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CENTRI EMOSTASI E TROMBOSI, SPECIALISTI OSPEDALIERI E MEDICINA DEL TERRITORIO NELLA GESTIONE DELLE MALATTIE EMORRAGICHE E TROMBOEMBOLICHE

La terapia delle complicanze e la gestione degli antidoti

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Complicanze emorragiche in corso di terapie anticoagulanti

- Quanto frequenti
- Quali conseguenze
- Quale approccio clinico ottimale

Incidence of major bleeding during VKA therapy

- 1999 patients followed up for 3865 patient-years
- incidence of life-threatening bleeding:

0.83 events/100 patient-years
(95% CI 0.54-1.12)

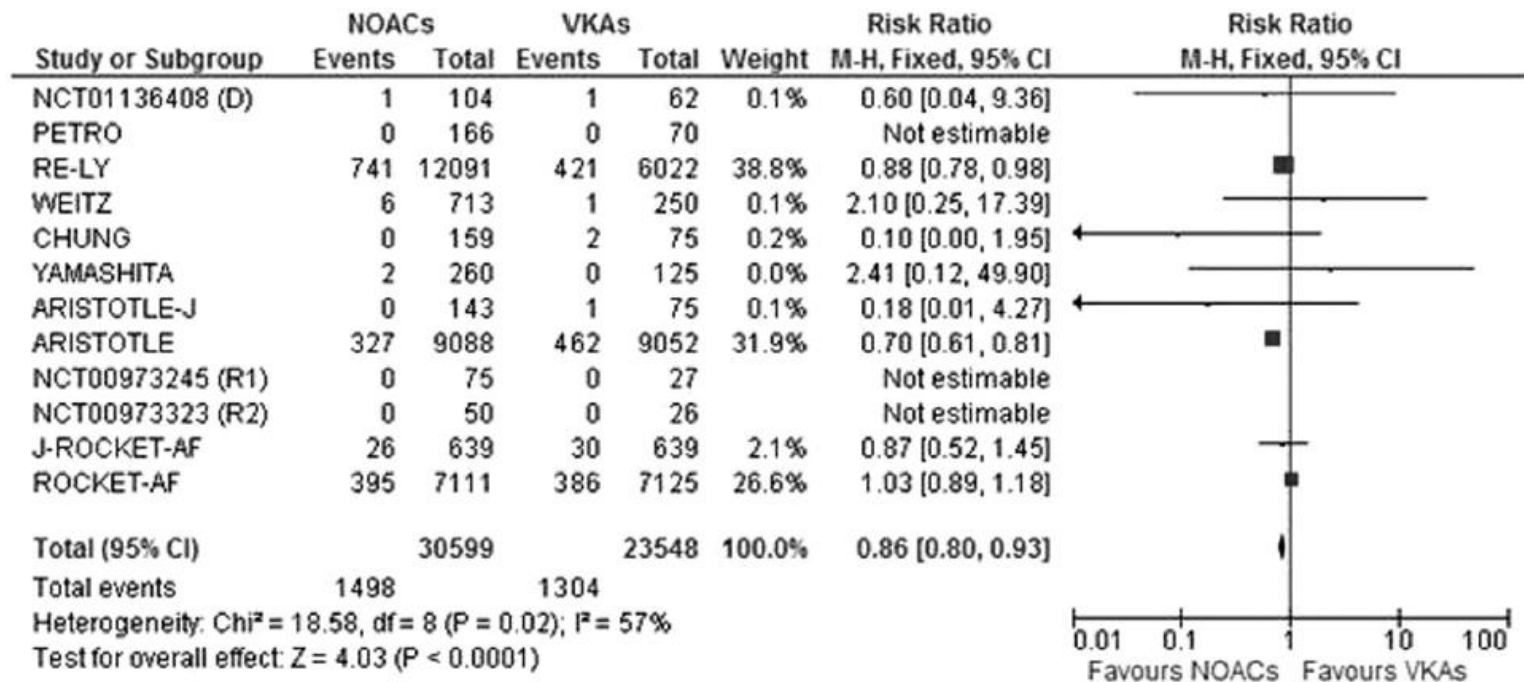
Incidence* of MB in VKA inception cohorts

Study	Intracranial	GIB	Other	Total
<i>Start, unpublished</i>	0.43	0.30	0.63	1.4
<i>Palareti et al. The Lancet, 1996.</i>	0.19	0.33	0.57	1.1
<i>Sjogren et al. Thromb Haemost, 2015. †</i>	0.37	0.73	1.16	2.2
<i>Hylek et al. Circulation, 2007.</i>	2.49	3.04	1.66	7.2
<i>Steffensen et al. J Intern Med, 1997.</i>	1.30	1.83	1.44	5.9
<i>Beyth et al. Am J Med, 1998.</i>	0.91	1.59	2.95	5.0

Incidence rates per 100 persons-years

† population-based, TTR 76.5%

DOAc: a significant safety profile



Major bleeding

Dentali et al. Circulation, 2012.

