Il ruolo di Rivaroxaban nelle medicine d'urgenza

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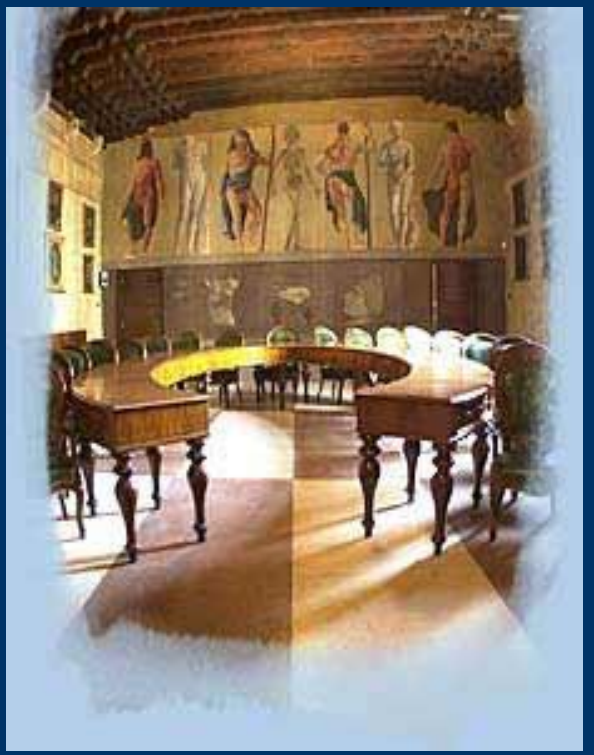


Palazzo del Bo, Università di Padov

X Congresso Nazionale SIMEU

Napoli, 18-20 Novembre 2016

FINANCIAL DISCLOSURES

Il sottoscritto

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

DICHIARA

che negli ultimi due anni ha avuto scientifici (advisory board, progetti di ricerca, consulenze) con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

BAYER HEALTHCARE

DAIICHI-SANKYO

ALFA WASSERMANN

Single Drug Approach in the past

- Before 90's → Warfarin
- 2000-2005 → Ximelagatran (THRIVE Study)
- 2007-2011 → Idraparinux & Idrabiotaparinux

VAN GOGH DVT & PE, CASSIOPEA

- 2012-future: → NOACs

Limitations of VKA therapy

VKA therapy has several limitations leading to underuse and leaving patients at risk of VTE or bleeding

- Narrow therapeutic window (INR range 2-3)
- Unpredictable response
- Numerous drug-drug interactions
- Numerous food-drug interactions
- Warfarin resistance
- Slow onset/offset of action
- Routine coagulation monitoring
- Frequent dose adjustments

1. Ansell J, et al. *Chest* 2008;133;160S-198S; 2. Umer Ushman MH, et al. *J Interv Card Electrophysiol* 2008; 22:129-137;
2. Nutescu EA, et al. *Cardiol Clin* 2008; 26:169-187.

Even With Close Monitoring in a Clinical Trial, Patients Frequently Out of Therapeutic Range

Clinical Trials

Only 58% of INR Values in Therapeutic Range

(INR = 2.0–2.85)

Real World Practice

As low as 37% of Time Spent Within Therapeutic Range

(INR = 2.0–2.85)

