GRANDE ATTESA, MA ADESSO CHE ABBIAMO GLI ANTIDOTI ?

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Abano, 9-12 Novembre 2016

I nuovi farmaci anticoagulanti orali

- Si sostiene che i DOAC abbiano un ampio intervallo terapeutico.

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- Ma, in linea di logica, se non c’è non c’è, mentre se c’è, la definizione di ampio è solo una questione di scala.

I nuovi farmaci anticoagulanti orali

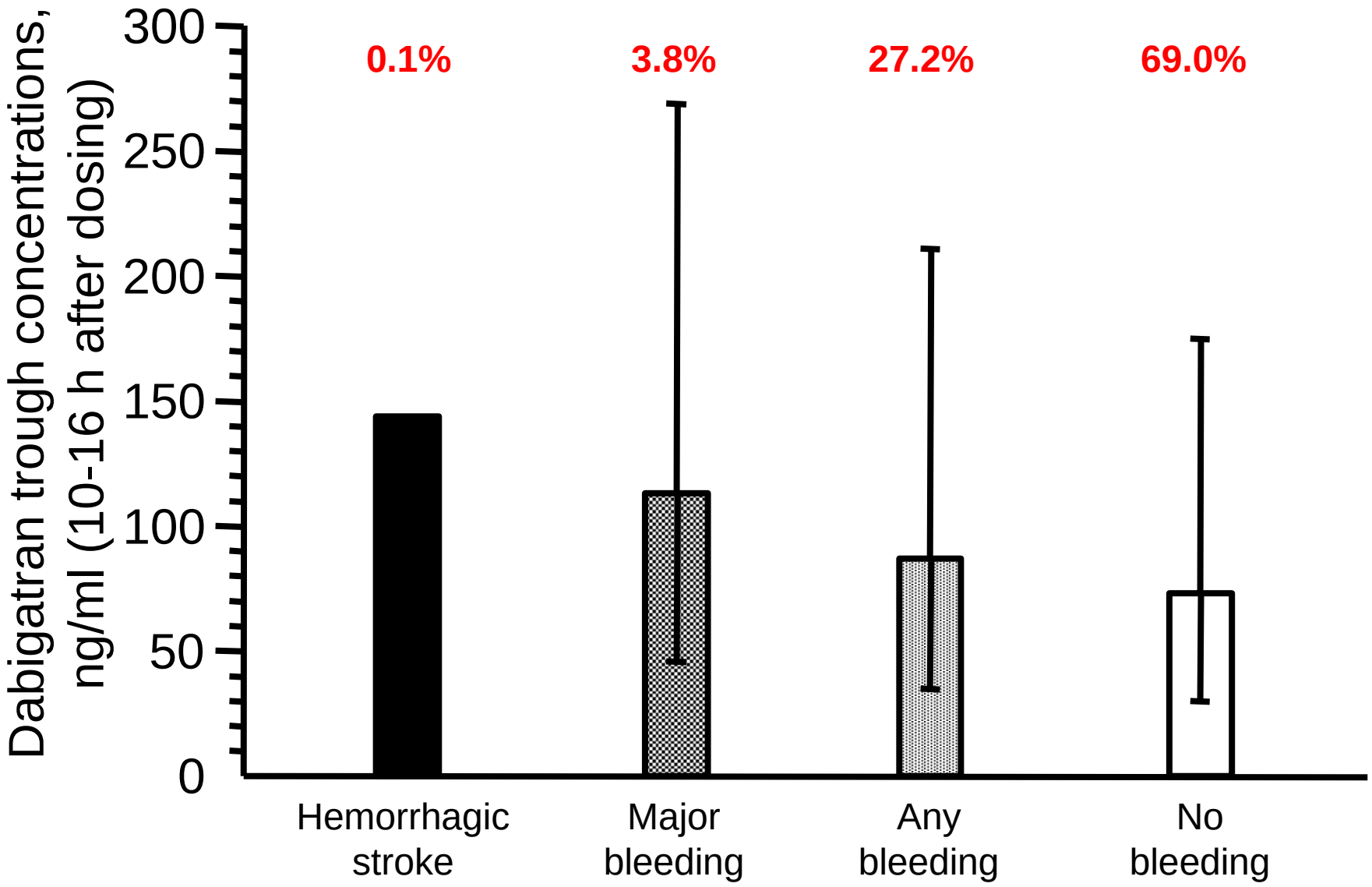
- Si sostiene che i DOAC abbiano un ampio intervallo terapeutico.
- Ma, in linea di logica, se non c'è non c'è, mentre se c'è, la definizione di ampio è solo una questione di scala.
- Il paradigma dell'ampio range terapeutico non è piuttosto solo ampia variabilità interindividuale ?

Steady state trough plasma concentrations of DOACs (ng/mL)

DOAC	Dosaggio (mg)	ng/ml (mediana)	ng/ml (intervallo)	Anti-Xa (UI)	Anti-Xa (intervallo)
Dabi	110 bid	66	28-155	-	-
Dabi	150 bid	93	40-215	-	-
Riva	20 sid	32	6-249	0.32	0.06-2.49
Apix	2.5 bid	79	34-162	1.20	0.51-2.40
Apix	5.0 bid	103	41-230	1.50	0.61-3.40
Edox	30 sid	18	10-32	0.35	0.21-0.57
Edox	60 sid	36	19-62	0.64	0.37-1.12

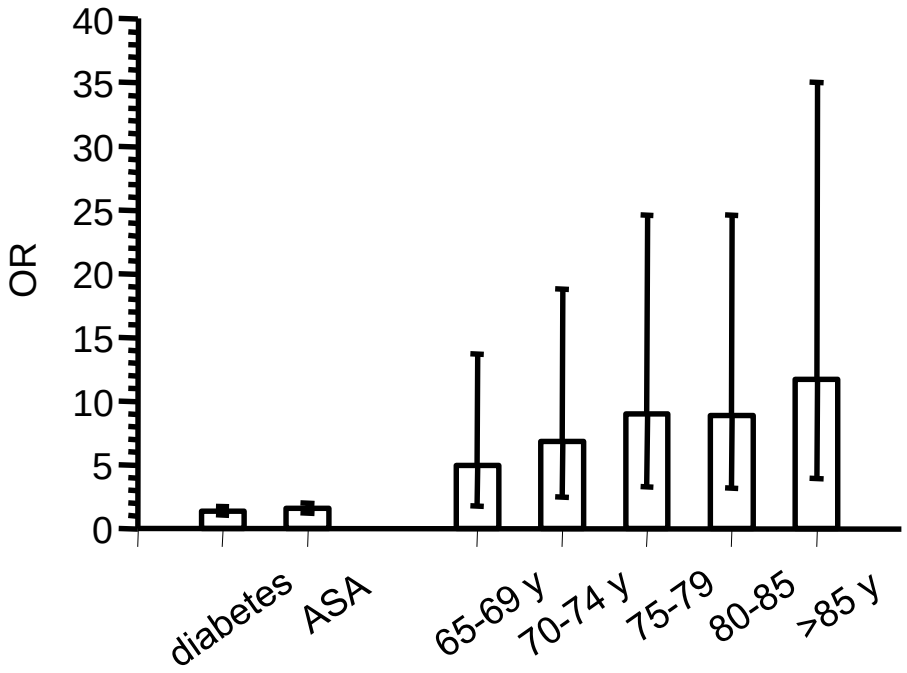
10-90° percentile
5-95° percentile
interquartile

