CANCER

Raskob G.E. et al., NEJM, 2017

ANTITUMORALI

		Edoxaban	Dalteparin
Anthracyclines	Doxorubicina,epirubicina,idarubicina, mitoxantrone,	22 (4.2)	25 (4.8)
Vinca alkaloids	Actinomicina, mitomicina C, bleomicina	16 (3.1)	18 (3.4)
Kinase inhibitors	Vinblastina, vincristina, vinorelbina	18 (3.4)	18 (3.4)
Immunomodulating agents	Imatinib, gefitinib, erlotinib,sunitinib, sorafenib , dasatinib, lapatinib, nilotinib,temsirolimus,everolimus , pazopanib,afatinib,bosutinib,vemurafenib, crizotinib,axitinib	16 (3.1)	9 (1.7)
Proteasome inhibitors	Ac.micofenolico,sirolimus,everolimus	7 (1.3)	8 (1.5)
Antitumor antibioticS	Bortezomib, carfilzomib	5 (1.0)	5 (1.0)
Miscellaneous	Etoposide	14 (2.7)	14 (2.7)

Hokusai VTE CANCER

Raskob G.E. et al., NEJM, 2017

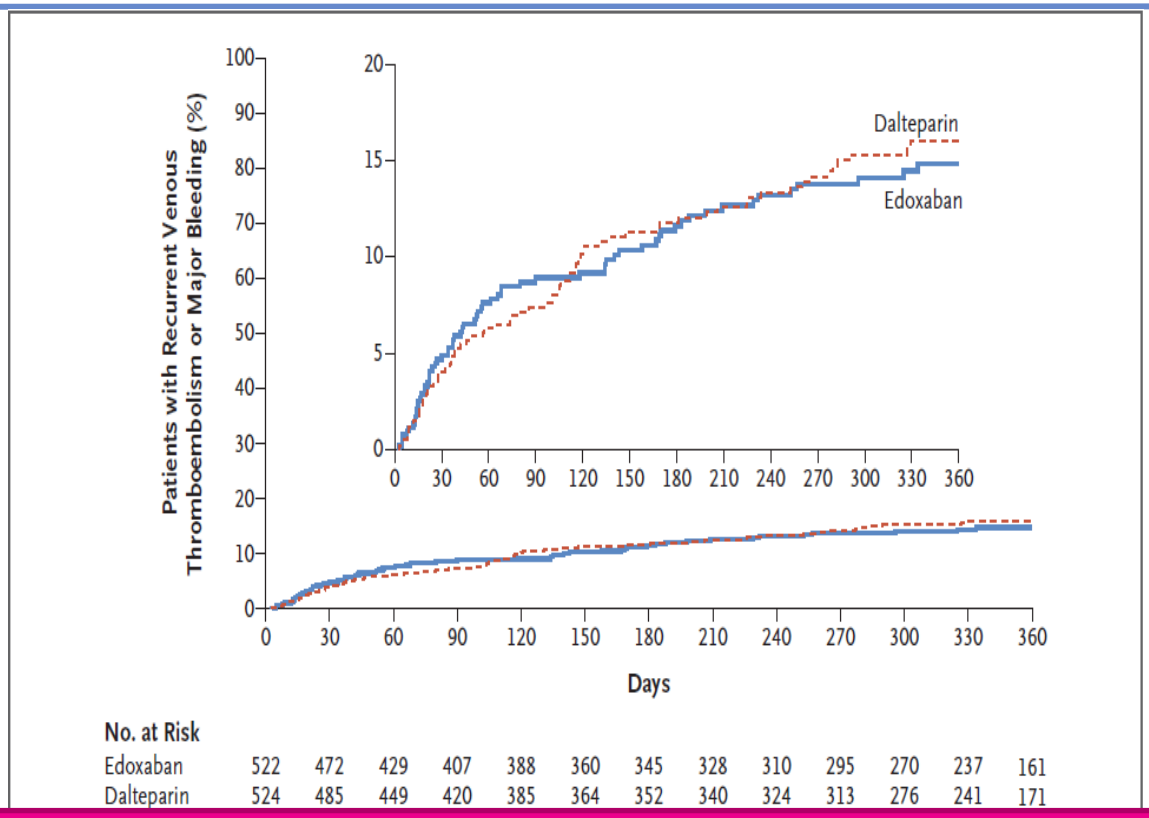
CAUSE INTERRUZIONE

	Edoxaban (N=522)	Dalteparin (N=524)
Reason for permanent study drug discontinuation		
Death	**86 (16.5)**	**100 (19.1)**
Clinical outcome/adverse event	**79 (15.1)**	**62 (11.8)**
Cancer progression	**53 (10.2)**	**33 (6.3)**
Cancer resolved	**10 (1.9)**	**15 (2.9)**
Investigator decision: benefit/risk judgement	**32 (6.1)**	**46 (8.8)**
Investigator decision: palliative treatment only	**10 (1.9)**	**7 (1.3)**
Investigator decision: patient non-compliance	**1 (0.2)**	**2 (0.4)**
Platelet count <50,000 per mL	**1 (0.2)**	**2 (0.4)**
Start of new chemotherapy	**6 (1.1)**	**3 (0.6)**
Patient decision: inconvenience of dosing	**21 (4.0)**	**78 (14.9)**
Withdrawal of study consent	**6 (1.1)**	**8 (1.5)**
Other reason	**17 (3.3)**	**14 (2.7)**