Rivaroxaban-related bleeding in the Dresden registry

	All patients	SPAF	VTE
n (%)	1775 (100)	1200 (67.6)	575 (32.4)
Any bleeding, % (95% CI)	59.4 (55.2-63.9)	59.3 (54.4-64.6)	59.6 (51.7-68.4)
Minor bleeding, % (95% CI)	36.3 (33.2-39.7)	35.8 (32.2-39.7)	37.8 (31.8-44.6)
NMCR bleeding, % (95% CI)	19.7 (17.6-22.1)	20.7 (18.1-23.5)	17.2 (13.5-21.6)
Major bleeding, % (95% CI)	3.4 (2.6-4.4)	3.1 (2.2-4.3)	4.1 (2.5-6.4)

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Short-term consequences of Major Bleeding in the RE-LY database

	VKA	Dabigatran
Hospitalization %	57	56.5
Length of stay, mean	8.9	8.4
Nights in ICU, mean	2.7	1.6
Surgery %	15	12.1
Hb loss g/dL,mean	3.0	3.8

Majeed et al. Circulation 2013

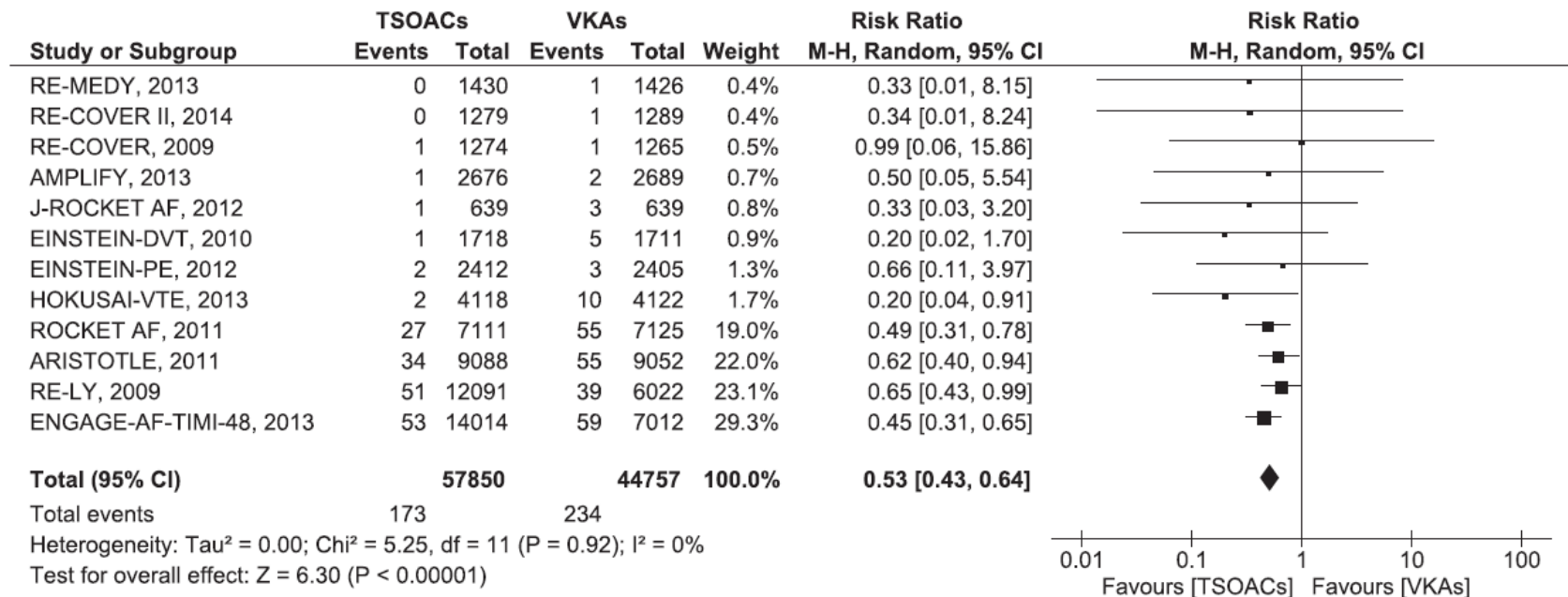
Rivaroxaban-related bleeding in the Dresden registry

1082 bleeding events in 762 patients	Conservative (no treatment/ compression/tamponade/transfusion)	Surgery or intervention	RBC	Vitamin K	FFP	PCC	rFVII
Minor 637/1082 (58.9%)	637/637 (100.0)	0	0	0	0	0	0
NMCR 379/1082 (35.0%)	328/379 (86.5)	51/379 (13.5)	0	0	0	0	0
Major 66/1082 (6.1%)	41/66 (62.1)	25/66 (37.9)	40/66 (60.6)	1/66 (1.5)	6/66 (9.1)	6/66 (9.1)	0
Total	1006/1082 (93.0)	76/1082 (7.0)	40/1082 (3.7)	1/1082 (0.1)	6/1082 (0.6)	6/1082 (0.6)	0

rFVII, recombinant factor VII; vitamin K, vitamin K supplementation.

