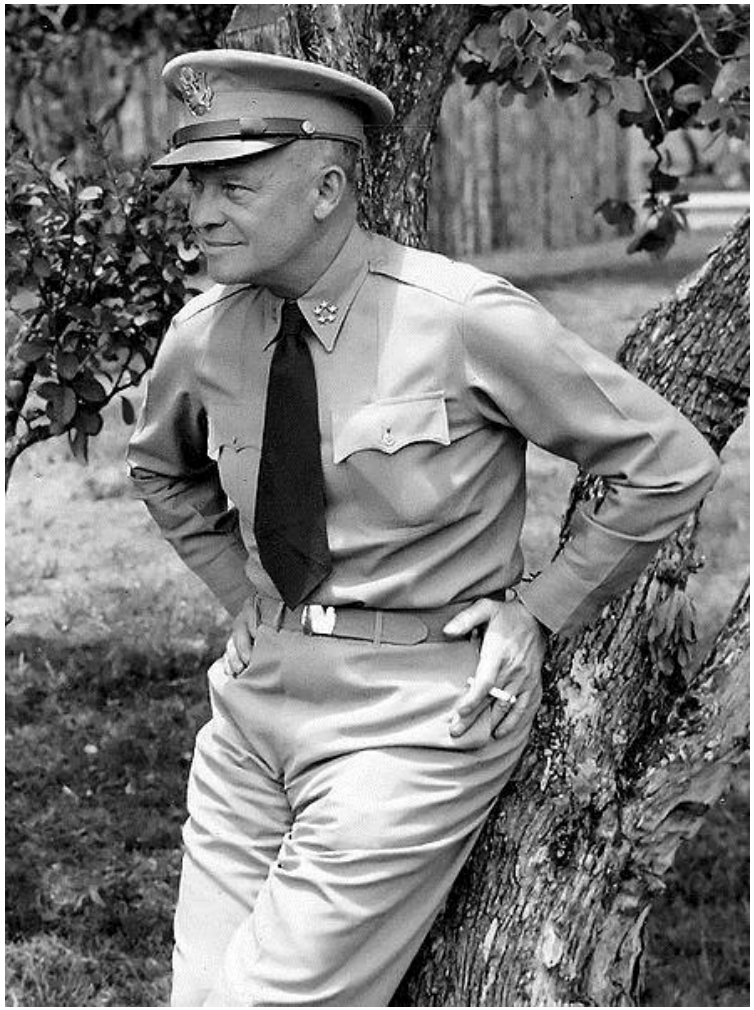
La gestione dell'anticoagulazione orale

Armando D'Angelo
Servizio di Coagulazione & Unità Ricerca Trombosi
IRCCS Ospedale San Raffaele, Milano, Italia