Hokusai VTE CANCER

Raskob G.E. et al., NEJM, 2017

ENDPOINT PRIMARIO COMPOSITO
Recidiva Di TEV O Sanguinamento Maggiore



Edoxaban (522)	Dalteparina (524)	HR (95% CI)
67 (12.8%)	71 (13.5%)	0.97 (0.70, 1.36) *P = 0.006*

SANGUINAMENTI MAGGIORI (Outcome Secondario)

	EDOXABAN N = 522	DALTEPARINA N = 524	HR (95% CI)
MAGGIORI	36 (7.9%)	21 (4%)	1.77 (1.03, 3.04) P = 0.04
Fatali	0	2	
Intracranici	2	4	

Hokusai VTE CANCER

Raskob G.E. et al., NEJM, 2017

SEDE SANGUINAMENTI MAGGIORI

Clinical Outcomes	Edoxaban (n = 522)	Dalteparin (n = 524)
Major bleeding – no. (%)	33 (6.3)	17 (3.2)
Fatal	0	2 (0.4)
Intracranial	2 (0.4)	4 (0.8)
Gastrointestinal	20 (3.8)	6 (1.1)
Upper	17 (3.3)	3 (0.6)
Lower	3 (0.6)	3 (0.6)
Urogenital	5 (1.0)	0
Other	6 (1.1)	7 (1.3)

Hokusai VTE CANCER

Raskob G.E. et al., NEJM, 2017

SEVERITA' SANGUINAMENTI MAGGIORI

1. Eventi di sanguinamento che si presentano **senza alcuna emergenza clinica**

2. Eventi di sanguinamento che non potevano essere classificati in nessuna delle altre tre categorie, in quanto presentavano la **necessità di alcune misure ma senza chiara urgenza**

3. Eventi di sanguinamento che si presentano con **grande urgenza medica**, come sanguinamento con instabilità emodinamica o emorragia intracranica che presenta sintomi neurologici

Raskob G.E. et al., NEJM, 2017

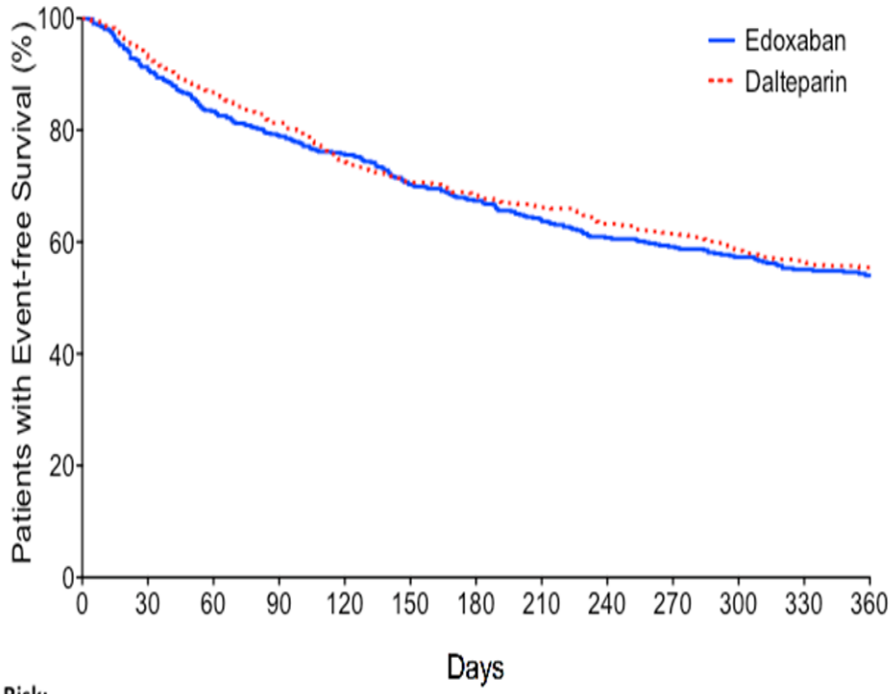
SEVERITA' SANGUINAMENTI MAGGIORI

SEVERITA'	EDOXABAN N = 36 s.m.	DALTEPARINA N = 21 s.m.
1	0	0
2	24 (66.7%)	8 (38%)
3	12 (33%)	12 (57%)
4	0	1

Hokusai VTE CANCER

Raskob G.E. et al., NEJM, 2017

SOPRAVVIVENZA LIBERA DA EVENTI
Recidiva di TEV, Sanguinamenti Maggiori, Morte



No. at Risk:													
Edoxaban:	522	472	429	407	388	360	345	328	310	295	270	237	161
Dalteparin:	524	485	449	420	385	364	352	340	324	313	276	241	171