Beyer-Westendorf et al. Blood, 2014.

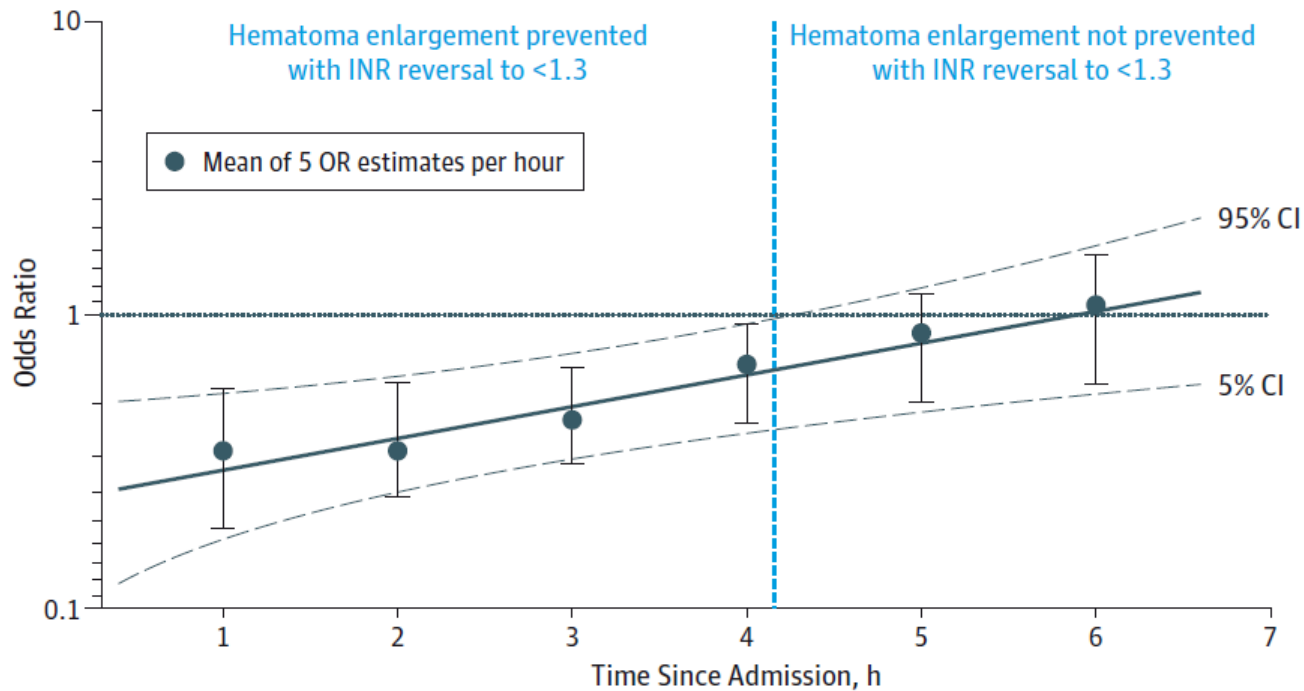
Bleeding in anticoagulation: impact on mortality



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In ICH, time to reverse VKA is critical