Reilly PA, et al. JACC 2014;63:321-8

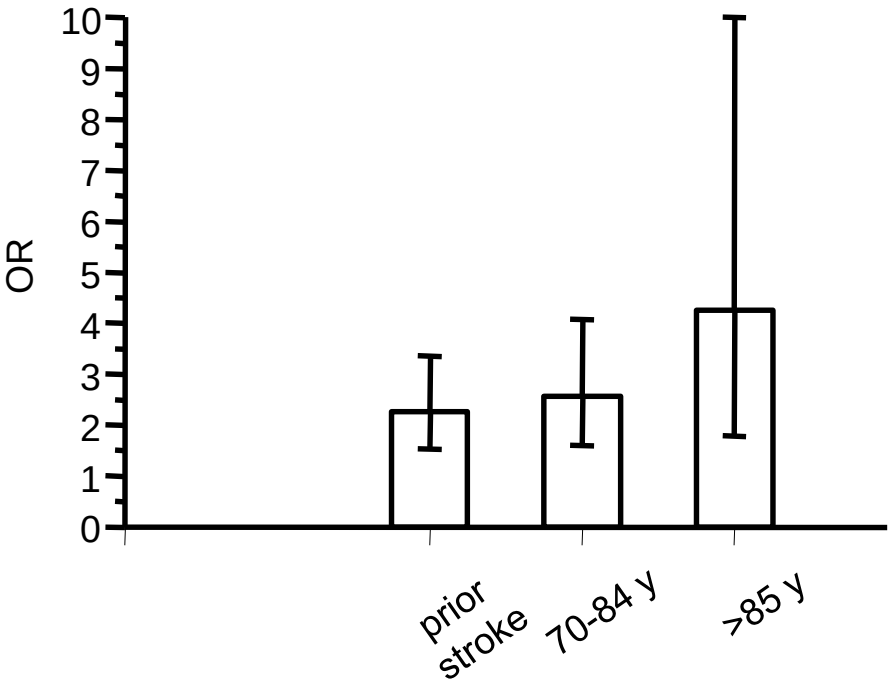


Reilly PA, et al. JACC 2014;63:321-8

Major Bleeding



Stroke/SE



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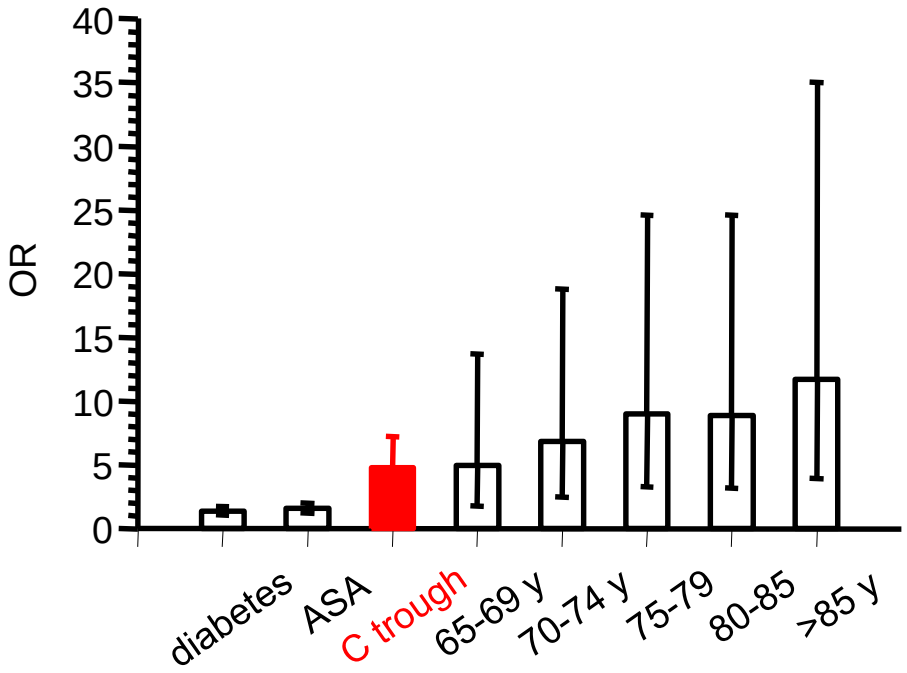
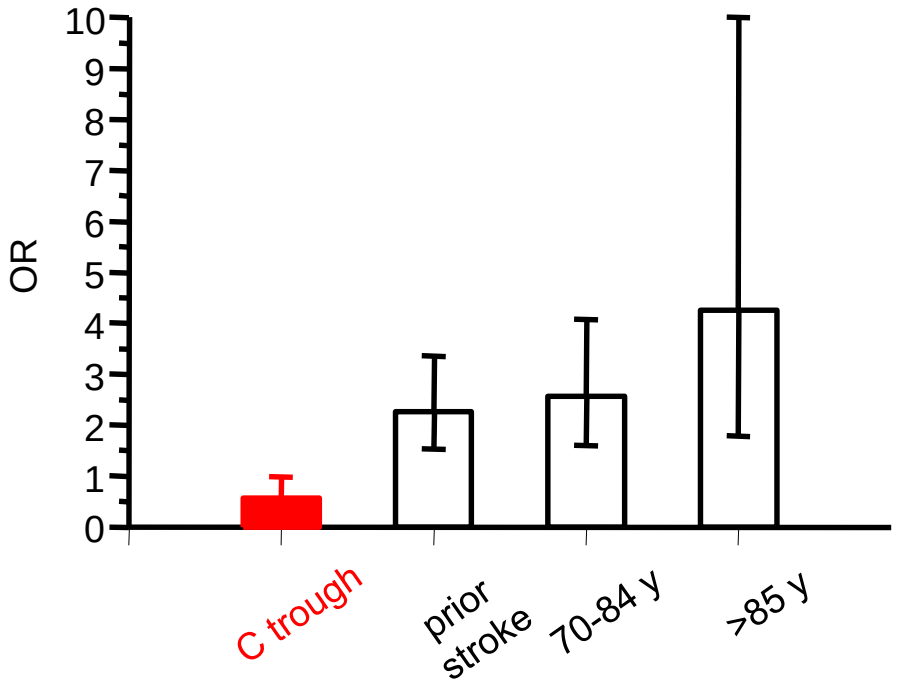
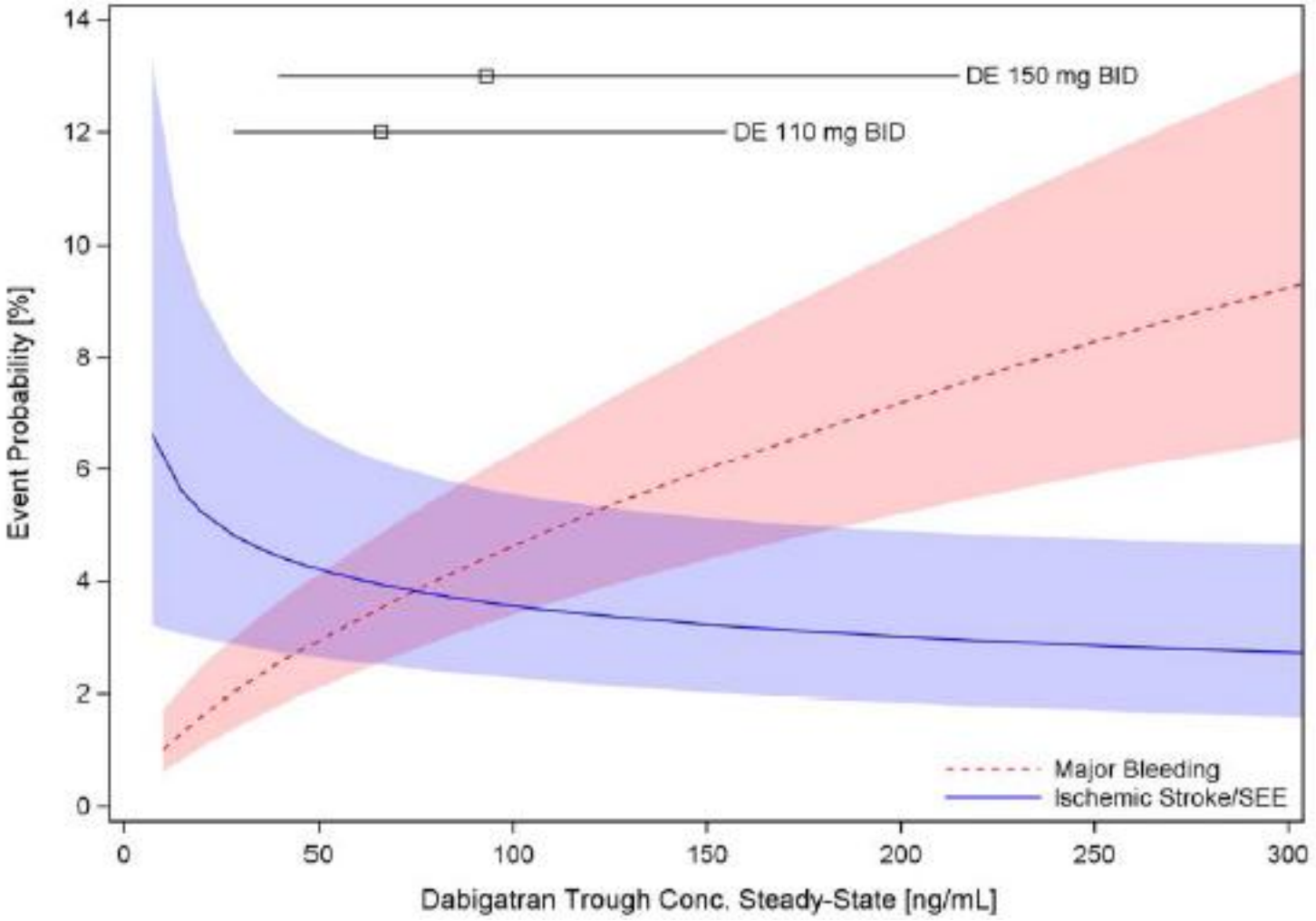