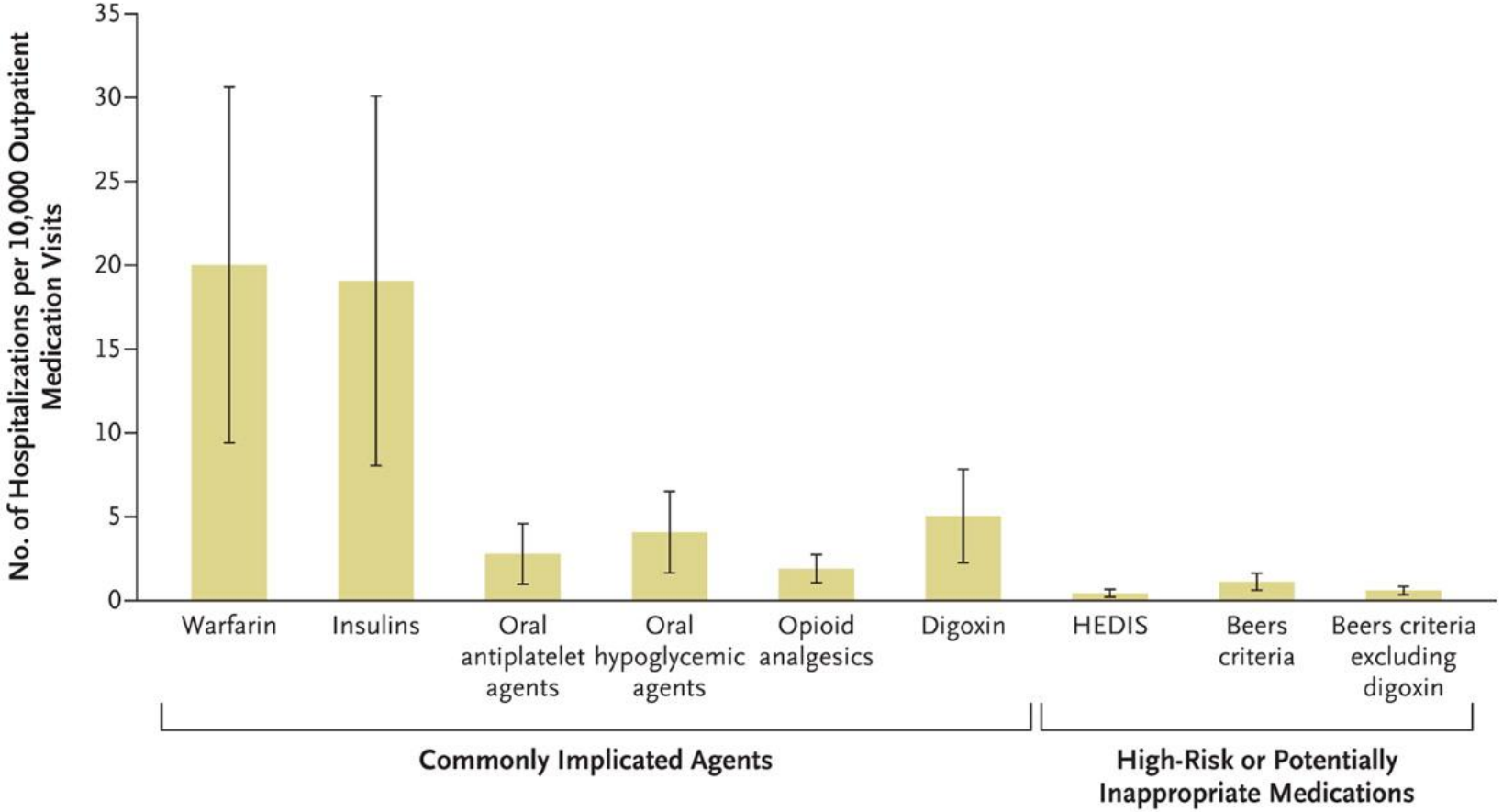
INR=international normalized ratio

Schulman S; and Duration of Anticoagulation (DURAC) Trial Study Group. *J Intern Med* 1994;236:143-152.

Willey et al. Clin Ther 2004;26:1149-1159

VKA

emergency admissions due to undesired effects



NOACs

- Oral administration
- No requirement for routine coagulation monitoring and dose adjustement
- Wide therapeutic window
- Rapid onset of action
- Predictable pharmacokinetics and pharmacodynamics
- Minimal interactions with foods and other drugs
- Ability to inhibit free and clot-bound coagulation factors
- Low non-specific binding
- Availability of an antidote
- No unexpected toxicities
- Acceptable costs

Gómez-Outes, et al. Thrombosis Res **2014**;134:774-782

Direct oral anticoagulants in the treatment of acute venous thromboembolism: A systematic review and meta-analysis

Study or Subgroup	DOAC Events	DOAC Total	STANDARD TREATMENT Events	STANDARD TREATMENT Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 DABIGATRAN STUDIES						
01. RE-COVER I	30	1280	27	1284	8.1%	1.11 [0.67, 1.86]
02. RE-COVER II	30	1294	28	1295	8.3%	1.07 [0.64, 1.78]
Subtotal (95% CI)		**2574**		**2579**	**16.4%**	**1.09 [0.76, 1.57]**
Total events	60		55			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 0.48 (P = 0.63)						
1.1.2 RIVAROXABAN STUDIES						
03. EINSTEIN DVT	36	1731	51	1718	12.1%	0.70 [0.46, 1.07]
04. EINSTEIN PE	50	2420	44	2413	13.3%	1.13 [0.76, 1.69]
Subtotal (95% CI)		**4151**		**4131**	**25.4%**	**0.89 [0.56, 1.43]**
Total events	86		95			
Heterogeneity: Tau² = 0.07; Chi² = 2.62, df = 1 (P = 0.11); I² = 62%						
Te						
1.						
07						
Su						
Total events						
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						
1.1.4 EDOXABAN STUDIES						
09. HOKUSAI-VTE	130	4143	146	4149	39.7%	0.89 [0.71, 1.12]
Subtotal (95% CI)		**4143**		**4149**	**39.7%**	**0.89 [0.71, 1.12]**
Total events	130		146			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
Total (95% CI)		**13561**		**13566**	**100.0%**	**0.91 [0.79, 1.06]**
Total events	335		367			
Heterogeneity: Tau² = 0.00; Chi² = 3.89, df = 5 (P = 0.57); I² = 0%						
Test for overall effect: Z = 1.21 (P = 0.23)						
Test for subgroup differences: Chi² = 1.26, df = 3 (P = 0.74), I² = 0%						

Risk Ratio M-H, Random, 95% CI

0.1 0.2 0.5 1 2 5 10

Favours DOAC Favours control

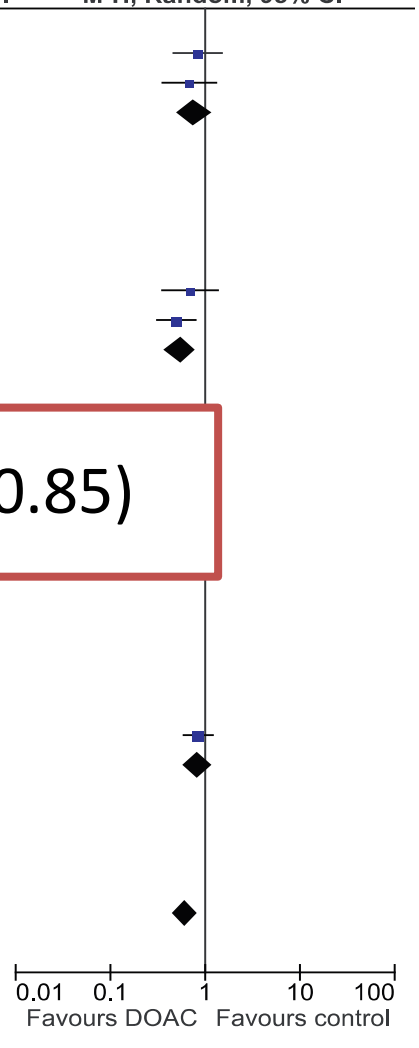
Risk-ratio recurrent VTE: 0.91 (0.79 to 1.06)

Gómez-Outes, et al. Thrombosis Res **2014**;134:774-782

Direct oral anticoagulants in the treatment of acute venous thromboembolism: A systematic review and meta-analysis