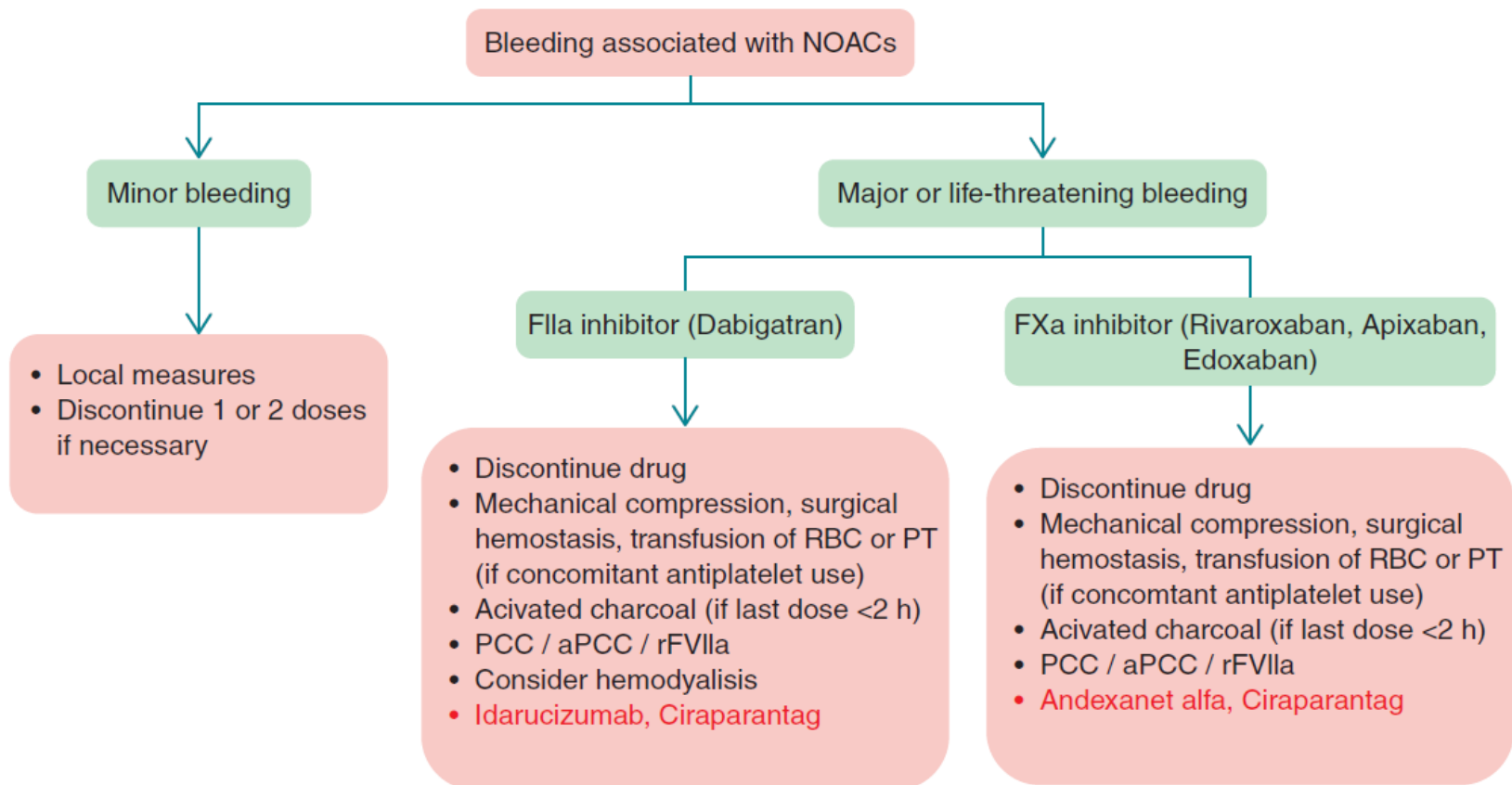
Kuramatsu et al. JAMA, 2015

Oral anticoagulants: time to spontaneous reversal

	Lag-time (hours)	$t_{1/2}$ (hours)	Time to reverse (Lag+2 $t_{1/2}$)	Time to reverse CrCl<30 ml/h
Warfarin	30	50	130 (5.4 days)	-
Dabigatran	-	13	≈26	60
Rivaroxaban	-	7-11	≈20	? 1.5x?
Apixaban	-	9-14	≈24	? 1.5x?
Edoxaban	-	9-11	≈24	? 1.5x?

Garcia, Blood 2010
Stangier, Clin Pharmacokin 2010
Agno, Chest 2012

Proposed management algorithm



Clinical Approach to DOAC-related bleeding

1. Assess patient condition

- Type of bleeding (e.g., intracranial? Other?)
- Hemodynamic stability
- Hemoglobin level
- Age and comorbidities (e.g., presence of cardiopathy)