Raskob G.E. et al., NEJM, 2017

Hokusai VTE CANCER

Trattamento con EBPM e NOAC
“Clinical challenges “

Eloise Beggiato

Gli **antidoti dei DOACs**

Eloise Beggiato

Bleeding risk and reversal strategies for old and new anticoagulants and antiplatelet agents

Time until restoration of hemostasis after cessation of therapeutic dose

	Time until restoration of hemostasis after cessation of therapeutic dose	Reversing agent	Remark
Vitamin K antagonists	Warfarin: 60–80 h Acenocoumarol: 18–24 h Phenprocoumon: 8–10 days	Vitamin K i.v.; reversal in 12–16 h Vitamin K orally; reversal in 24 h PCC's; immediate reversal	Dose of vitamin K or PCCs depend on INR and bodyweight
Heparin	3–4 h	Protamine sulphate 25–30 mg; immediate reversal	1 mg of protamin per 100 anti-Xa units given in the last 2–3 h
LMW heparin	12–24 h	(Partially) protamine sulphate 25–50 mg; immediate (partial) reversal	1 mg of protamine per 100 anti-Xa units given in the last 8 h
Pentasaccharides	Fondaparinux: 24–30 h Idraparinux: 5–15 days Idrabiotaparinux: 5–15 days	Recombinant factor VIIa 90 μg kg^{-1}; immediate thrombin generation* Avidin for idrabiotaparinux*	Based on laboratory endpoints, no systematic experience in bleeding patients
Oral factor Xa inhibitors	Dependent on compound, usually within 12 h	Prothrombin complex concentrate (3000 U)*	Based on laboratory endpoints, no systematic experience in bleeding patients
Oral thrombin inhibitors	Dependent on compound, usually within 12 h	None so far	
Aspirin	5–10 days (time to produce unaffected platelets)	DDAVP (0.3–0.4 μg kg^{-1}) and/or platelet concentrate; reversal in 15–30 min	Cessation not always required, also dependent on clinical situation and indication
Clopidogrel Prasugrel	1–2 days	Platelet concentrate, possibly in combination with DDAVP (0.3–0.4 μg kg^{-1}); reversal in 15–30 min	Cessation not always desirable, also dependent on clinical situation and indication

Levi et M al. JTH 2011; 9:1705-12

Cosa è necessario sapere per ridurre il rischio emorragico nei pazienti in NAO?

Molecola	◆Tipo ◆Dosaggio ◆Indicazione
Paziente	◆Rischio trombombolico/emorragico ◆Funzione renale (CrCl – Cockroft-Gault) ◆Funzione epatica ◆Terapie concomitanti ◆Indicazione NAO approvata
Procedura	◆Tipo e tecnica ◆Rischio emorragico ◆Data dell'intervento
Anestesia	◆Generale e/o regionale (neuroassiale o blocco periferico)

Dincq AS et al, Biomed Res Int. 2014;2014:385014

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

Table 10 Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban–edoxaban–rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥ 80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–80 mL/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h
CrCl 30–50 mL/min[a]	**≥48 h**	**≥96 h**	≥24 h	≥48 h
CrCl 15–30 mL/min[a]	Not indicated	Not indicated	**≥36 h**	**≥48 h**
CrCl < 15 mL/min	No official indication for use			