Study or Subgroup	DOAC Events	DOAC Total	STANDARD TREATMENT Events	STANDARD TREATMENT Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 DABIGATRAN STUDIES						
01. RE-COVER I	20	1280	24	1284	15.4%	0.84 [0.46, 1.51]
02. RE-COVER II	15	1294	22	1295	13.7%	0.68 [0.36, 1.31]
Subtotal (95% CI)		**2574**		**2579**	**29.1%**	**0.76 [0.49, 1.18]**
Total events	35		46			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.21 (P = 0.22)						
1.2.2 RIVAROXABAN STUDIES						
03. EINSTEIN DVT	14	1731	20	1718	13.1%	0.69 [0.35, 1.37]
04. EINSTEIN PE	26	2420	52	2413	19.0%	0.50 [0.31, 0.80]
Subtotal (95% CI)		**4151**		**4131**	**32.1%**	**0.55 [0.38, 0.82]**
Total events	40		72			
Total events	15		49			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.01 (P < 0.0001)						
1.2.4 EDOXABAN STUDIES						
09. HOKUSAI-VTE	56	4143	66	4149	23.1%	0.85 [0.60, 1.21]
Subtotal (95% CI)		**4143**		**4149**	**23.1%**	**0.85 [0.60, 1.21]**
Total events	56		66			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
Total (95% CI)		**13559**		**13563**	**100.0%**	**0.62 [0.45, 0.85]**
Total events	146		233			
Heterogeneity: Tau² = 0.08; Chi² = 10.71, df = 5 (P = 0.06); I² = 53%						
Test for overall effect: Z = 2.97 (P = 0.003)						
Test for subgroup differences: Chi² = 9.84, df = 3 (P = 0.02), I² = 69.5%						

Risk-ratio major bleeding: 0.62 (0.45 to 0.85)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

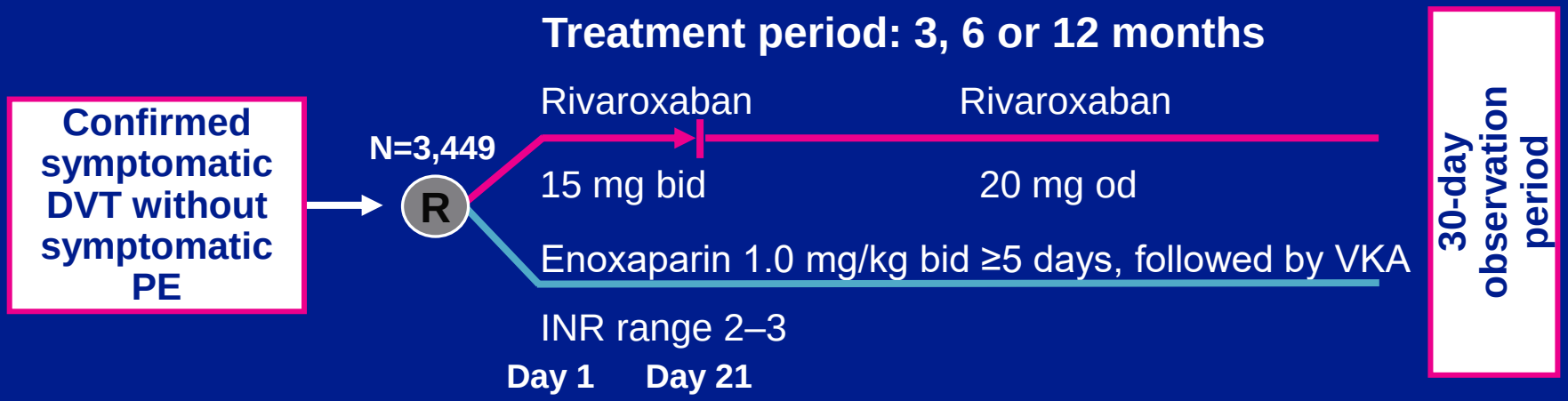
The EINSTEIN Investigators*

Harry R Büller
on behalf of the EINSTEIN Investigators
Academic Medical Center, Amsterdam, The Netherlands

EINSTEIN DVT: study design

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

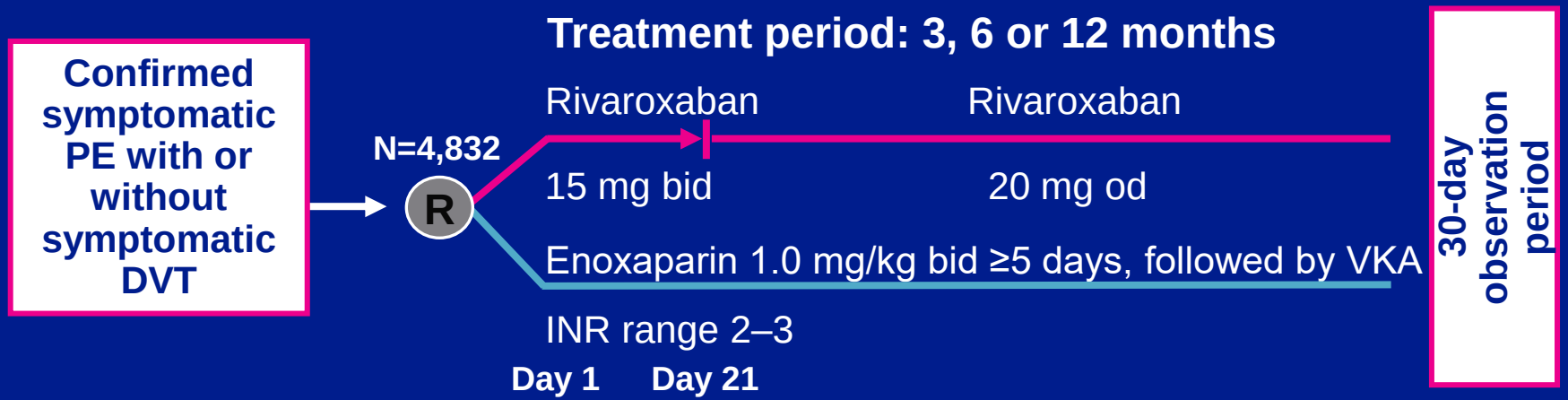
- Up to 48 hours' heparins/fondaparinux treatment permitted before study entry
- 88 primary efficacy outcomes needed