Stroke/SE

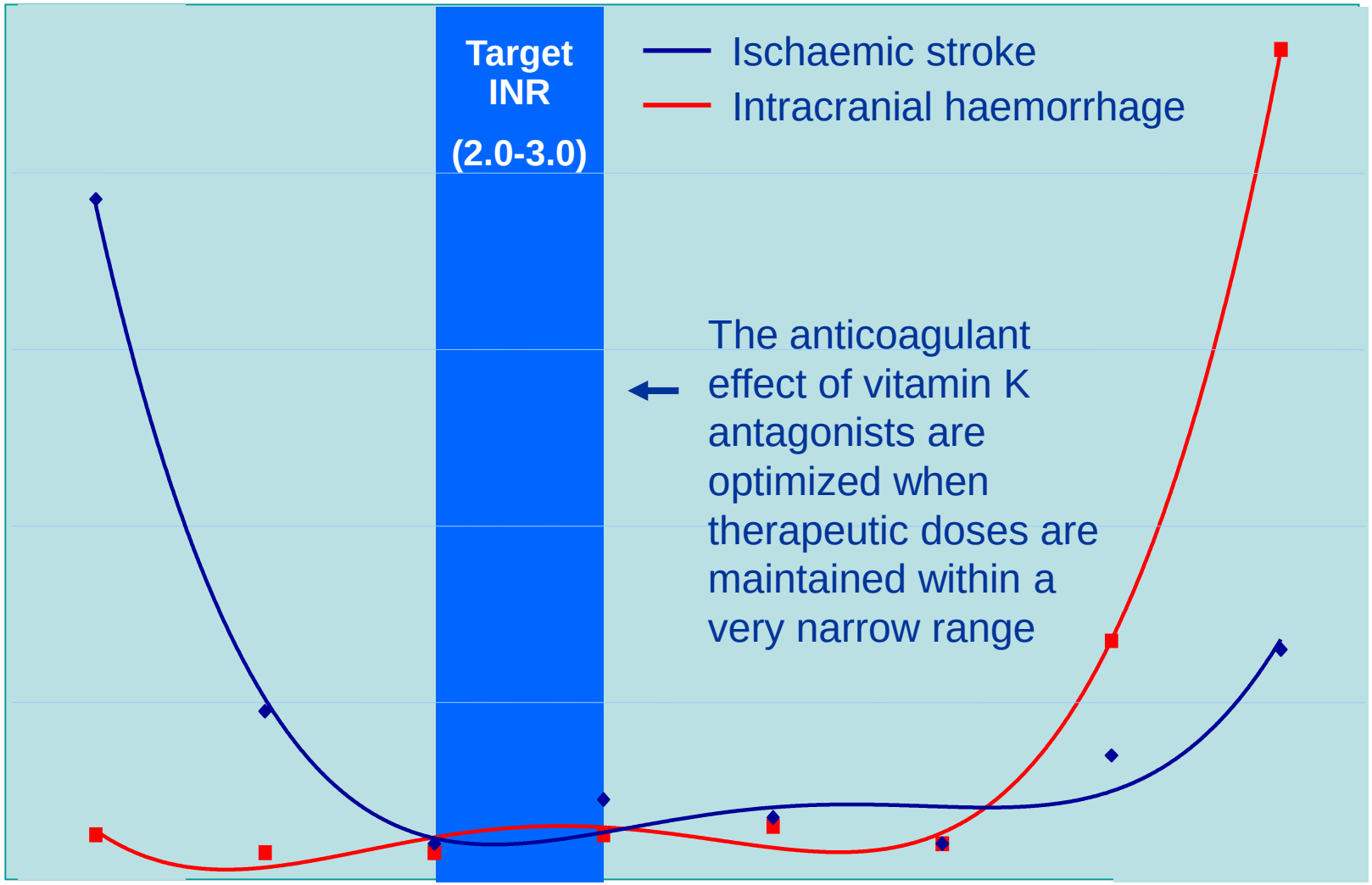


Reilly PA, et al. JACC 2014;63:321-8



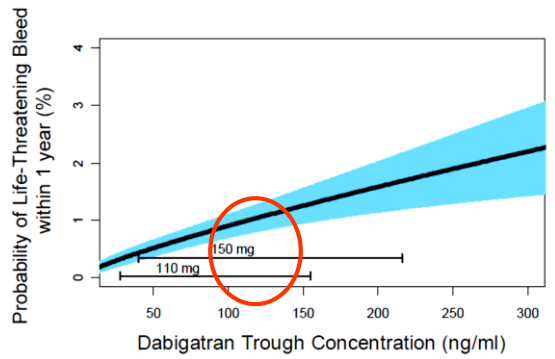
72 year old male AF patient with diabetes and prior stroke (10th and 90th percentile)

Narrow therapeutic range with VKA in AF/VTE



Migliorare efficacia e sicurezza ?

Figure 6. Probability of life-threatening bleed within 1 year vs. dabigatran trough concentration. The blue shaded region represents the 95% confidence interval. The bars on the bottom on the plot region represent the 10th to 90th percentiles of observed dabigatran pre-dose concentrations in the RE-LY trial.



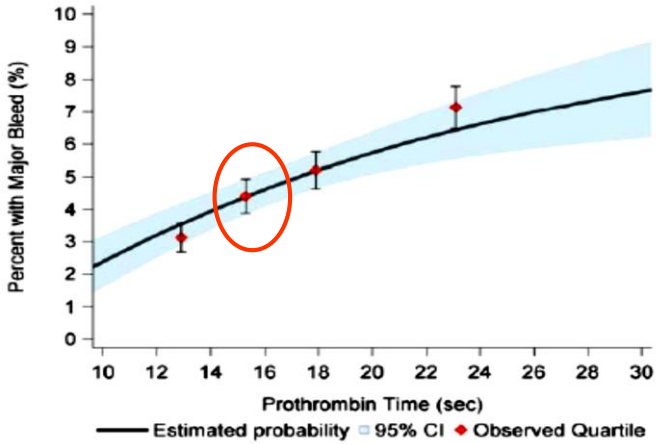


Figure 5. Probability of ischemic stroke within 1 year vs. dabigatran trough concentration. The blue shaded region represents the 95% confidence interval. The bars on the bottom on the plot region represent the 10th to 90th percentiles of observed dabigatran pre-dose concentrations in the RE-LY trial.

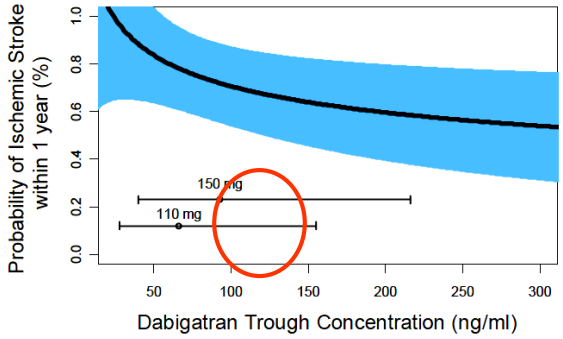
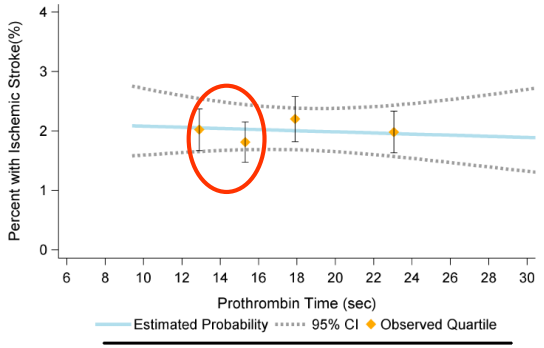


Figure 7. ROCKET ischemic stroke vs. PT (LD+2, pp pop)



	N	N of Event
Per-Protocol Analysis Set	7008	150
PT-outcome subset	6193 (88%)	124 (83%)

Ruf et al, Lancet 2015

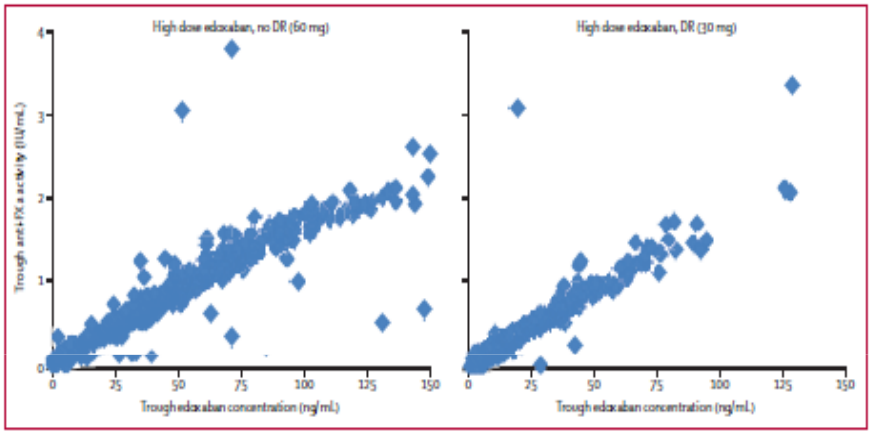


Figure 1: Correlation between edoxaban concentration and anti-FXa Activity
Trough edoxaban plasma concentration and anti-FXa activity at 1 month after randomisation. Spearman correlation: overall, r=0·96, 95% CI 0·95–0·96; low-dose edoxaban, dose reduced, r=0·92, 95% CI 0·89–0·94; low-dose edoxaban, no dose reduction, r=0·93, 95% CI 0·92–0·94; higher-dose edoxaban, dose reduced, r=0·95, 95% CI 0·93–0·96; higher-dose edoxaban, no dose reduction, r=0·97, 95% CI 0·96–0·97; p<0·0001 for all. IU=international units. DR=dose reduction.