There is no need for bridging with LMWH/UFH

Heidbuchel H. Europace 2015; doi:10.1093/europace/euv309

NAO e interventi chirurgici

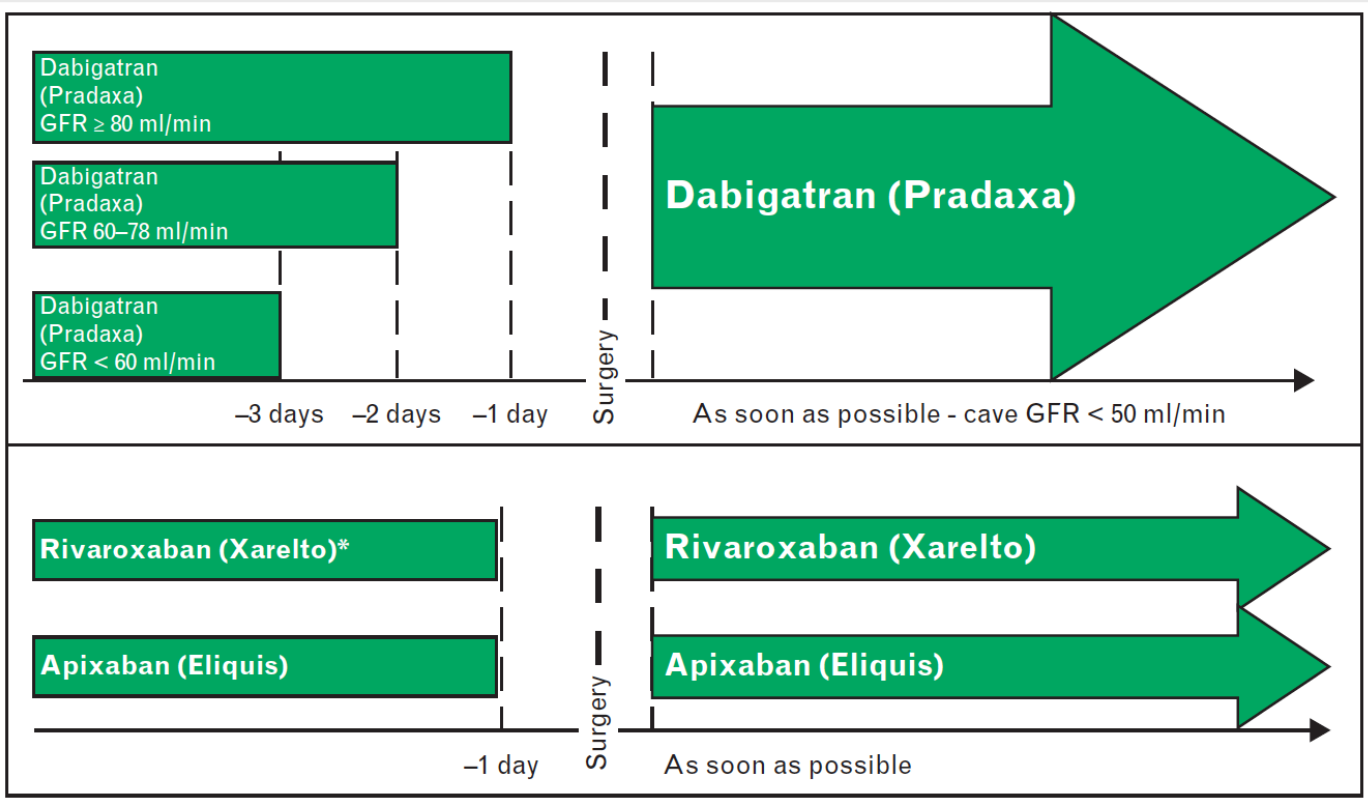
Interventi che non richiedono necessariamente la sospensione dell'anticoagulazione	Interventi a basso rischio emorragico	Interventi ad alto rischio emorragico
Procedure odontoiatriche •Estrazione da 1 a 3 denti •Chirurgia parodontale •Incisione di ascessi •Posizionamento di impianti	Endoscopia con biopsia	Anestesia spinale o epidurale, puntura lombare diagnostica
Oftalmologia •Interventi per cataratta o glaucoma	Biposia prostatica o vescicale	Chirurgia Toracica
Endoscopia senza chirurgia	Studi elettrofisiologici o ablazione con catetere a radiofrequenza per tachicardia SV e (inclusa ablazione sinistra via singola puntura trans-settale)	Chirurgia addominale
Chirurgia superficiale (es. incisione di ascessi, piccole escissioni dermatologiche etc)	Angiografia	Chirurgia ortopedica maggiore
	Impianto di pacemaker o ICD	Biopsia epatica
		Resezione prostatica transuretrale
		Biopsia renale
		Ablazione sin.complessa (es isolamento della vena polmonare, VT ablation)

Heidbuchel H. et al . EHRA practical guide for use of NOAC. Europace (2013) 15,

'New' direct oral anticoagulants in the perioperative setting

Low bleeding risk:

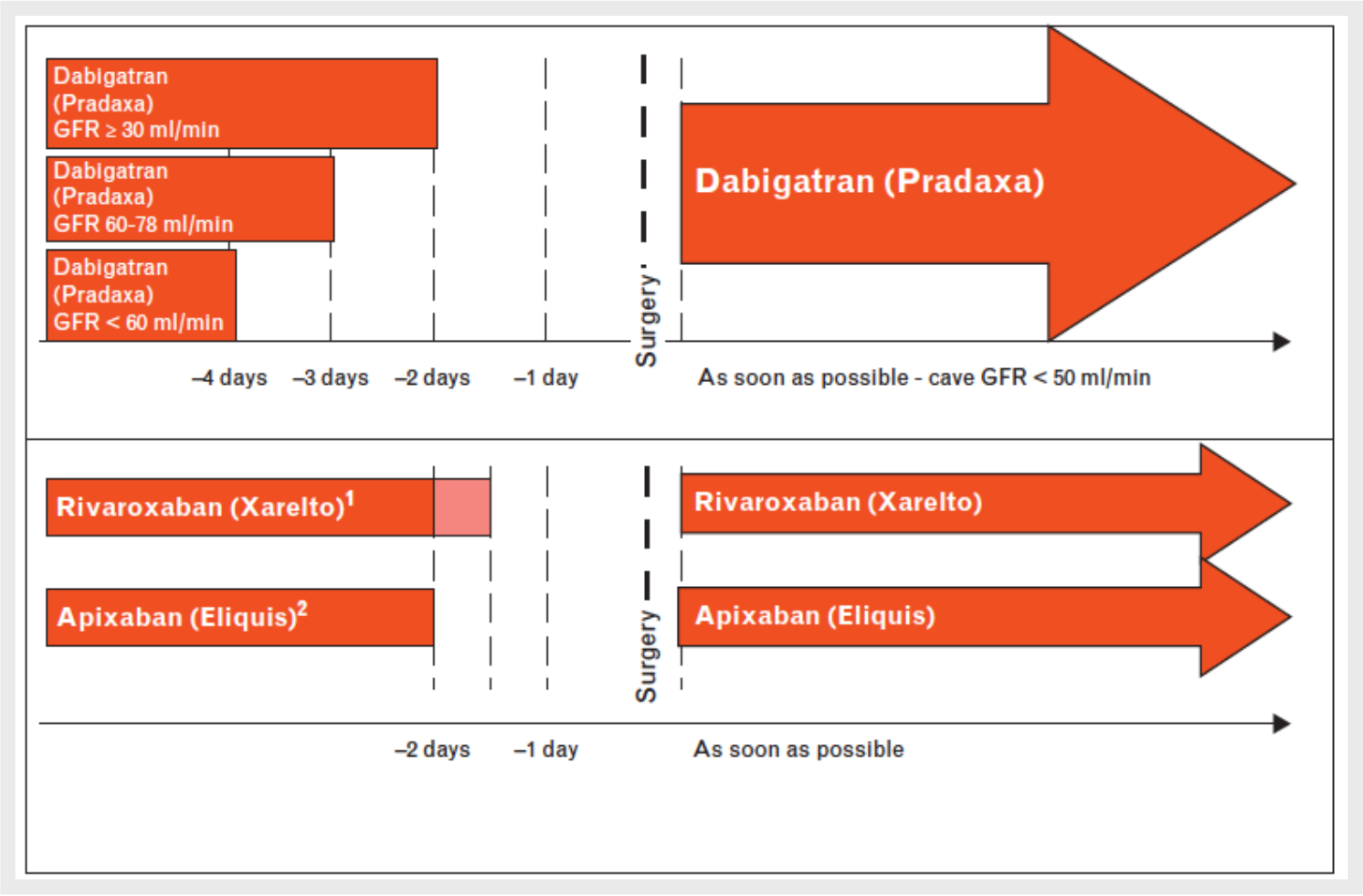
(minimal bleeding, uncritical localization, easy to manage)



Breuer G et al. Curr Opin Anesthesiol. 2014; 27:409-19

High bleeding risk:

(risk of bleeding not acceptable, relevant bleeding could not be precluded)