EINSTEIN PE: study design

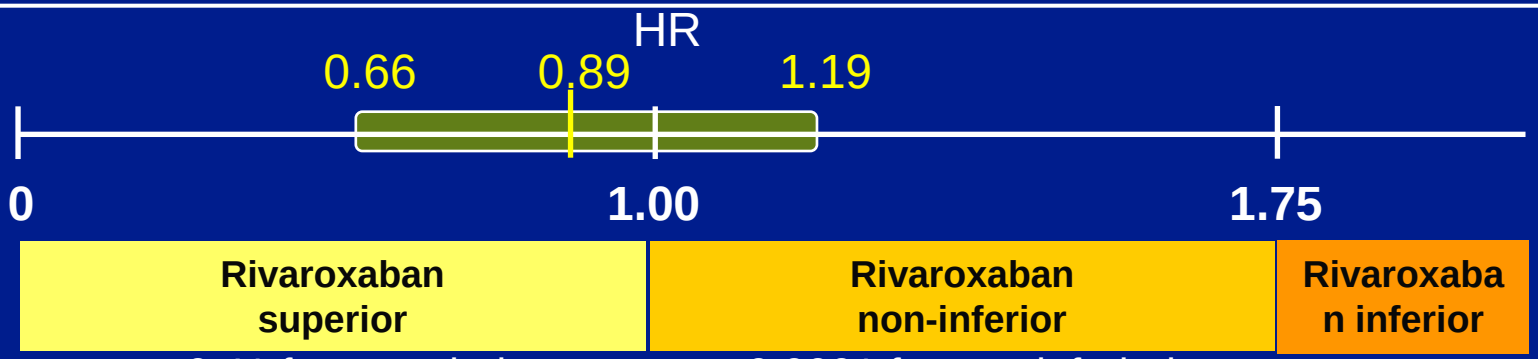
Randomized, open-label, event-driven, non-inferiority study

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



EINSTEIN DVT and PE pooled analysis: primary efficacy outcome analysis

	Rivaroxaban (N=4150)		Enoxaparin/VKA (N=4131)	
	n	(%)	n	(%)
First symptomatic recurrent VTE	**86**	**(2.1)**	**95**	**(2.3)**
Recurrent DVT	32	(0.8)	45	(1.1)
Recurrent DVT + PE	1	(<0.1)	2	(<0.1)
Non-fatal PE	43	(1.0)	38	(0.9)
Fatal PE/unexplained death where PE cannot be ruled out	15	(0.4)	13	(0.3)



p=0.41 for superiority (two-sided)

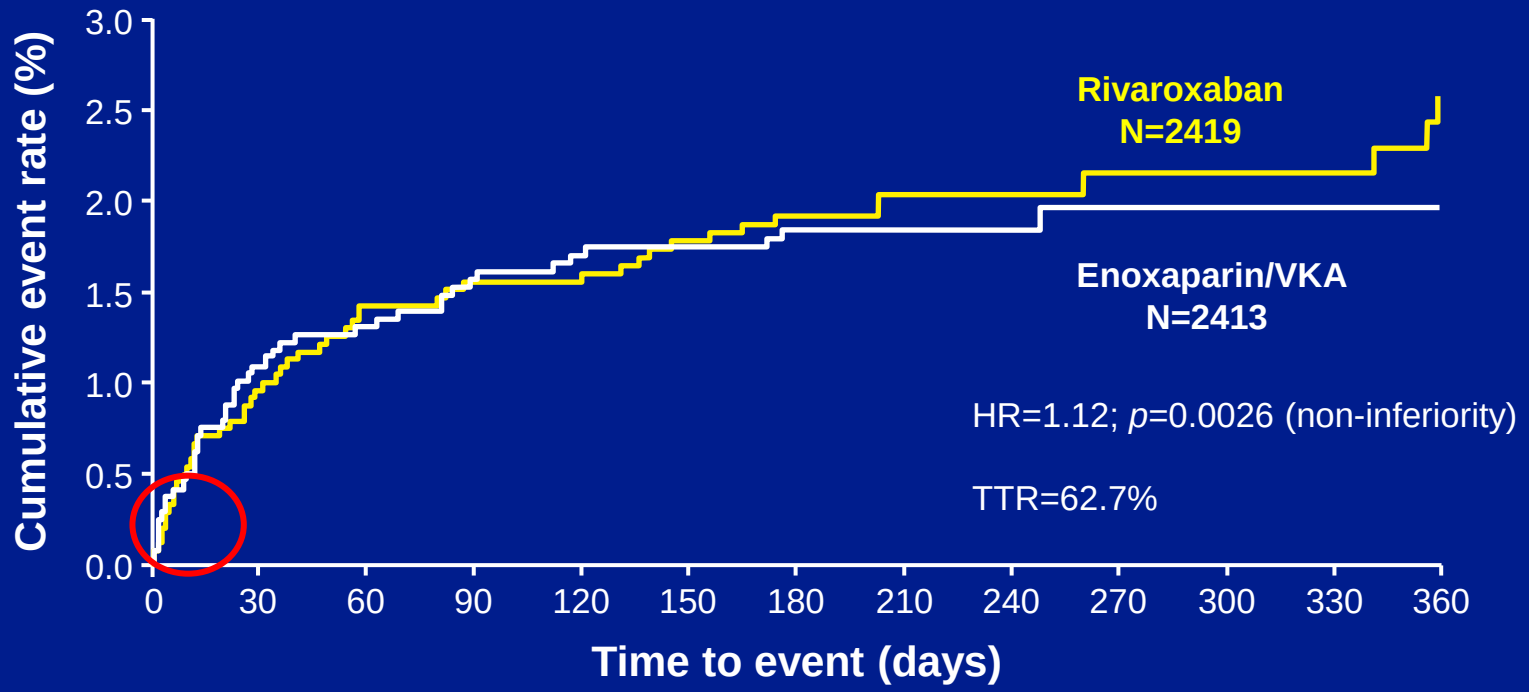
p<0.0001 for non-inferiority (one-sided)