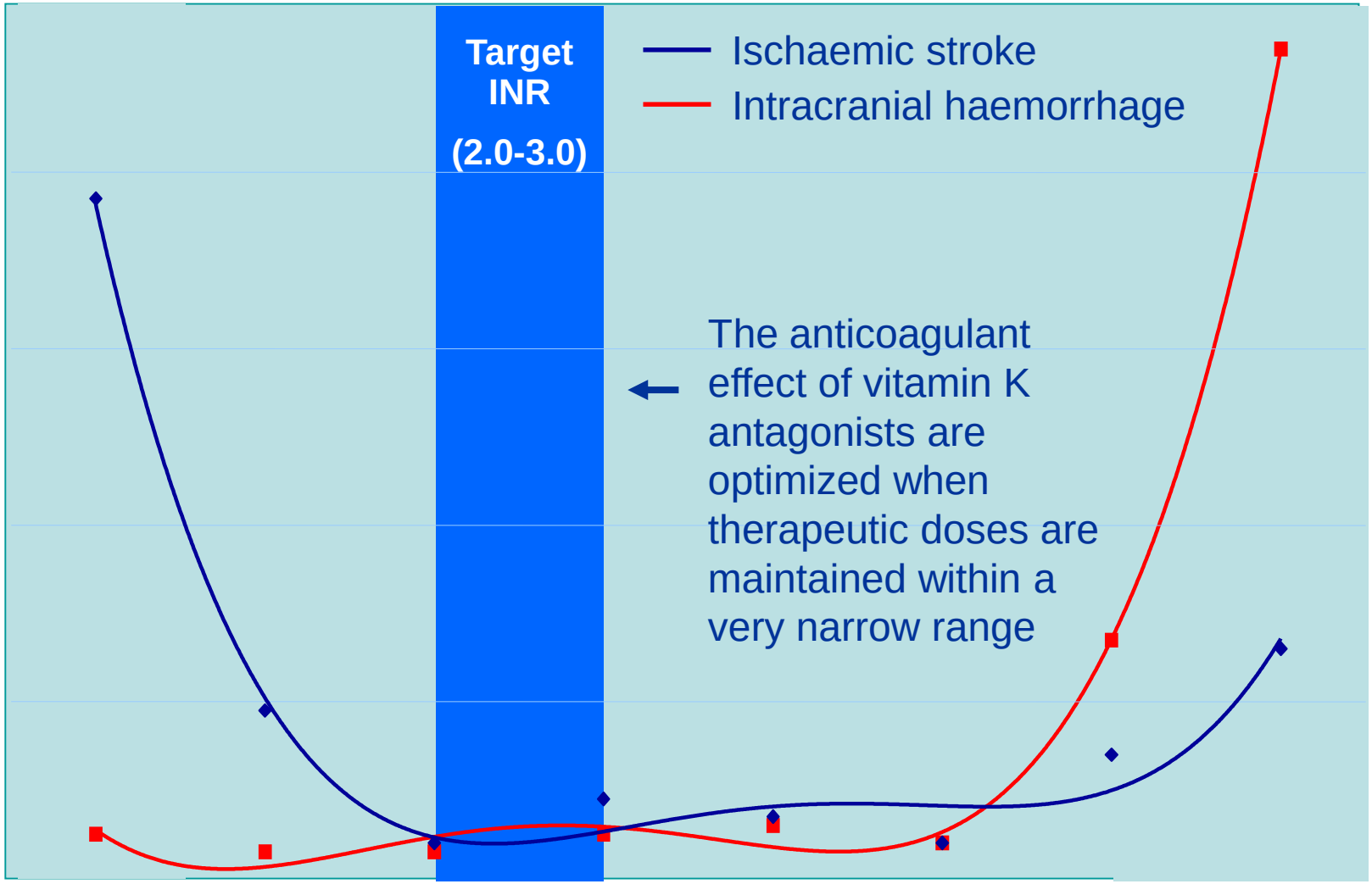
1° Corso SISET

Cremona 20 settembre 2016

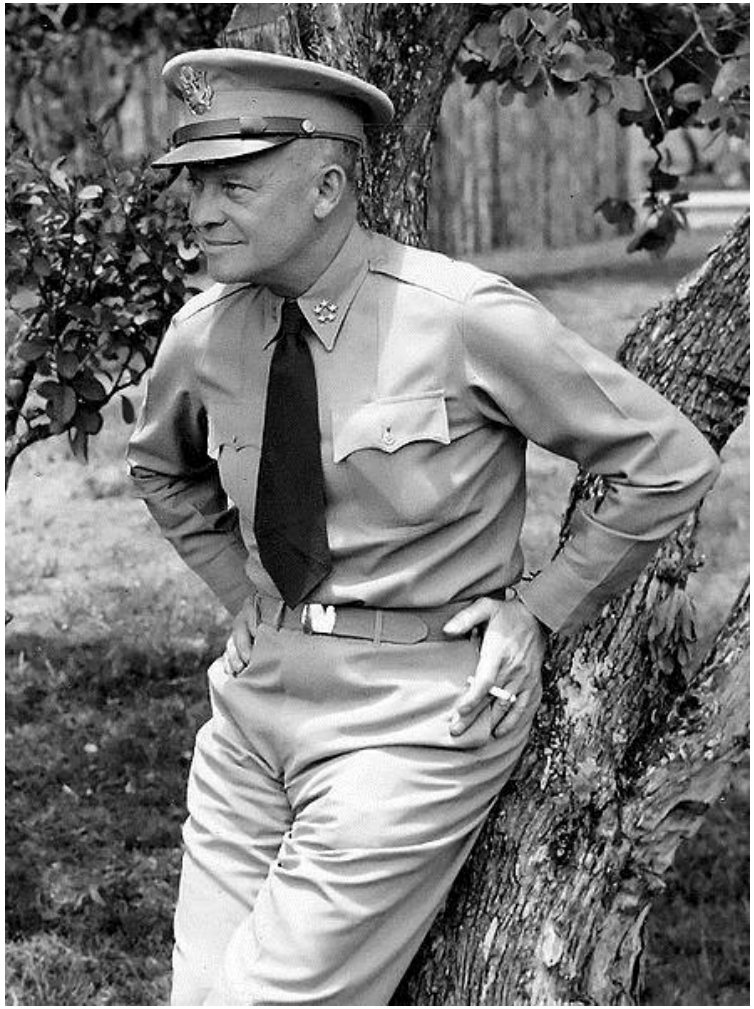
Warfarin

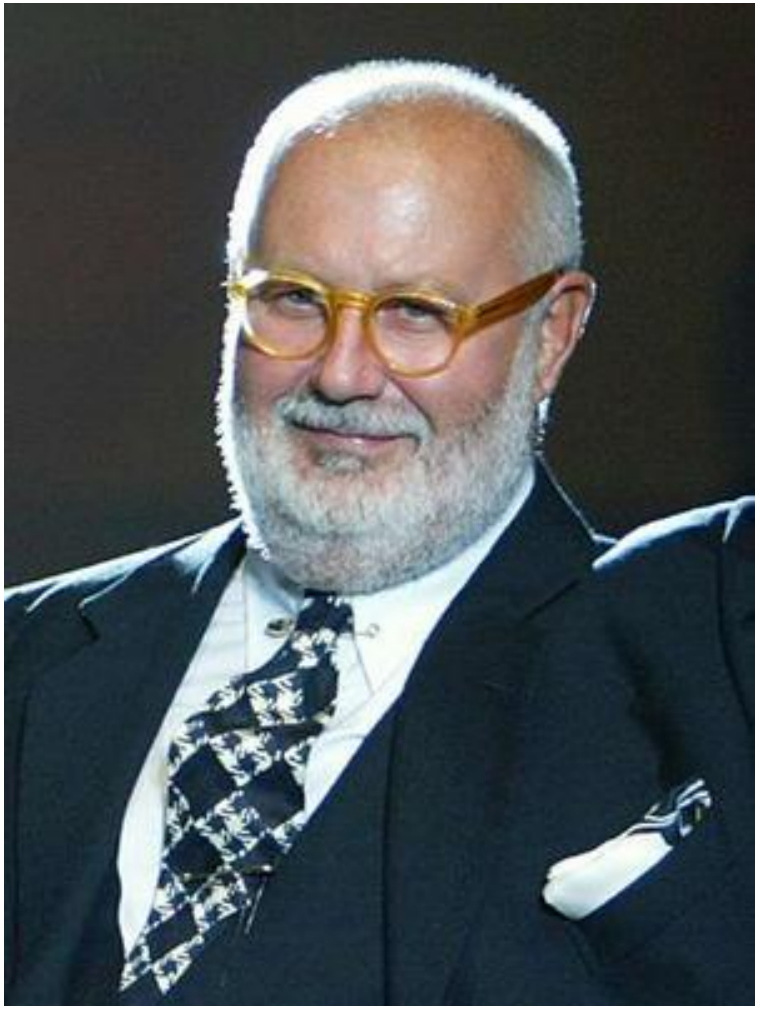