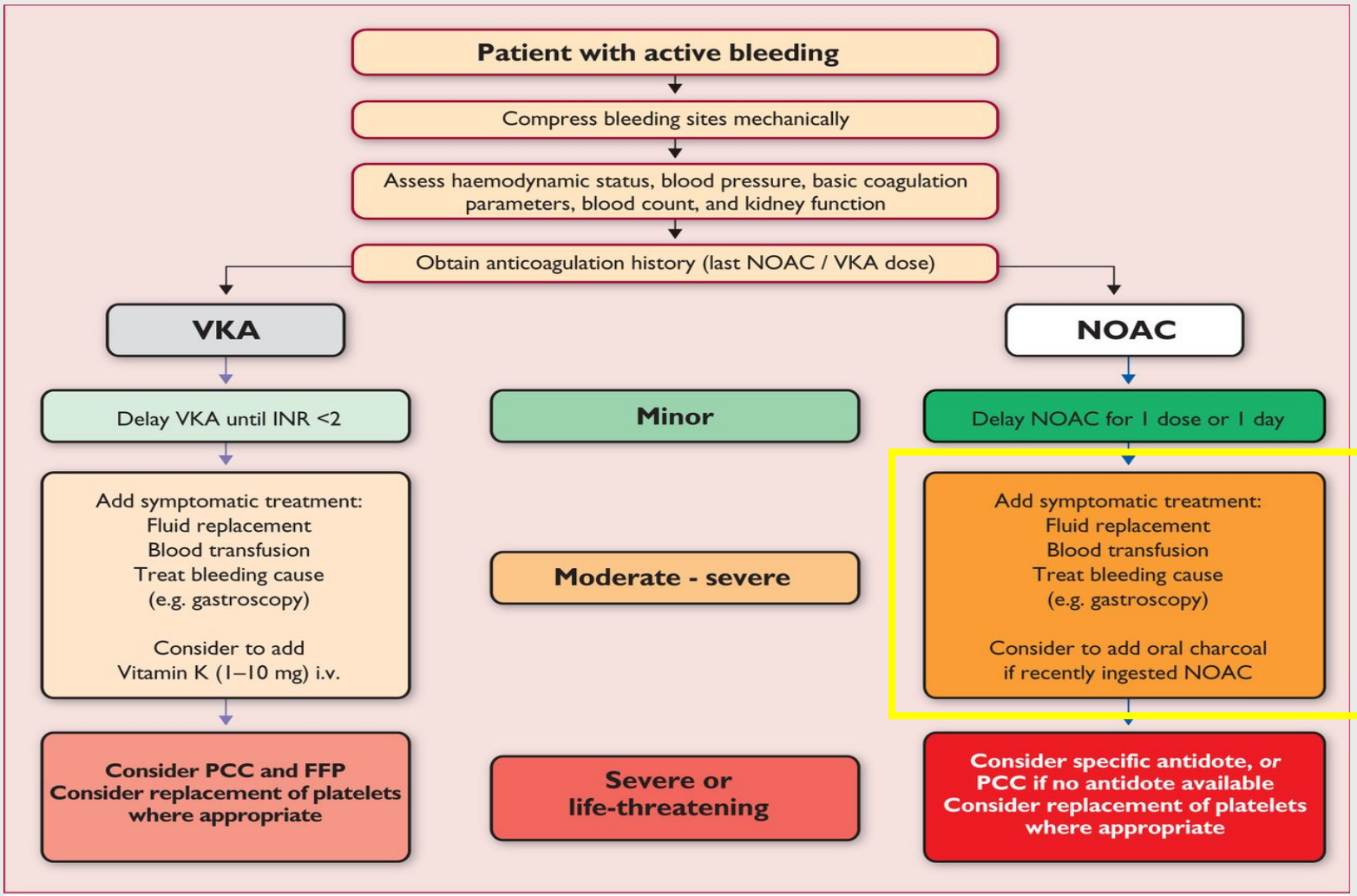


Breuer G et al. Curr Opin Anesthesiol. 2014; 27:409-19

European Heart Journal
doi:10.1093/eurheartj/ehw210

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)



FFP = fresh frozen plasma; INR = international normalized ratio; i.v. = intravenous; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; PCC = prothrombin complex concentrates; VKA = vitamin K antagonist.

Kirchhof et al; EHJ 2016

Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients

International Society on Thrombosis and Haemostasis

Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients

MAJOR BLEEDING

1. Fatal bleeding

and/or

2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartmentsyndrome,

and/or

3. Bleeding causing a fall in hemoglobin level of 2 g/dL or more, or leading to transfusion of two or more units of whole blood or red cells.

Schulman S et al. JTH 2005; 3:692-694

Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients

LIFE THREATENING BLEEDING

1. Fatal bleeding

and/or

2. intracranial bleeding

and/or

3. Bleeding causing a fall in hemoglobin level of 5 g/dL or more, or leading to transfusion of 4 or more units of whole blood or red cells or inotropic agents or necessitating surgery

Schulman S et al. JTH 2005; 3:692-694

Schulman S et al. JTH 2005; 3:692-694

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

! **2015** !

Life-threatening bleeding	All of the above Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence)	Life-threatening bleeding	All of the above Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available Activated factor VII (rFVIIa; 90 μg/kg) no data about additional

All of the above.

Prothrombin complex concentrate (PCC) 50 U/kg
(with additional 25 U/kg if clinically needed)
(healthy volunteer data)

Activated PCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available.

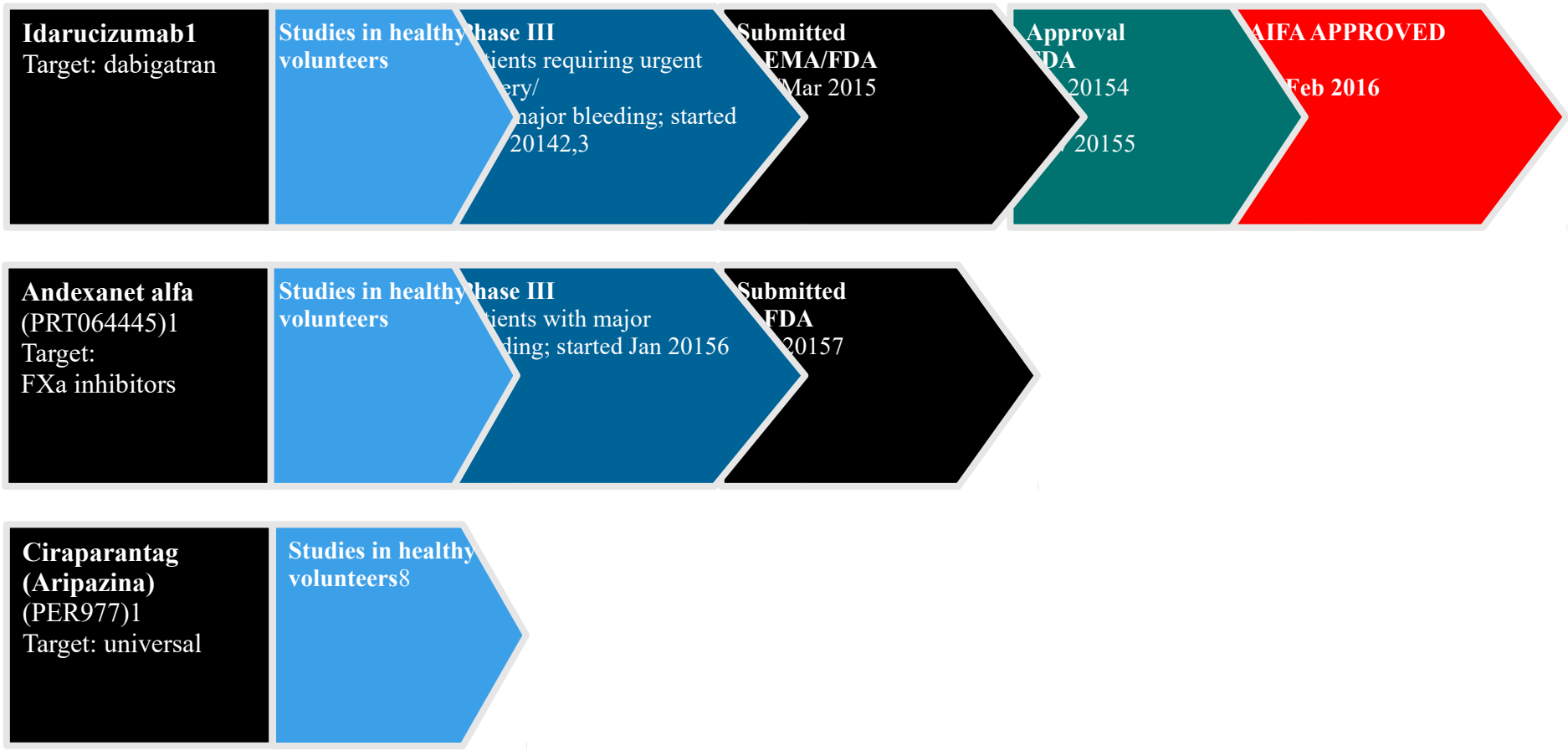
Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence)