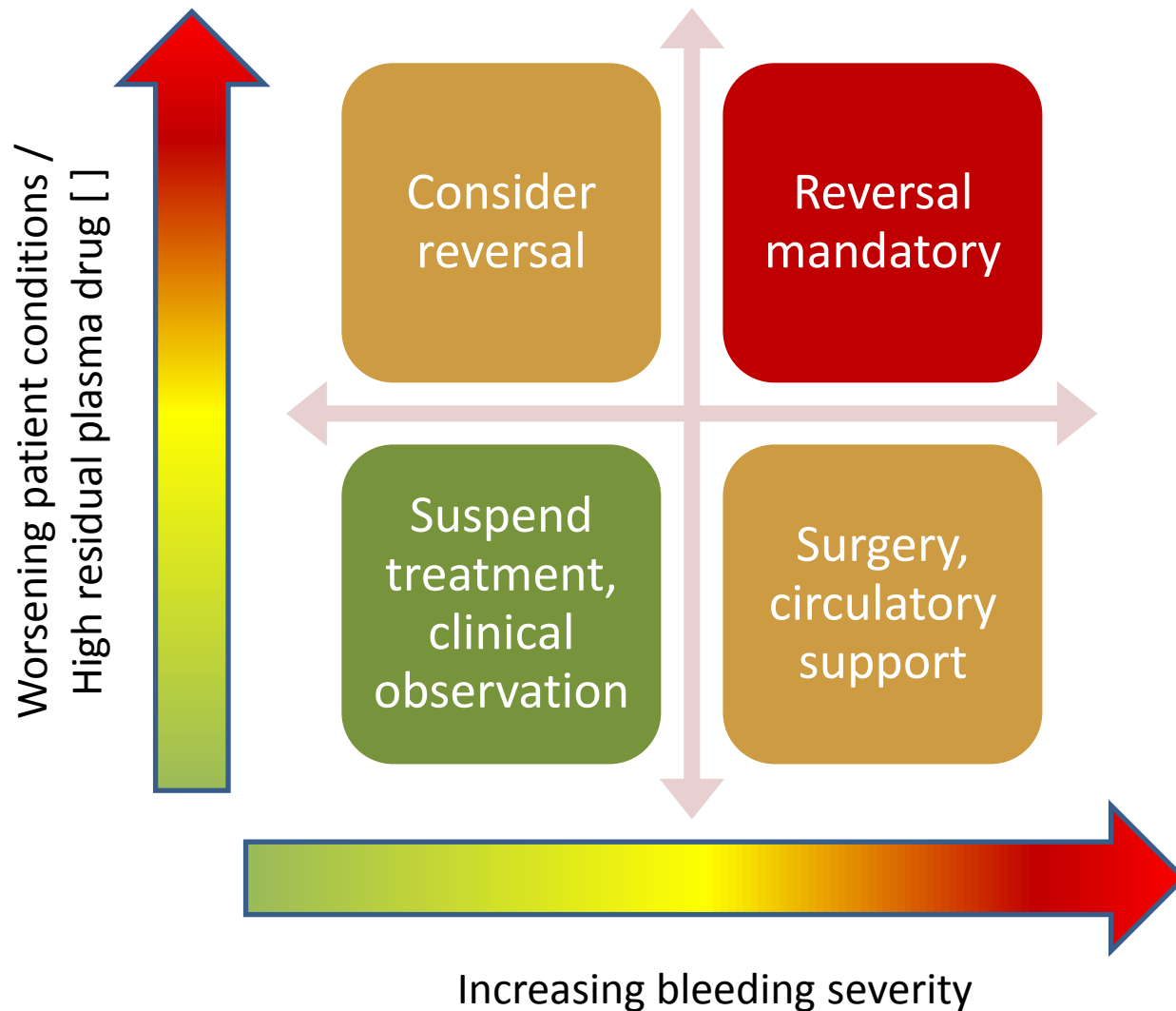
Clinical Approach to DOAC-related bleeding

1. Assess patient condition
2. Assess anticoagulant status
 - Measure PT, PTT, TT, AND specific tests if available
 - Type of DOAC used
 - Determine time of last drug intake
 - Concomitant use of antiplatelet agents

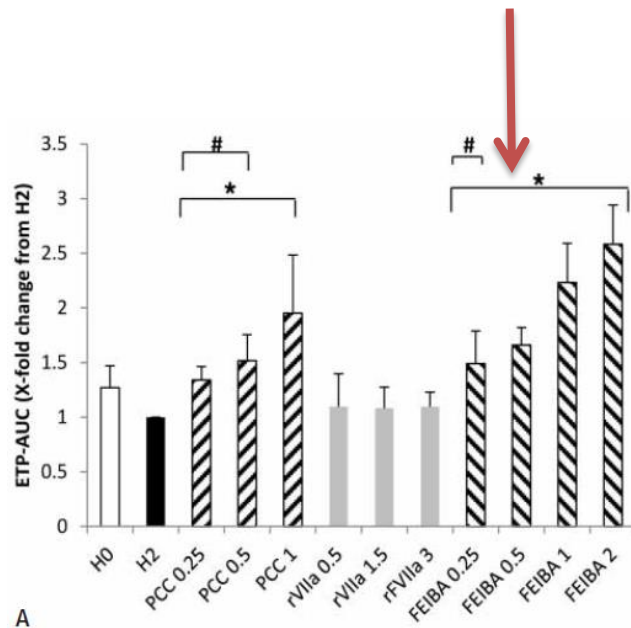
Clinical Approach to DOAC-related bleeding

1. Assess patient condition
2. Assess anticoagulant status
3. Assess excretory function
 - Measure CrCl/hepatic function
 - Maintain diuresis and circulatory support

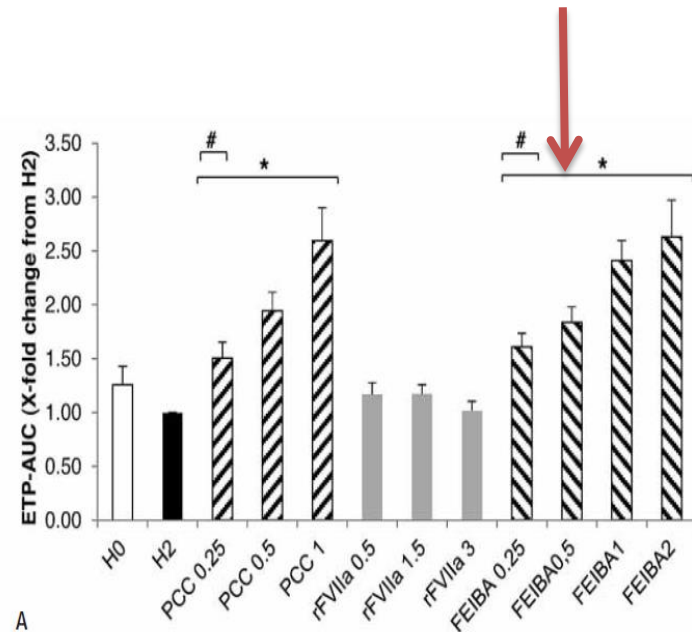
Clinical Approach to DOAC-related bleeding