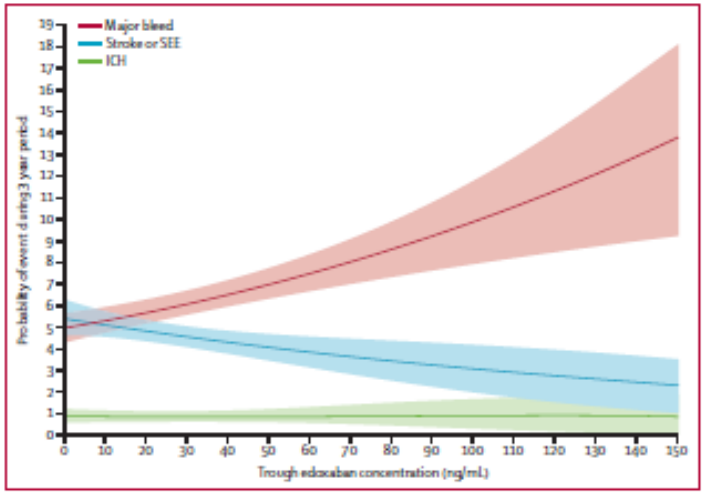


Figure 2: Probability of clinical outcomes versus edoxaban concentration
Trough edoxaban plasma concentration at 1 month after randomisation versus probability of efficacy and safety outcomes (median follow-up 2·8 years). ICH=intracranial haemorrhage. SEE=systemic embolic event.

Intervallo terapeutico

- Quindi l’intervallo c’è

Perché non usare il laboratorio per valutare l’attività anticoagulante dei nuovi farmaci e garantire maggiore sicurezza ai pazienti ?

Non è difficile…

DOA: QUALI TEST?

FARMACO	DOSAGGIO DELL'ATTIVITA' ANTICOAGULANTE
Dabigatran (ng/ml)	dTT ECT /ECA
Rivaroxaban (ng/ml) Apixaban (ng/ml) Edoxaban (ng/ml)	aXa

Pengo V et al, T&H 2011; Douxfils J et al, T&H 2012, 2013; Baglin T, JT&H 2013.

Il rivedere i pazienti ad intervalli regolari, misurandone le concentrazioni di farmaco, costituisce anche un supporto educazionale importante per la loro aderenza/persistenza alla terapia anticoagulante

Cosa abbiamo imparato dagli studi degli antidoti ?

Idarucizumab

Original Article

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

N Engl J Med 1915; 373:511-520

The NEW ENGLAND JOURNAL of MEDICINE

Idarucizumab

Table 1. Clinical Characteristics of the Patients.*

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)
Race or ethnic group — no. (%)†			
Asian	5 (10)	1 (3)	6 (7)
Hawaiian or Pacific Islander	3 (6)	3 (8)	6 (7)
White	43 (84)	35 (90)	78 (87)
Weight — kg			
Median	70.5	73.0	71.9
Range	42.4–127.5	49.5–116.0	42.4–127.5
Creatinine clearance‡			
Value — ml/min			
Mean	59±33	65±36	62±35
Median	54	60	58
Range	16–187	11–171	11–187
Distribution — no. (%)			
<30 ml/min	5 (10)	7 (18)	12 (13)
30 to <50 ml/min	14 (27)	6 (15)	20 (22)
50 to <80 ml/min	16 (31)	11 (28)	27 (30)
≥80 ml/min	6 (12)	9 (23)	15 (17)
Missing data	10 (20)	6 (15)	16 (18)
Dose of dabigatran — no. (%)			
150 mg twice daily	14 (27)	15 (38)	29 (32)
110 mg twice daily	34 (67)	24 (62)	58 (64)
75 mg twice daily	1 (2)	0	1 (1)
Other	2 (4)	0	2 (2)
Indication for dabigatran — no. (%)			
Atrial fibrillation	47 (92)	39 (100)	86 (96)
Venous thromboembolism	1 (2)	0	1 (1)
Other	3 (6)	0	3 (3)
Time since last intake of dabigatran			
Median — hr	15.2	16.6	15.4
Distribution — no. (%)			
<12 hr	17 (33)	15 (38)	32 (36)
12 to <24 hr	21 (41)	10 (26)	31 (34)
24 to <48 hr	12 (24)	10 (26)	22 (24)
≥48 hr	1 (2)	4 (10)	5 (6)
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)

* Plus–minus values are means ±SD. Group A included patients who had serious bleeding. Group B included patients who required urgent surgery or intervention.
† Race or ethnic group was self-reported.
‡ Creatinine clearance was estimated by the Cockroft–Gault equation.
§ Patients may have had more than one type of bleeding.