ITT population

Büller HR *et al*. *N Engl J Med* 2012. DOI: 10.1056/NEJMoa1113572

The EINSTEIN–PE Investigators. *N Engl J Med* 2012; DOI: 10.1056/NEJMoa1113572

EINSTEIN PE: primary efficacy outcome: time to first event



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

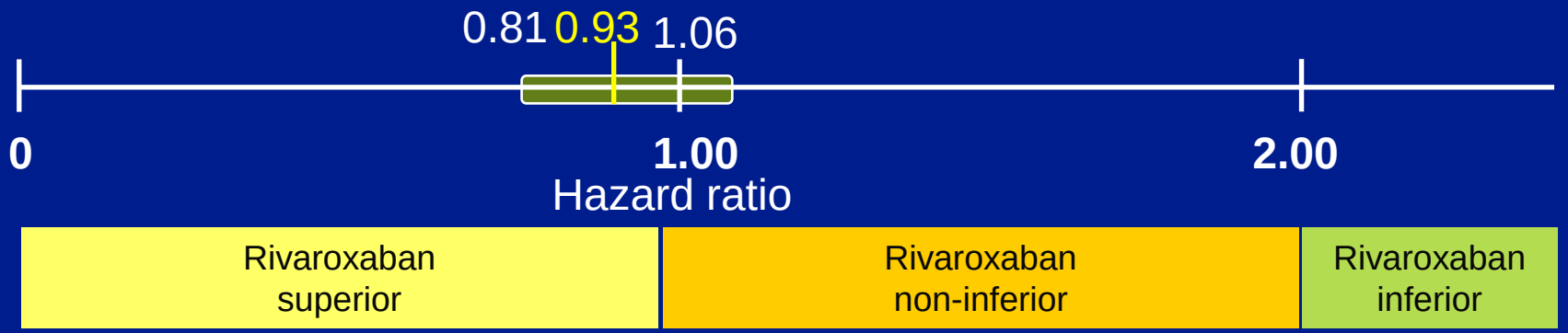
ITT population

Büller HR *et al*. *N Engl J Med* 2012. DOI: 10.1056/NEJMoa1113572

The EINSTEIN–PE Investigators. *N Engl J Med* 2012; DOI: 10.1056/NEJMoa1113572

EINSTEIN DVT and PE pooled bleeding analysis

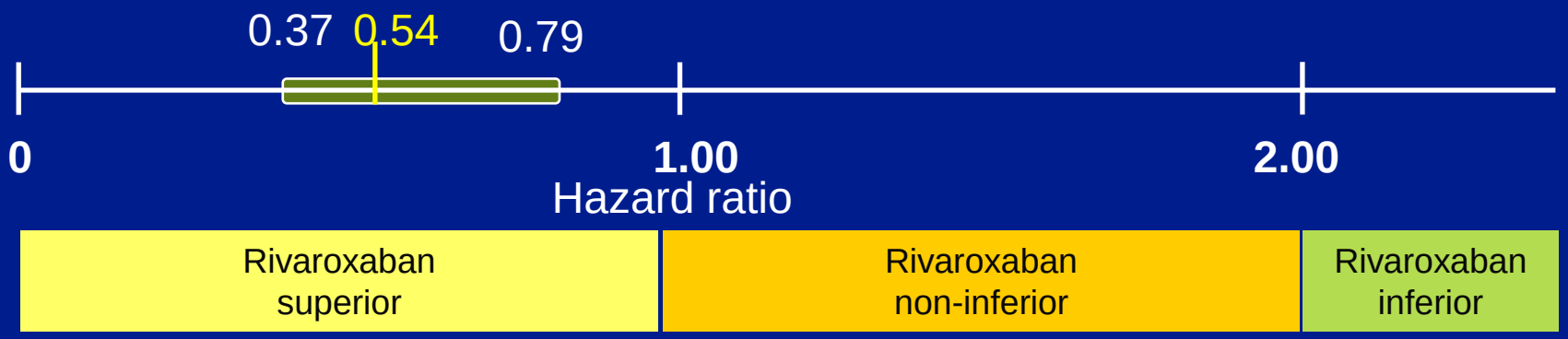
First major or non-major clinically relevant bleeding



p=0.27 for superiority (two-sided)