Idarucizumab 5 g IV (approval waiting)

… *for Dabigatran*

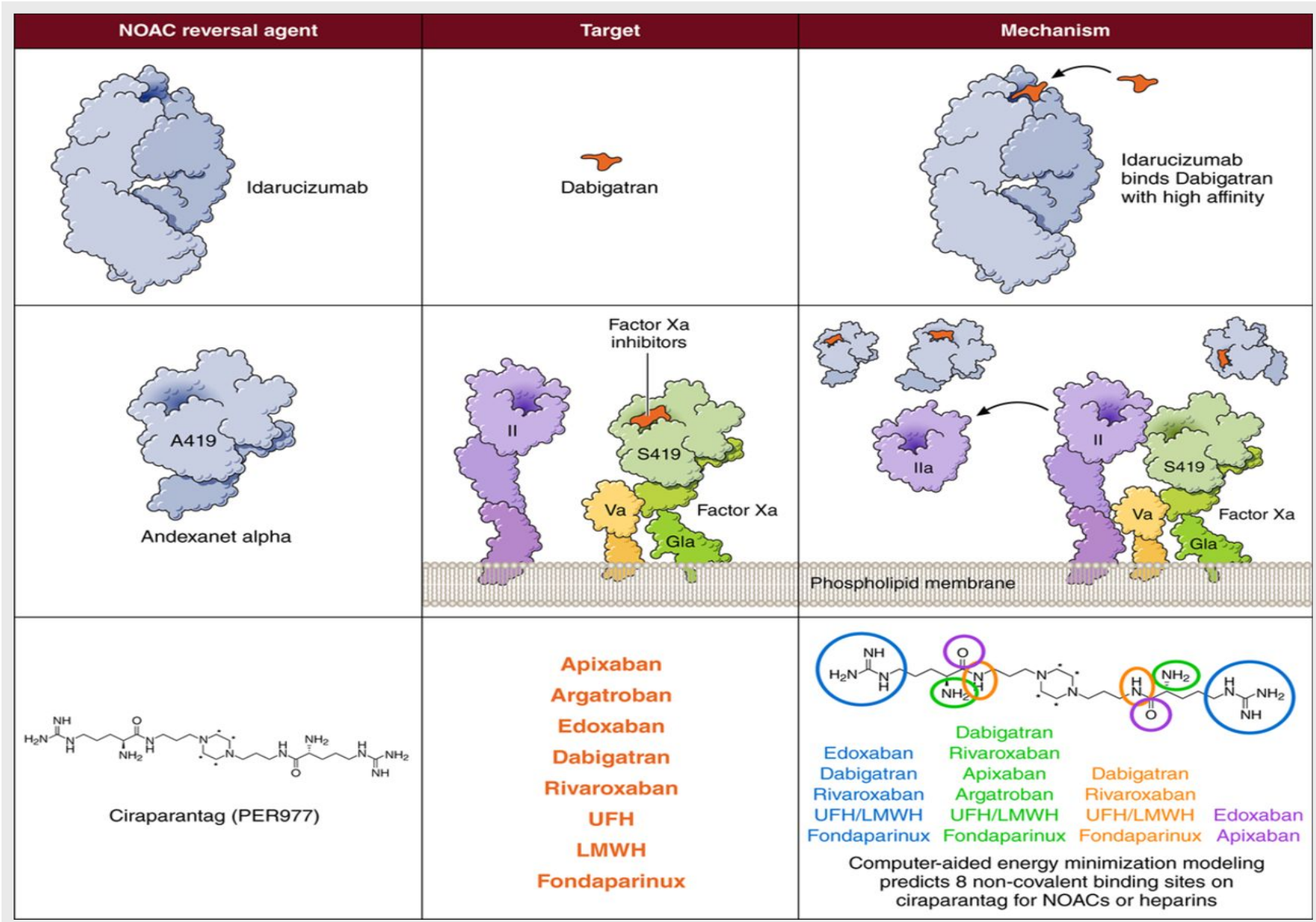
Heidbuchel H. Europace 2015; doi:10.1093/europace/euv309