FEIBA 40U/kg revert rivaroxaban *and* dabigatran *ex-vivo*



A

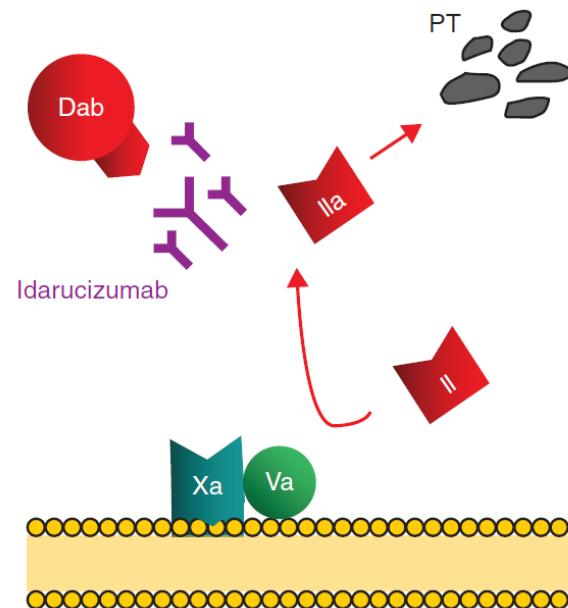


A

Marlu et al. Thromb Haemostas 2012

Specific inhibitors: idarucizumab

- Monoclonal antibody to dabigatran
- $K_m \sim 350\times$ thrombin
- Filtered by normal kidney
- Risk of anti-X antibodies unknown



Idarucizumab (PraxBind TM): clinical study

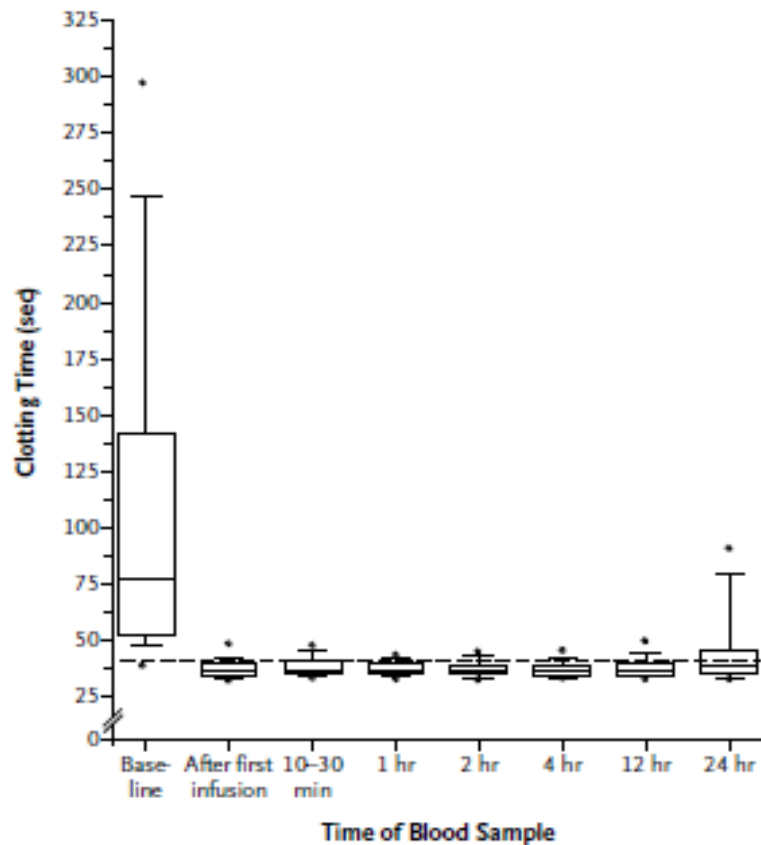
Characteristic	Group A (N= 51)	Group B (N= 39)	Total (N= 90)
Age — yr			
Median	77.0	76.0	76.5
Range	48–93	56–93	48–93
Male sex — no. (%)	32 (63)	18 (46)	50 (56)
Elevated dilute thrombin time at baseline — no. (%)	40 (78)	28 (72)	68 (76)
Elevated ecarin clotting time at baseline — no. (%)	47 (92)	34 (87)	81 (90)
Type of bleeding — no. (%)§			
Intracranial	18 (35)	—	18 (20)
Trauma-related	9 (18)	—	9 (10)
Gastrointestinal	20 (39)	—	20 (22)
Other	11 (22)	—	11 (12)

Pollack et al. New England Journal of Medicine, 2015.