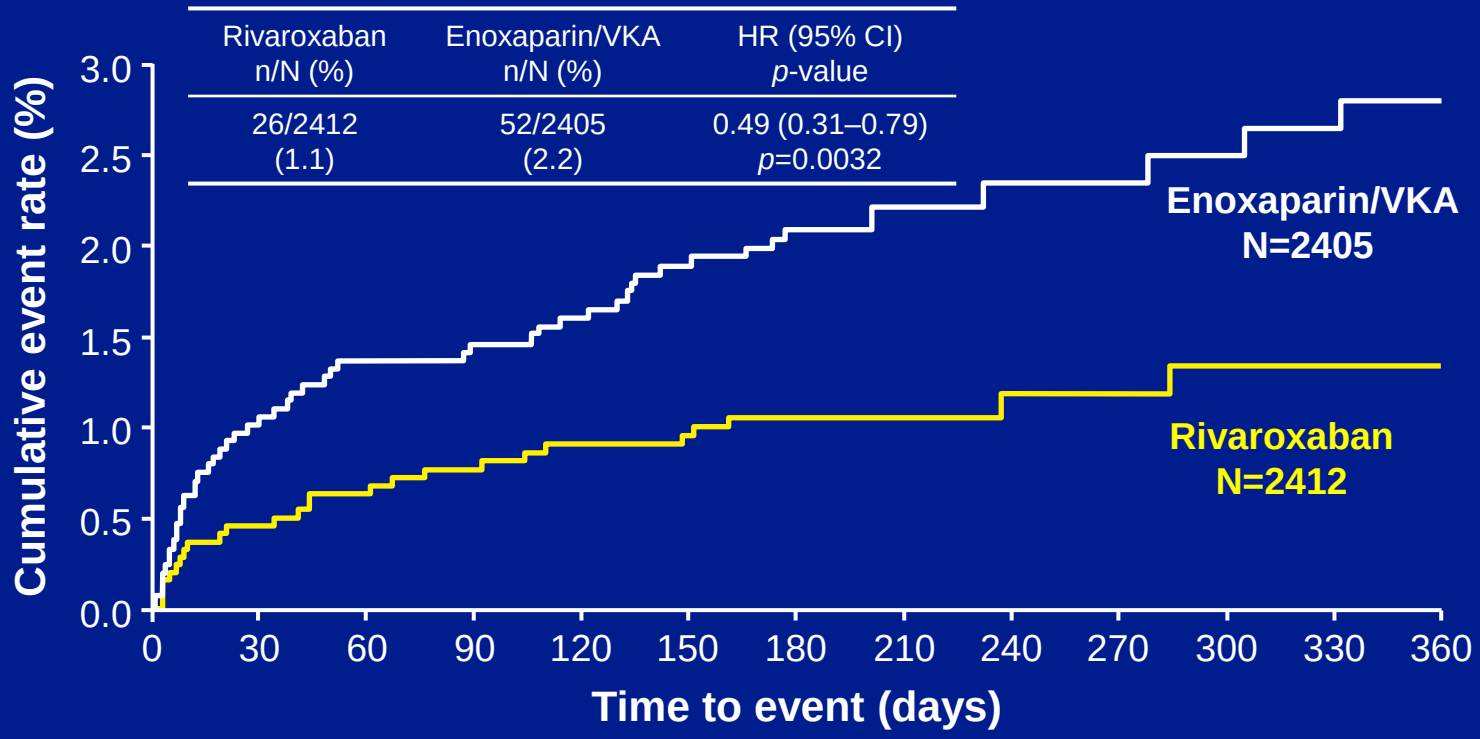
p<0.0001 for non-inferiority (one-sided)

Major bleeding



p=0.0018 for superiority (two-sided)

EINSTEIN PE: major bleeding



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

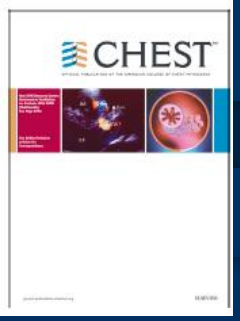
Safety population

Büller HR *et al*. *N Engl J Med* 2012. DOI: 10.1056/NEJMoa1113572

The EINSTEIN–PE Investigators. *N Engl J Med* 2012; DOI: 10.1056/NEJMoa1113572

NOACs

- Oral administration
- No requirement for routine coagulation monitoring and dose adjustement
- Wide therapeutic window
- Rapid onset of action
- Predictable pharmacokinetics and pharmacodynamics
- Minimal interactions with foods and other drugs
- Ability to inhibit free and clot-bound coagulation factors
- Low non-specific binding
- Availability of an antidote
- No unexpected toxicities
- Acceptable costs
- Ideal drugs for home treatment of DVT and PE



10th ACCP Guidelines 2016

2. **In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban or edoxaban over VKA therapy** (all Grade 2B). **For patients with DVT of the leg or PE and no cancer who are not treated with dabigatran, rivaroxaban, apixaban or edoxaban, we suggest VKA therapy over LMWH** (Grade 2C).

Treatment of Acute Pulmonary Embolism Out of Hospital

20. **In patients with low-risk PE and whose home circumstances are adequate, we suggest treatment at home or early discharge over standard discharge (e.g. after first 5 days of treatment)** (Grade 2B).

Othieno R, Cochrane Review 2011

Study	Setting	N. pat	Hep	Mean hs	r-VTE (%)	mb(%)	MB(%)	Death
Koopman	Hosp	198	UFH	8.1 d	8.6	7.6	2.0	8.1
	Home	202	LMWH	2.7 d	6.9	13.4	0.5	6.9
Levine	Hosp	253	UFH	6.5 d	6.7	2.3	1.2	6.7
	Home	247	LMWH	2.1 d	5.3	2.4	2.0	4.5
Boccalon	Hosp	102	LMWH	9.5 d	2.0	10.8	2.0	2.0
	Home	99	LMWH	1.4 d	1.0	17.2	2.0	0
Chong	Hosp	148	UFH	------	9.5	11.5	2.0	1.4
	Home	150	LMWH	------	2.7	10.0	0	1.3
Daskalopoulos	Hosp	53	UFH	------	11.3	5.7	7.5	3.8
	Home	55	LMWH	------	9.1	5.5	3.6	1.8
Ramacciotti	Hosp	97	UFH	7 d	7	9	3	------
	Home	104	LMWH	3 d	2	12	2	------

Ambulatory treatment of proximal lower-limb DVT in routine practice is effective and safe, is cost-effective and improves quality of life.