NOAC reversal agents: stages of development



1. Adapted from Greinacher et al. Thromb Haemost 2015; **2.** Clinicaltrials.gov: NCT02104947; **3.** Pollack et al. Thromb Haemost 2015; **4.** US FDA press release 16 Oct 2015; **5.** European Commission Community Register of Medicinal Products for Human Use 20 November 2015; **6.** ClinicalTrials.gov Identifier: NCT02329327; **7.** ClinicalTrials.gov Identifier: NCT02207257

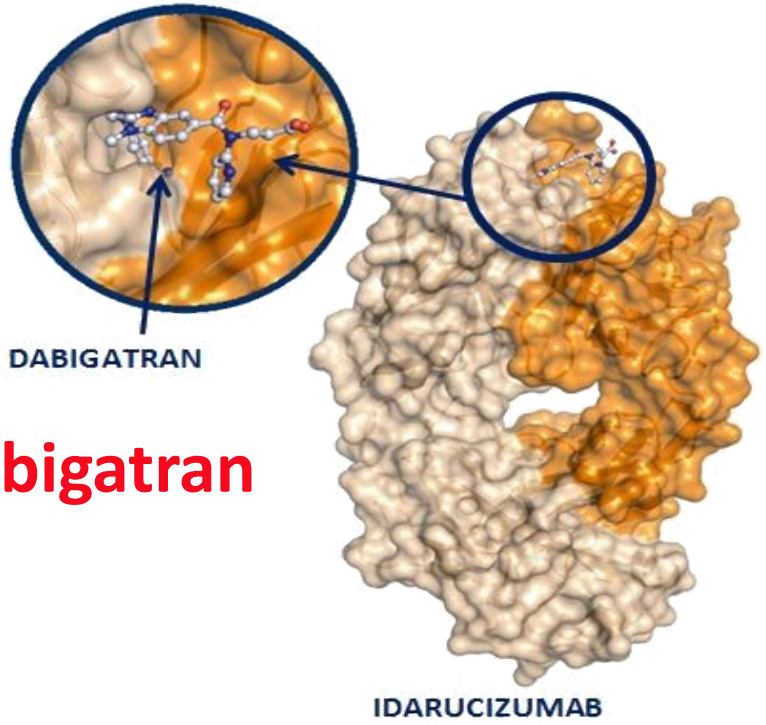
DOACs: Antidoti



Ruff et al. Circulation 2016;375:1131-41

Idarucizumab

(frammento di anticorpo monoclonale)



Dabigatran

Idarucizumab is in late-stage development and has not yet been approved for clinical use

Idarucizumab

Humanized Fab fragment

Binding affinity ~350× higher than dabigatran to thrombin

No intrinsic procoagulant or anticoagulant activity

IV dosing by bolus or rapid infusion, immediate onset of action

Short half-life

- Schiele et al. Blood 2013; Stangier et al. OR 320; presented at ISTH 2015

When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH

International Society on Thrombosis and Haemostasis

Indications for use

Bleeding

Indications for use	• Life-threatening bleeding: Intracranial hemorrhage, symptomatic or expanding extradural hemorrhage, or uncontrollable hemorrhage • Bleeding in a closed space or critical organ: Intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, or intramuscular with compartment syndrome • Persistent major bleeding despite local hemostatic measures, or risk of recurrent bleeding because of delayed DOAC clearance or DOAC overdose • Need for urgent intervention that is associated with a high risk of bleeding and that cannot be delayed to allow for drug clearance • Emergency surgery or intervention in patients at high risk for procedural bleeding: Neurosurgery (intracranial, extradural, or spinal), lumbar puncture, cardiac or vascular surgery (aortic dissection/aneurysm repair), hepatic or other major organ surgery
Potential indication for use	• Need for urgent surgery or intervention in patients with acute renal failure
Antidotes should not be used	• Elective surgery • Gastrointestinal bleeds that respond to supportive measures • High drug levels or excessive anticoagulation without associated bleeding • Need for surgery or intervention that can be delayed long enough to permit drug clearance

Surgery

Indications for use	• Life-threatening bleeding: Intracranial hemorrhage, symptomatic or expanding extradural hemorrhage, or uncontrollable hemorrhage • Bleeding in a closed space or critical organ: Intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, or intramuscular with compartment syndrome • Persistent major bleeding despite local hemostatic measures, or risk of recurrent bleeding because of delayed DOAC clearance or DOAC overdose • Need for urgent intervention that is associated with a high risk of bleeding and that cannot be delayed to allow for drug clearance • Emergency surgery or intervention in patients at high risk for procedural bleeding: Neurosurgery (intracranial, extradural, or spinal), lumbar puncture, cardiac or vascular surgery (aortic dissection/aneurysm repair), hepatic or other major organ surgery
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Levy JH et al. JTH 2016; 14:623-7