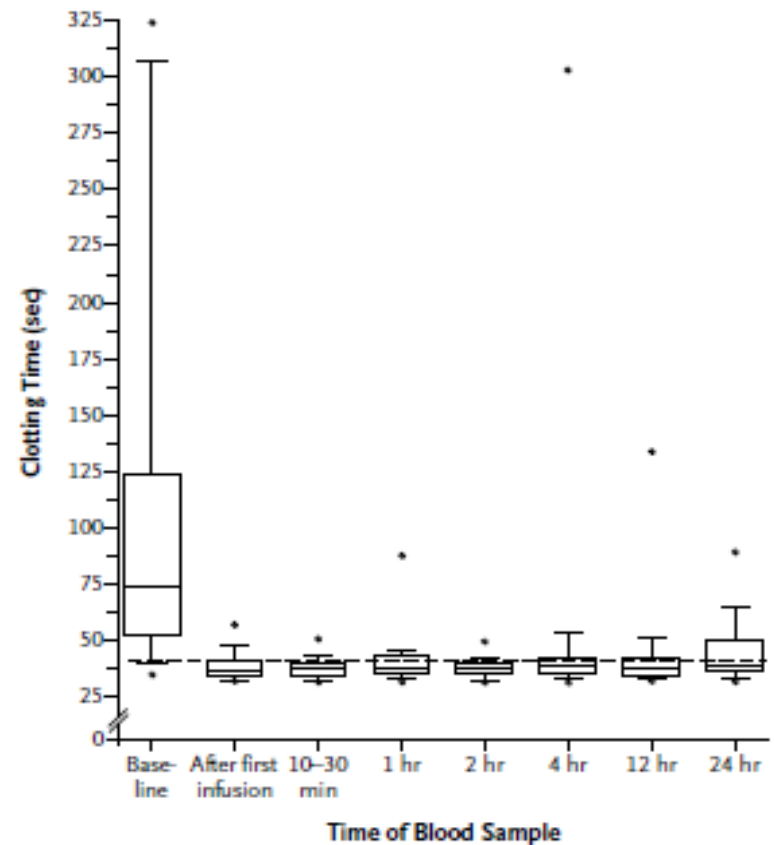
Idarucizumab: clinical study

two 50-ml bolus infusions, each containing 2.5 g of idarucizumab, no more than 15 minutes apart: 88-89% ECT reversal

C Ecarin Clotting Time in Group A



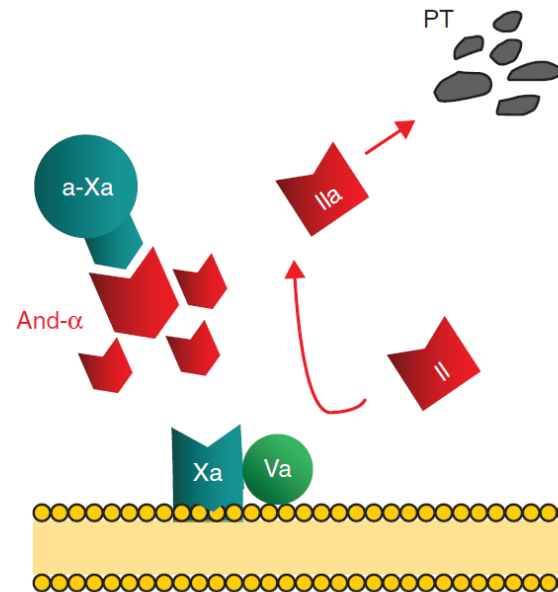
D Ecarin Clotting Time in Group B



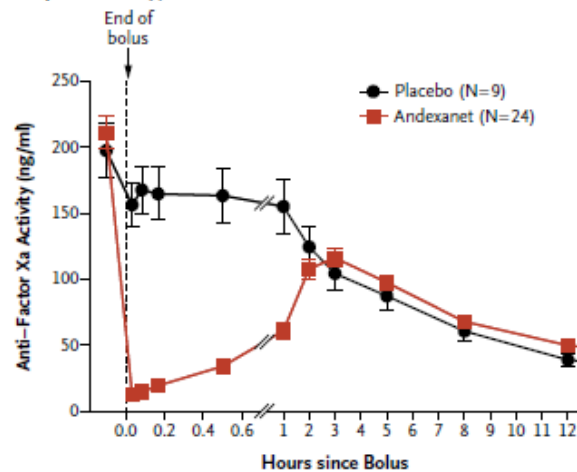
Pollack et al. New England Journal of Medicine, 2015.