No increase in any of the 3 major outcomes (all-cause mortality, life-threatening bleeding, rVTE)

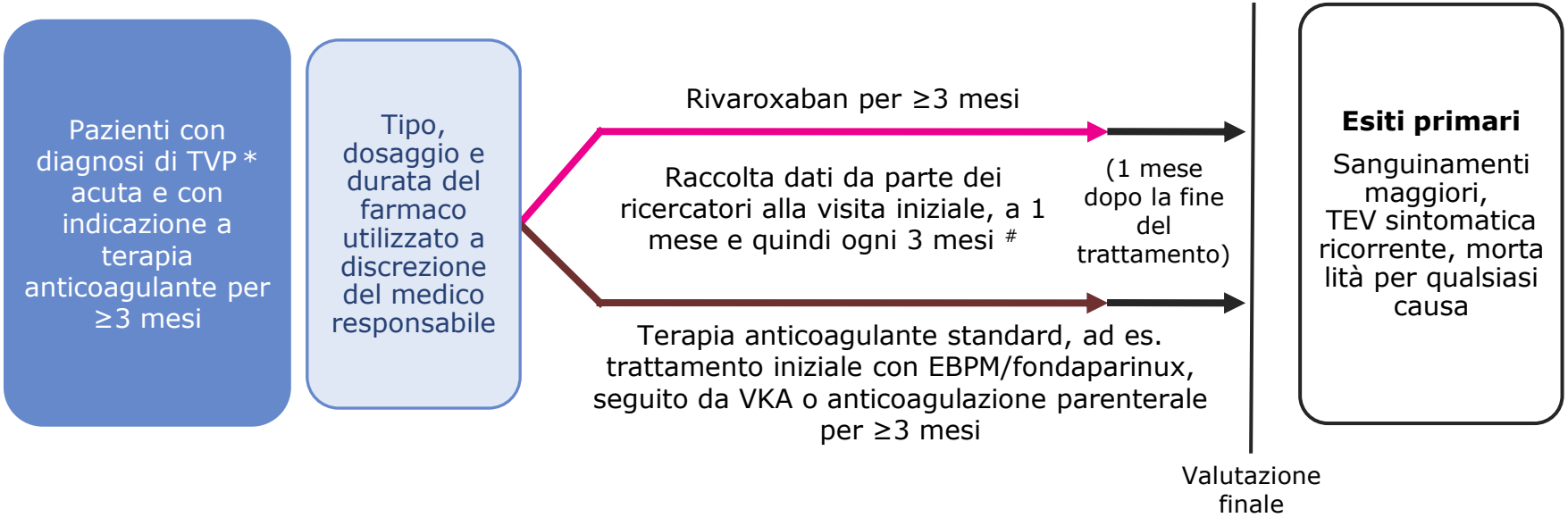
Othieno R, 2007; Levine M, 1996; Boccalon H, 2000; Schwarz T, 2001; Grau E, 2001; Lozano F, 2014

Progressive increase of number of patients treated at home with NOACs as compared to SOC with improvement of management, readmission, bleeding and quality of life

Mausbach LS, 2016

XALIA: Studio prospettico, non interventistico

Obiettivo: raccogliere dati *real-life* in pazienti con TVP acuta trattati con rivaroxaban o con terapia anticoagulante standard



ClinicalTrials.gov NCT01619007;
* Dopo approvazione EU per EP, TVP con EP concomitante consentita; EP isolata esclusa
# I dati sono stati raccolti durante la visita iniziale e le visite di follow-up di routine o per posta, telefono e posta elettronica
Ageno W, et al. *Thromb J* 2014;12:16

Esiti Clinici in corso di trattamento (propensity-score)

	Rivaroxaban (n=2505) n (%)	Anticoagulazione standard (n=2010) n (%)	Hazard ratio (95% CI)	*p*-value
Sanguinamento maggiore	**19** (0.8)	**43** (2.1)	**0.77** (0.40-1.50)	**0.44**
TEV ricorrente	**36** (1.4)	**47** (2.3)	**0.91** (0.54-1.54)	**0.72**
Mortalità, tutte le cause	**11** (0.4)	**69** (3.4)	**0.51** (0.24-1.07)	**0.07**

Popolazione secondo propensity score

Ospedalizzazioni, Durata Ospedalizzazioni e Durata del Trattamento

	Rivaroxaban % (n/N)	Anticoagulazione standard % (n/N)	Means ratio (95% CI)
Descrizione			
Numero pazienti ospedalizzati	27.6% (727/2619)	47.0% (1011/2149)	
Lunghezza ricovero media, (giorni)	4.8	7.5	0.64 (0.60-0.69)
Durata media del trattamento (giorni)	184	190	
Score di propensità aggiustato			
Numero pazienti ospedalizzati	28.6% (717/2505)	45.9% (923/2010)	
Lunghezza ricovero media (giorni)	5.0	7.7	0.66 (0.61-0.72)
Durata media del trattamento (giorni)	182	190	

Lunghezza di ricovero media calcolata dal numero di pazienti ospedalizzati

Durata di ricovero aggiustata per cancro

Trends in LOS in acute PE over the years. What is changing in the era of DOACs?

	DOACs	No DOACs	Total	*p*
Number	100	228	328	-
Males/Females	41%/59%	44,7%/55,3%	43,6%/56,4%	ns
Mean age ± SD (years)	77 ± 13	75 ± 13	76 ± 13	ns
Median age (IQR) (years)	80 (72-85)	77 (69-84)	78 (69-85)	ns
Mean LOS ± SD (days)	9± 5	11± 6	10 ± 6	<0.005
		VKAs 11± 6		
		LMWH/fondaparinux 11± 6		
Median LOS (IQR) (days)	7 (5-10)	10 (6-14)	9 (6-13)	<0.001
		VKAs 9 (7-14)		
		LMWH/fondaparinux 10 (5-14)		

Conclusion: DOACs are a real pharmacological option in acute pulmonary embolism, even in patients at high/intermediate-high risk.
Since the marketing of DOACs, LOS seems significantly lower in patients treated by using DOACs compared with patients treated by using the other anticoagulant molecules.
In patients prescribed DOACs, hospital costs could be dramatically saved.