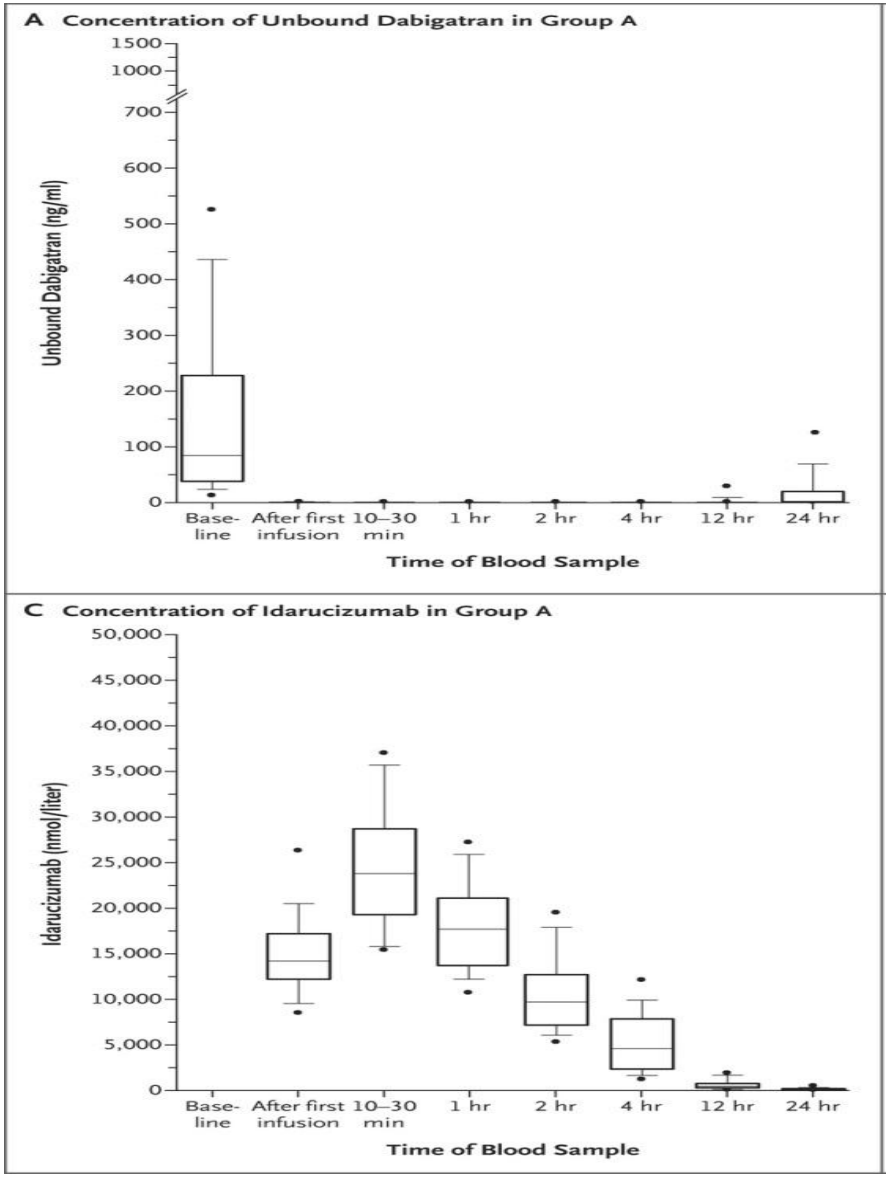
Clinical characteristics of patients

The NEW ENGLAND JOURNAL of MEDICINE

Idarucizumab

Clinical Characteristics of Patients		Group A (N=51)	Group B (N=39)	Total (N=90)
Age (years)	Median	77.0	76.0	76.5
	Range	48-93	56-93	48-93
Estimated CrCl n.(%)	30 to <50 ml/min	14 (27)	6 (15)	20 (22)
	50 to <80 ml/min	16 (31)	11 (28)	27 (30)
Dose of dabigatran no. (%)				
Dose n. (%)	110 mg bid	34 (67)	24 (62)	58 (64)
Time since last intake of dabigatran	12 to<24 hr	21 (41)	10 (26)	31 (34)
n. (%)	24 to<48 hr	12 (24)	10 (26)	22 (24)
Elevated dilute thrombin time at baseline n. (%)		40 (78)	28 (72)	68 (76)
Elevated ecarin clotting time at baseline n. (%)		47(92)	34(87)	81(90)
Type of bleeding n. (%)	Intracranial	18(35)	-	18(20)

Idarucizumab



Time Courses of Plasma Concentrations of Unbound Dabigatran and Idarucizumab before and after the Administration of Idarucizumab

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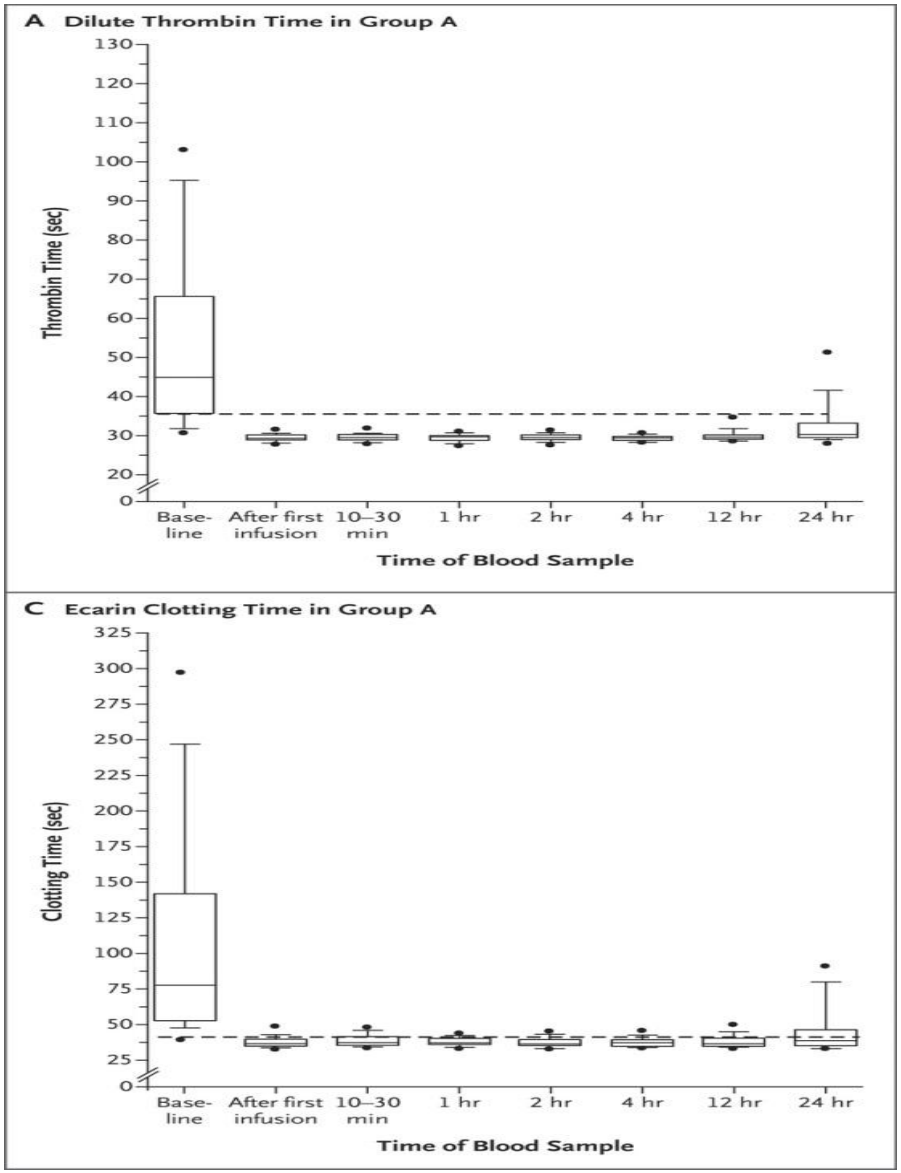
Idarucizumab



Time Course of the Dilute Thrombin Time and Ecarin Clotting Time before and after the Administration of Idarucizumab.

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Idarucizumab

- Intravenous idarucizumab, an antibody fragment of a human antibody specific for dabigatran, produced rapid reversal of the anticoagulant effect in patients with bleeding or an urgent surgical indication with no apparent toxic effects or rebound hypercoagulable state.

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Idarucizumab

- Idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes.

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Idarucizumab

Table 2. Serious Adverse Events Leading to Death.

Event	Characteristics of the Patients		Study Group*	Time from Treatment to Death
	Age	Sex		
	yr			*days*
Cardiac arrest	82	Female	B	<1
Circulatory collapse	93	Male	B	<1
Hemodynamic collapse	88	Female	B	<1
Septic shock	87	Female	B	1
Sepsis, shock, and gastrointestinal bleeding	60	Male	B	1
Progression of respiratory failure	60	Male	A	1
New intracranial hemorrhage	77	Male	A	1
Progression of intracranial hemorrhage	69	Male	A	2
Multiorgan failure	87	Male	B	2
Progression of intracranial hemorrhage	69	Male	A	4
Pulmonary edema	83	Female	A	11
Cardiac arrest	78	Female	B	21
Ischemic stroke	72	Female	B	26
Congestive heart failure	73	Male	A	30
Parkinson's disease	80	Male	A	43
General health deterioration	83	Male	A	42
Pneumonia	86	Female	A	94
Progression of cancer	80	Male	B	101

* Group A included patients who had serious bleeding. Group B included patients who required urgent surgery or intervention.

Serious Adverse Events Leading to Death.

Death rate: 20% (50% within day2)

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Idarucizumab

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* Group A included patients who had serious bleeding. Group B included patients who required urgent surgery or intervention.

Serious Adverse Events Leading to Death.

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Andexanet

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Leeds, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.Eng., Juliet Nakamya, Ph.D., W. Ting Lim, M.Sc., and Mark Crowther, M.D., for the ANNEXA-4 Investigators*

N Engl J Med 2016; 30 Aug

The NEW ENGLAND JOURNAL of MEDICINE

Andexanet

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Safety Population (N=67)	Efficacy Population (N=47)
Age — yr	77.1±10.0	77.1±10.1
Male sex — no. (%)	35 (52)	24 (51)
White race — no. (%)†	54 (81)	36 (77)
Body-mass index‡	28.1±6.3	28.8±6.7
Time from patient consent until andexanet bolus — hr	1.7±0.8	1.8±0.9
Time from presentation until andexanet bolus — hr	4.8±1.9	4.8±1.8
Estimated creatinine clearance — no. (%)		
<30 ml/min	6 (9)	4 (9)
30 to <60 ml/min	31 (46)	25 (53)
≥60 ml/min	26 (39)	17 (36)
Missing data	4 (6)	1 (2)
Indication for anticoagulation — no. (%)		
Atrial fibrillation	47 (70)	32 (68)
Venous thromboembolism§	15 (22)	12 (26)
Atrial fibrillation and venous thromboembolism	5 (7)	3 (6)
Medical history — no. (%)		
Myocardial infarction	13 (19)	7 (15)
Stroke	17 (25)	15 (32)
Deep-vein thrombosis	20 (30)	16 (34)
Pulmonary embolism	6 (9)	4 (9)
Atrial fibrillation	49 (73)	34 (72)
Heart failure	23 (34)	19 (40)
Diabetes mellitus	23 (34)	17 (36)
Factor Xa inhibitor		
Rivaroxaban		
No. of patients	32	26
Median daily dose (IQR) — mg	20 (15–20)	20 (20–20)
Time from last dose to andexanet bolus — hr	12.8±4.2	12.0±4.1
Baseline anti–factor Xa activity — ng/ml	247.4±186.0	297.0±171.0
Median unbound fraction of the plasma level (IQR) — ng/ml	16.7 (10.2–25.5)	19.3 (12.0–26.9)
Apixaban		
No. of patients	31	20
Median daily dose (IQR) — mg	5 (5–10)	5 (5–10)
Time from last dose to andexanet bolus — hr	12.1±4.7	11.0±4.7
Baseline anti–factor Xa activity — ng/ml	137.7±102.3	174.5±97.0
Median unbound fraction of the plasma level (IQR) — ng/ml	9.4 (6.0–19.2)	10.5 (8.1–19.2)
Enoxaparin		
No. of patients	4	1
Median daily dose (IQR) — mg	90 (80–150)	200
Time from last dose to andexanet bolus — hr	10.8±3.5	13.1
Baseline anti–factor Xa activity — IU/ml	0.4±0.2	0.6

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† Race was reported by the investigators.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Venous thromboembolism includes the treatment or prevention of deep-vein thrombosis and pulmonary embolism.