Specific inhibitors: andexenet α

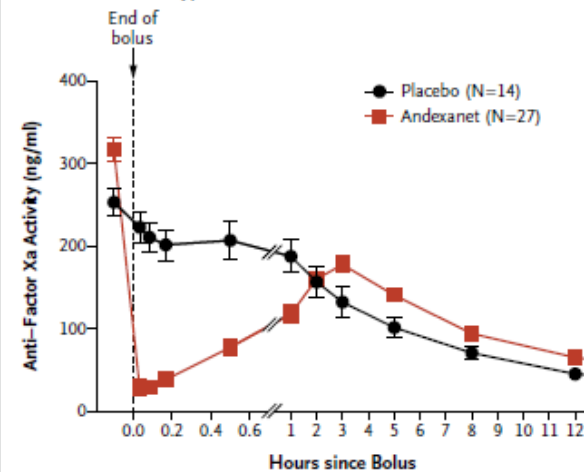
- Modified rFXa
- Ser419→Ala
- Variable inactivation of rivaroxaban, edoxaban and apixaban
- Risk of anti-X antibodies unknown



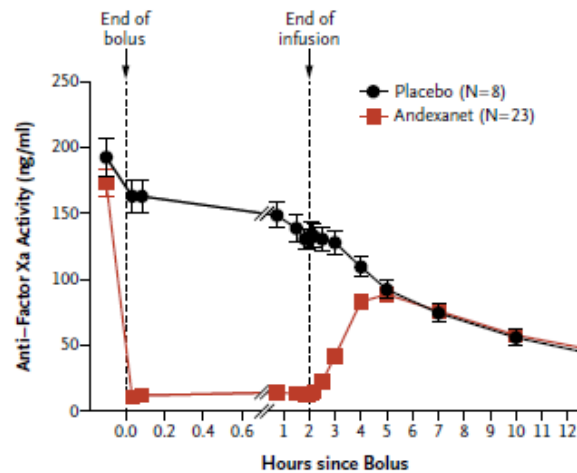
A Apixaban Study, Andexanet Bolus



B Rivaroxaban Study, Andexanet Bolus

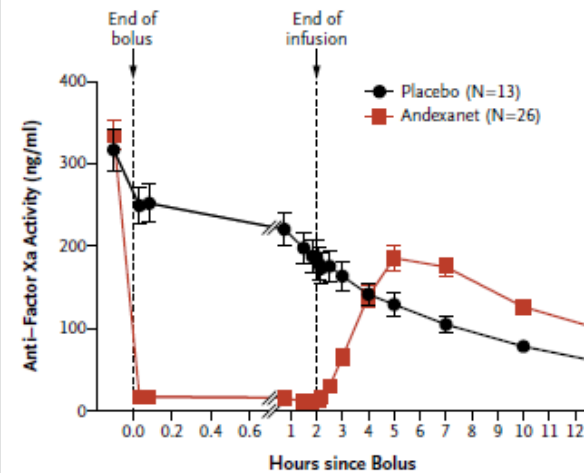


C Apixaban Study, Andexanet Bolus plus Infusion



400 mg +- 4 mg ev/hr

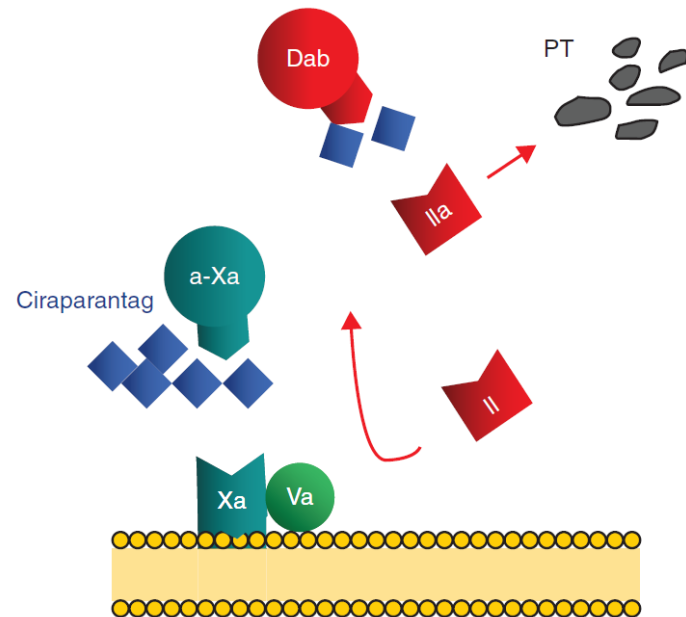
D Rivaroxaban Study, Andexanet Bolus plus Infusion



800 mg +- 8 mg ev/hr

Aspecific inhibitors: Aripazine (cirapantag)

- Small molecule binding most anticoagulants
- Unclear mechanism
- Variable effect on clotting



Conclusioni

- Il sanguinamento in corso di terapia con DOAC va affrontato in maniera «globale»
- Probabilmente nella maggior parte dei casi può bastare un atteggiamento conservativo
- Giudizio clinico, uso corretto del laboratorio e disponibilità di antidoto sono fattori chiave per la sicurezza nel paziente critico