Masotti L. et al. J Cardiovasc Med 2016; [Epub ahead of print]

Angiology Padova

- 239 patients treated with Rivaroxaban from march 12, 2014 to November 7, 2016 for VTE; from march 2014 only 2% of patients still treated with VKAs
- **88/239** patients switched from VKAs to Rivaroxaban, **151** naive patients
- Rivaroxaban 20 mg 90%, Rivaroxaban 15 mg 10%
- Median follow up 7,6 months (IQR 3-32)
- EOT 55 patients (39 for 3 mts, 12 for 6 mts, 4 for 12 mts)
- Death: 5 patients (4 for cancer, 1 for severe heart failure)
- Great satisfaction of all patients
- 94% of patients treated immediately at home

Source: personal data on file

Antidoti

Specific reversal agents in development for NOACs

Reversal Agents in DOACS

	Idarucizumab	Andexanet alfa	Ciraparantag PER 977
Structure	Fully humanized Fab	Recombinant, modified human inactive Factor Xa	Di-arginine piperazine
Target	Dabigatran only	Factor Xa Inhibitors (Riva; Apix; Edox)	All NOACs (Dabi; Riva; Apix; Edox) UFH, LMWH, fondaparinux
Mechanism	Non-competitive binding to Dabigatran with 350 times greater affinity than thrombin	Binds competitively to direct FXa inhibitors	Binds to heparins and oral FXa and IIa inhibitors through hydrogen Bonding

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

Siegal D et al, N Engl J Med 2015;373:2413-24.

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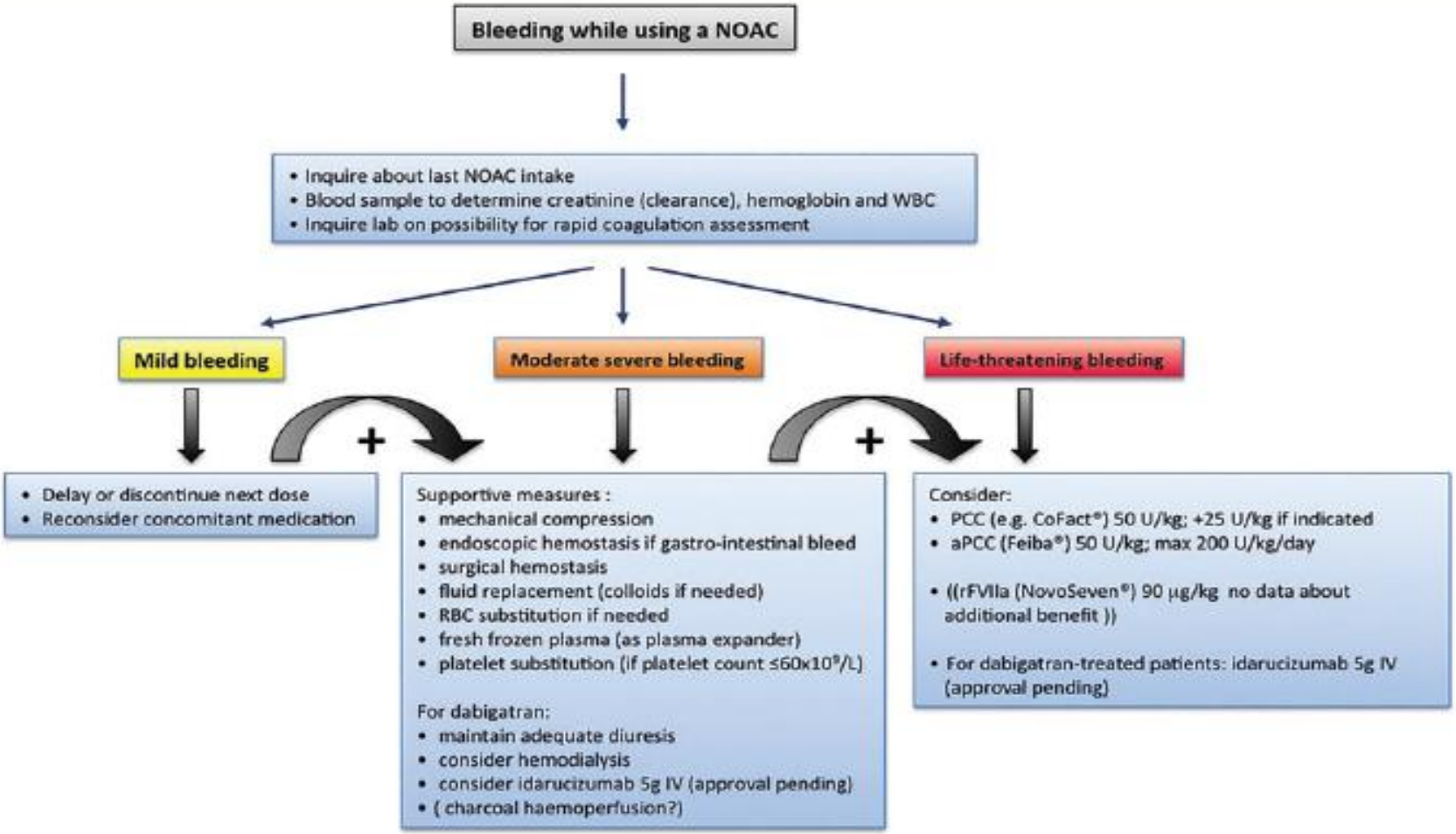
- Cohort study in older healthy volunteers
- Andexanet bolus +/- infusion
- a 400-mg intravenous bolus (30 mg per minute) (part 1) or as a 400-mg intravenous bolus followed by a continuous infusion of 4 mg per minute for 120 minutes (480 mg in total) (part 2)

- Effect on anti-Xa activity of apixaban (5 mg x 2 x 3 days) or rivaroxaban (20 mg x days)
- Andexanet reversed the anticoagulant activity of apixaban and rivaroxaban in
  older healthy participants within minutes after administration and for the duration of infusion, without evidence of clinical toxic effects.

Gestione dei sanguinamenti




LOONEY TUNES
"That's all Folks!"