Characteristics of the Patients at Baseline.

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Andexanet

Characteristic of patients at baseline	Safety Population (N=67)	Efficacy Population (N=47)
Age (years)	77.1 ± 10.0	77.1 ± 10.0

Andexanet

Characteristic of patients at baseline		Safety Population (N=67)	Efficacy Population (N=47)
Age (years)		77.1 ± 10.0	77.1 ± 10.0
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Andexanet

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Factor Xa inhibitor		**Rivaroxaban**	

Steady state trough plasma concentrations of DOACs (ng/mL)

DOAC	Dosaggio (mg)	ng/ml (mediana)	ng/ml (intervallo)	Anti-Xa (UI)	Anti-Xa (intervallo)
Dabi	110 bid	66	28-155	-	-
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Riva	20 sid	32	6-249	0.32	0.06-2.49
Apix	2.5 bid	79	34-162	1.20	0.51-2.40
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Edox	30 sid	18	10-32	0.35	0.21-0.57
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10-90° percentile
5-95° percentile
interquartile

Andexanet

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Factor Xa inhibitor		**Rivaroxaban**	
	No.of patients	32	26
	Median daily dose (IQR)-mg	20 (15-20)	20 (20-20)
	Time from last dose to andexanet bolus hr	12.8 ± 4.2	12.0 ± 4.1
	Baseline anti-factor Xa activity-ng/ml	247 ± 186	297 ± 171

Andexanet

Characteristic of patients at baseline	Safety Population (N=67)	Efficacy Population (N=47)
Factor Xa inhibitor	**Apixaban**	

Steady state trough plasma concentrations of DOACs (ng/mL)

DOAC	Dosaggio (mg)	ng/ml (mediana)	ng/ml (intervallo)	Anti-Xa (UI)	Anti-Xa (intervallo)
Dabi	110 bid	66	28-155	-	-
Dabi	150 bid	93	40-215	-	-
Riva	20 sid	32	6-249	0.32	0.06-2.49
Apix	2.5 bid	79	34-162	1.20	0.51-2.40
Apix	5.0 bid	103	41-230	1.50	0.61-3.40
Edox	30 sid	18	10-32	0.35	0.21-0.57
Edox	60 sid	36	19-62	0.64	0.37-1.12

10-90° percentile
5-95° percentile
interquartile

Andexanet

Characteristic of patients at baseline	Safety Population (N=67)	Efficacy Population (N=47)
Factor Xa inhibitor	**Apixaban**	
No.of patients	31	20
Median daily dose (IQR)-mg	5 (5-10)	5 (5-10)
Time from last dose to andexanet bolus hr	12.1 ± 4.7	11.0 ± 4.7
Baseline anti-factor Xa activity-ng/ml	138 ± 102	175 ± 97

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Intracranial bleeding * n./total n. (%)	28/67 (42)	20/47 (43)
Patients receiving rivaroxaban	10/28 (36)	8/20 (40)
Patients receiving apixaban	17/28 (61)	12/20 (60)

* Only patients with volumes < 60 ml enrolled

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Patients receiving apixaban	17/28 (61)	12/20 (60)
Gastrointestinal bleeding n./total n. (%)	33/67 (49)	25/47 (53)
Patients receiving rivaroxaban	20/33 (61)	16/25 (64)
Patients receiving apixaban	11/33 (33)	8/25 (32)

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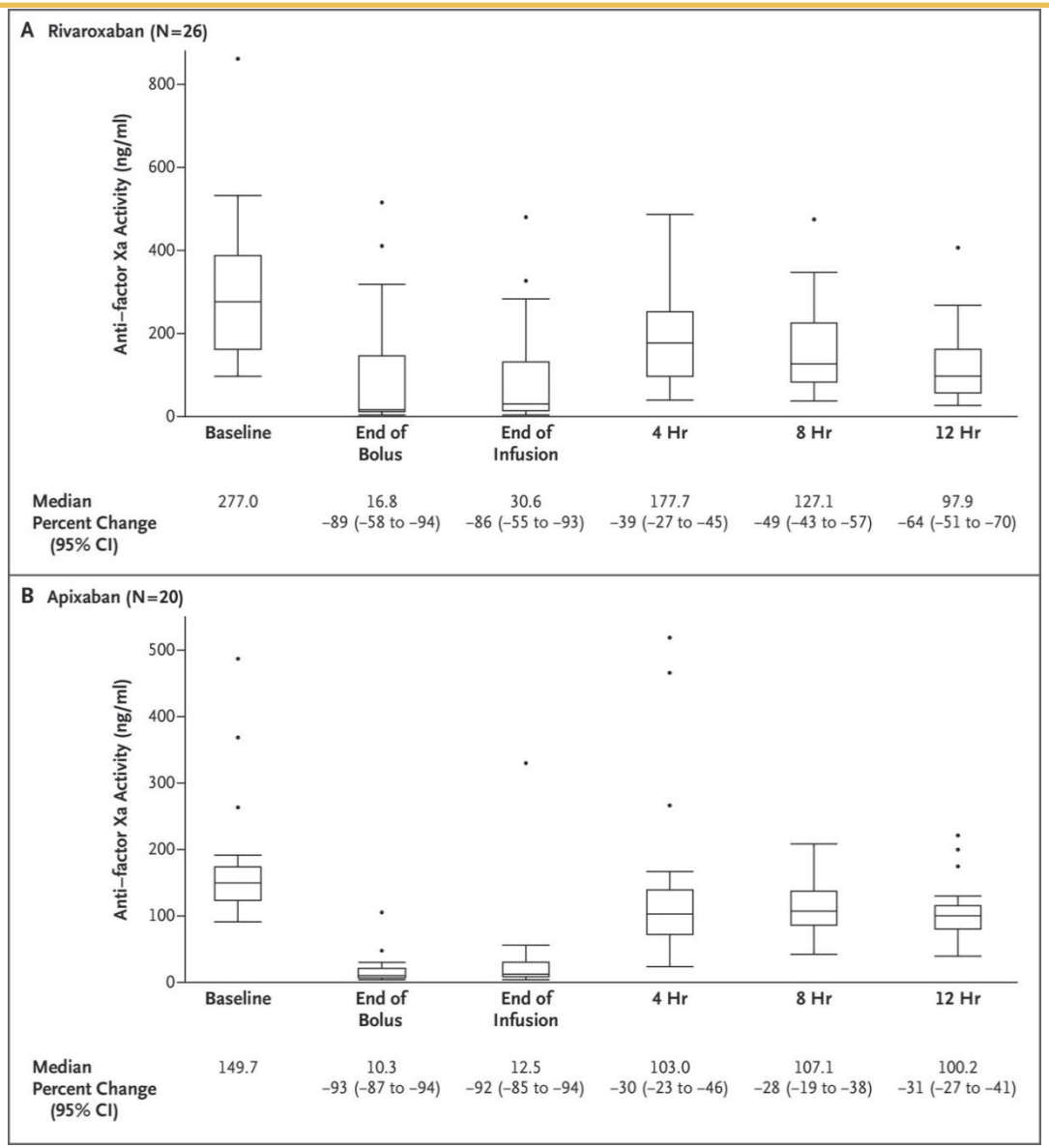
Andexanet



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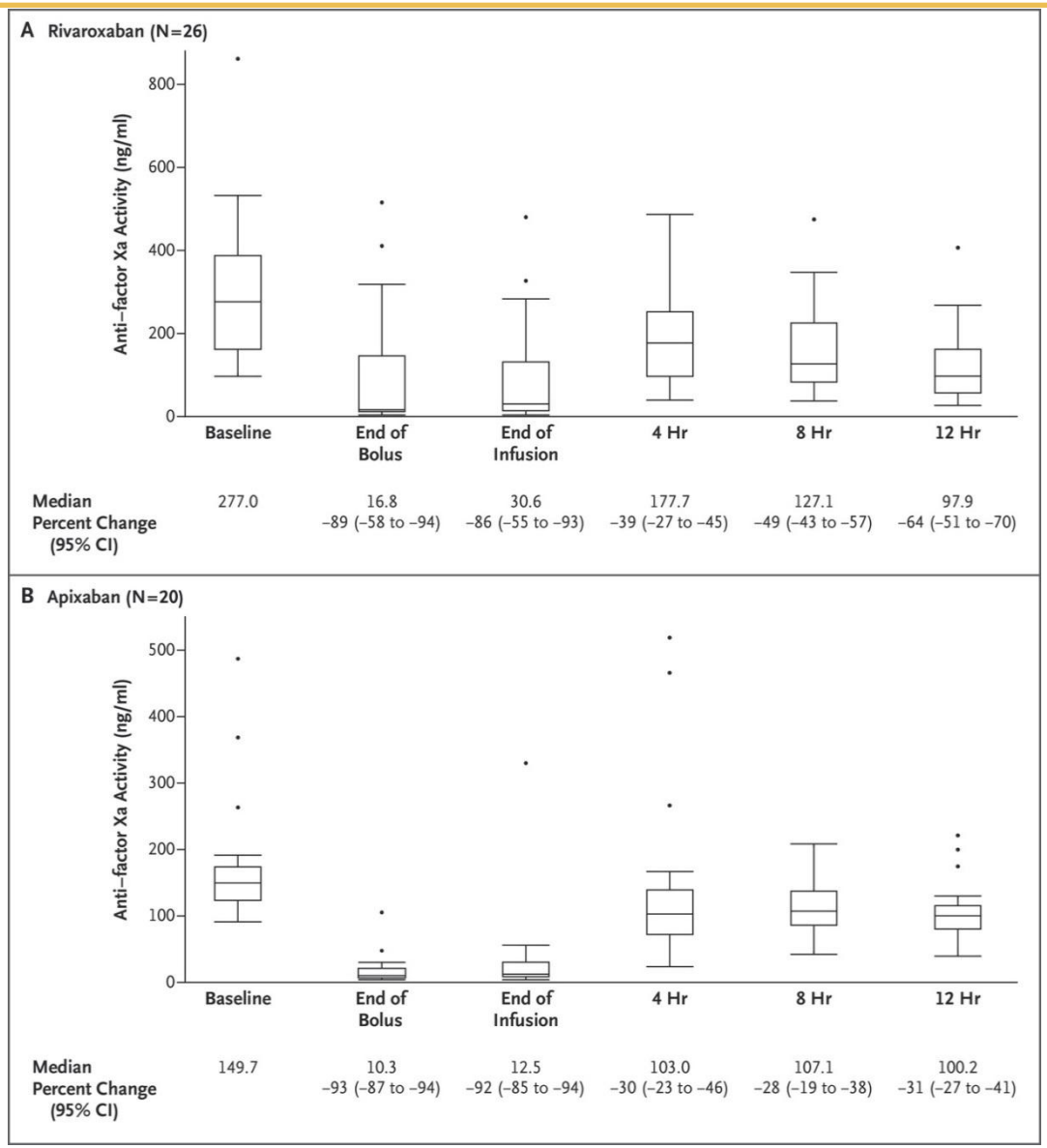

Andexanet dosing

The following doses were used: for patients who had taken apixaban or rivaroxaban more than 7 hours before the administration of andexanet, the bolus dose was 400 mg and the infusion dose was 480 mg. For patients who had taken enoxaparin, edoxaban, or rivaroxaban 7 hours or less before the administration of the bolus dose or at an unknown time, the bolus dose was 800 mg and the infusion dose was 960 mg.

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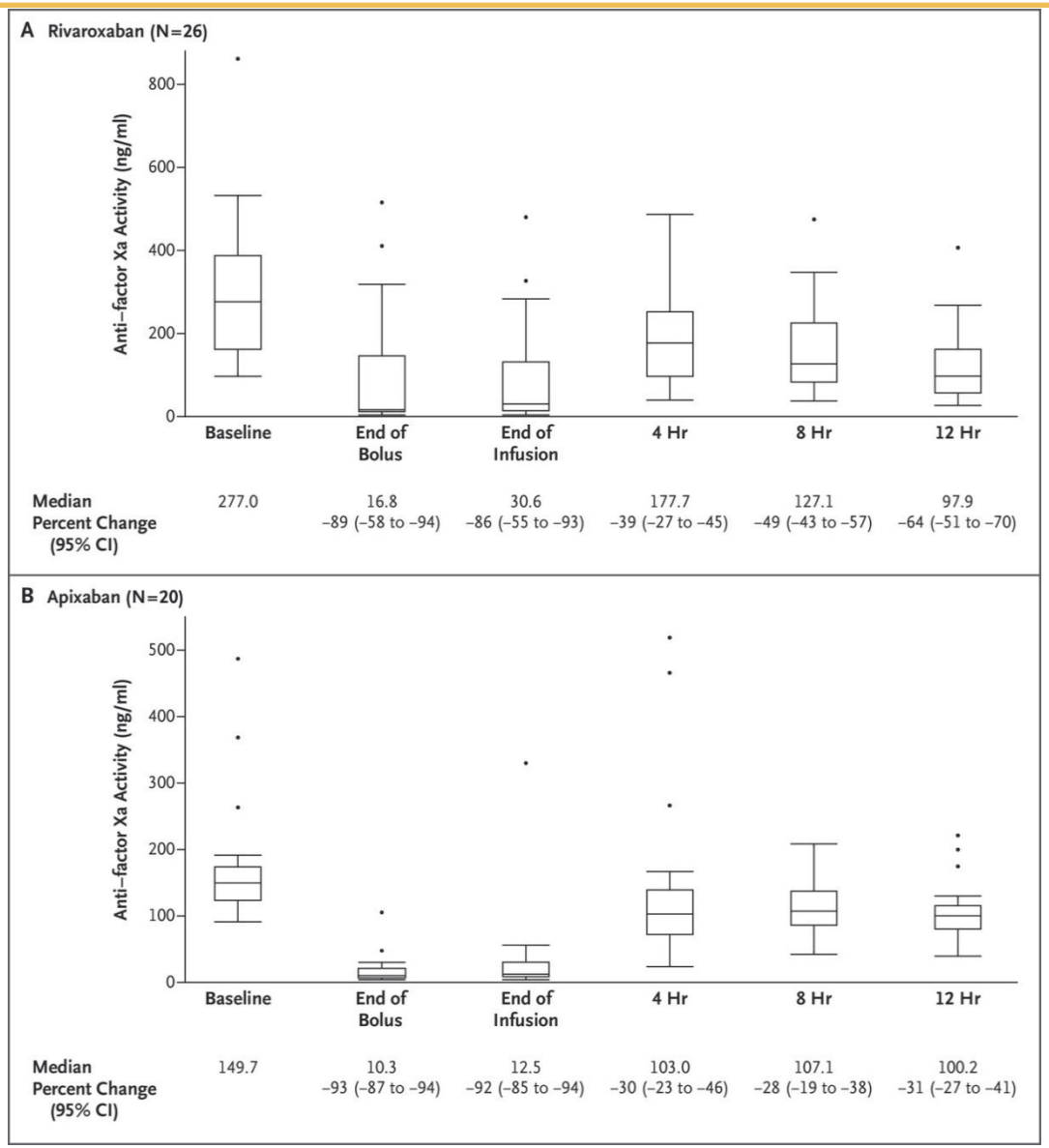

Anti–Factor Xa Activity and Percent Change from Baseline in Patients Receiving Rivaroxaban and Apixaban (Efficacy Population).

Of the 10% of patients with the highest anti–factor Xa activity at the end of the infusion, 4 had received rivaroxaban and 1 had received apixaban; all received the lower dose of andexanet. The median values for anti–factor Xa activity in these patients were 327.4 ng per milliliter (interquartile range, 283.9 to 330.1) at the end of the infusion. All these patients were adjudicated as having excellent or good hemostasis.

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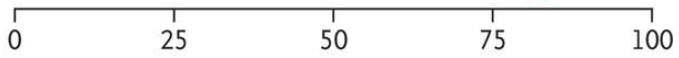
Subgroup	No. of Patients	Percent Adjudicated as Excellent or Good Hemostasis (95% CI)
All patients with efficacy analyses	47	79 (64–89)
Drug		
Rivaroxaban	26	81 (61–93)
Apixaban	20	75 (51–91)
Enoxaparin	1	100
Sex		
Male	24	71 (49–87)
Female	23	87 (66–97)
Site of bleeding		
Gastrointestinal	25	84 (64–96)
Intracranial	20	80 (56–94)
Other	2	0
Age		
<65 yr	7	71 (29–96)
65–75 yr	9	89 (52–100)
≥75 yr	31	77 (59–90)
Andexanet dose		
Low	42	76 (61–88)
High	5	100 (48–100)
Anti–factor Xa <75 ng/ml or <0.5 IU/ml	17	82 (57–96)



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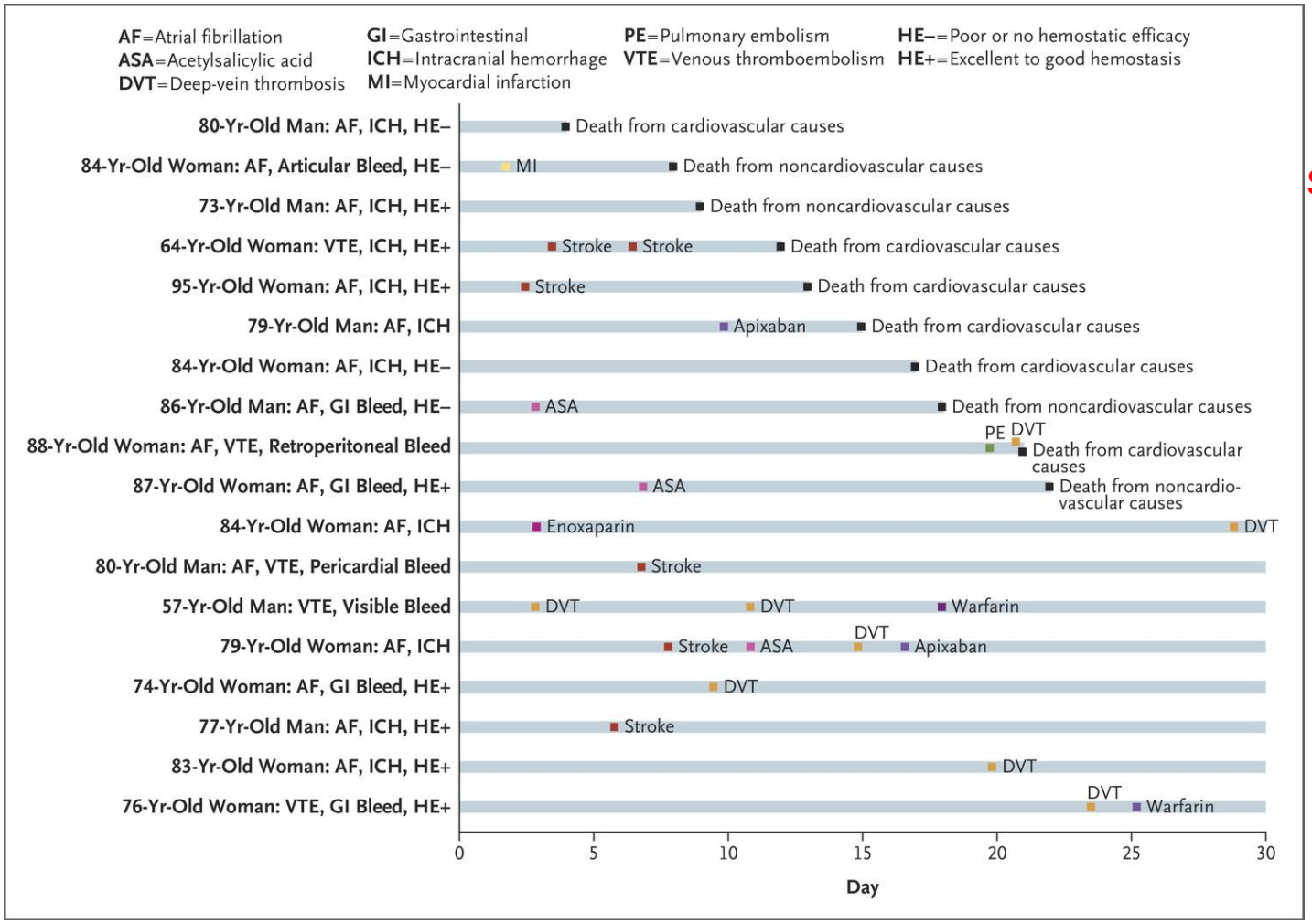

Death rate: 15%
Stroke/VTE rate 15%

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Table 3. Demographics and Baseline Characteristics (Intention-to-Treat Efficacy Population)

	4F-PCC (n=98)	Plasma (n=104)
Female sex, n (%)	48 (49.0)	53 (51.0)
Age, mean (SD; range), y	69.8 (13.93; 29–96)	69.8 (12.78; 26–92)
Age group, n (%), y		
<65	33 (33.7)	31 (29.8)
≥65 to <75	24 (24.5)	29 (27.9)
≥75	41 (41.8)	44 (42.3)
Race, n (%)		
White	93 (94.9)	88 (84.6)
Nonwhite	5 (5.1)	16 (15.4)
Region, n (%)		
United States	68 (69.4)	72 (69.2)
Europe	30 (30.6)	32 (30.8)
Body mass index, mean (SD), kg/m²	27.66 (8.54)	27.64 (6.47)
Baseline INR, median (range)	3.90 (1.8–20.0)	3.60 (1.9–38.9)
Type of bleeding, n (%)		
Gastrointestinal/other nonvisible	63 (64.3)	64 (61.5)
Visible	16 (16.3)	21 (20.2)
Intracranial hemorrhage	12 (12.2)	12 (11.5)
Musculoskeletal	7 (7.1)	7 (6.7)
Reason for oral VKA therapy, n (%)		
Arrhythmia	56 (57.1)	53 (51.0)
Thromboembolic event	18 (18.4)	21 (20.2)
Artificial heart valve/joint	13 (13.3)	13 (12.5)
Vascular disease	10 (10.2)	13 (12.5)
Other	1 (1.0)	4 (3.8)
Time from first VKA dose to start of study product infusion, median (range), d	720 (3–8476)	757 (3–10734)
Previous antiplatelet therapy (<2 wk before study entry), n (%)		
Clopidogrel	3 (3.1)	5 (4.8)
Prasugrel	1 (1.0)	0
Cilostazol	0	1 (1.0)
Medical history (most frequently listed terms), n (%)*		
Hypertension	87 (84.5)	88 (80.7)
Atrial fibrillation	69 (67.0)	63 (57.8)
Anemia	42 (40.8)	35 (32.1)
Coronary artery disease	38 (36.9)	33 (30.3)
Cardiac failure congestive	34 (33.0)	33 (30.3)
Hyperlipidemia	26 (25.2)	33 (30.3)
Myocardial infarction	25 (24.3)	20 (18.3)
Chronic obstructive pulmonary disease	23 (22.3)	26 (23.9)
Appendectomy	14 (13.6)	27 (24.8)
Type 2 diabetes mellitus	18 (17.5)	24 (22.0)
Baseline hemoglobin, mean (SD), g/dL*	9.33 (2.526)	9.86 (2.817)
Baseline platelet count, mean (SD), ×10⁹/L*	228.0 (95.37)	218.3 (81.19)

4F-PCC indicates 4-factor prothrombin complex concentrate; INR, international normalized ratio; and VKA, vitamin K antagonist.
*Intention-to-treat safety population.

Table 8. Summary of AEs (Intention-to-Treat Safety Population)

AE	No. (%) of Patients: 4F-PCC (n=103)	Plasma (n=109)
Any nonserious AE*	66 (64.1)	71 (65.1)
Related AE†	10 (9.7)	23 (21.1)
AE leading to treatment discontinuation	0	3 (2.8)
Serious AE*	32 (31.1)	26 (23.9)
Related serious AE†	2 (1.9)	4 (3.7)
AEs of interest		
Deaths to day 30	6 (5.8)	5 (4.6)
Deaths to day 45	10 (9.7)	5 (4.6)
Related deaths (to day 45)‡	1 (1.0)	0
Thromboembolic AE	8 (7.8)	7 (6.4)
Related thromboembolic AE†	4 (3.9)	3 (2.8)
Fluid overload or similar cardiac event	5 (4.9)	14 (12.8)
Related fluid overload or similar cardiac event†	0	7 (6.4)

Sarode R, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation 2013;128:1234-43.

Conclusioni

- Ma detto tra di noi sarà meglio prevenire – e cambiare dose o farmaco - od usare l'antidoto miracoloso ?