Narrow thrapeutic range

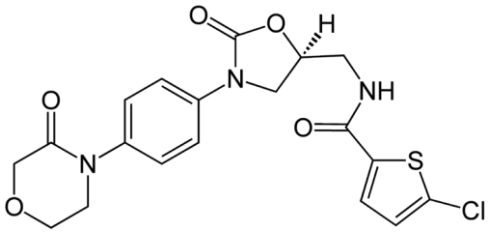


Warfarin

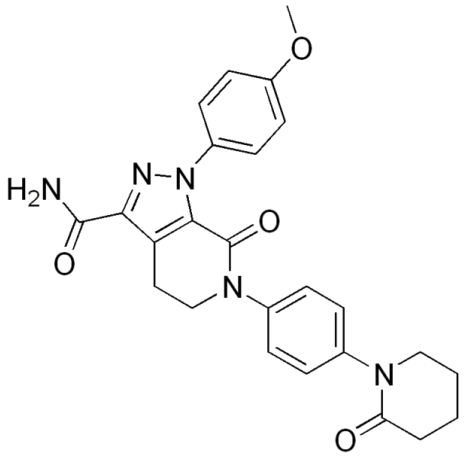




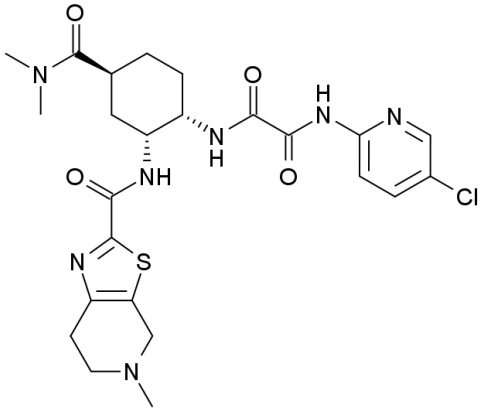
New oral anticoagulants



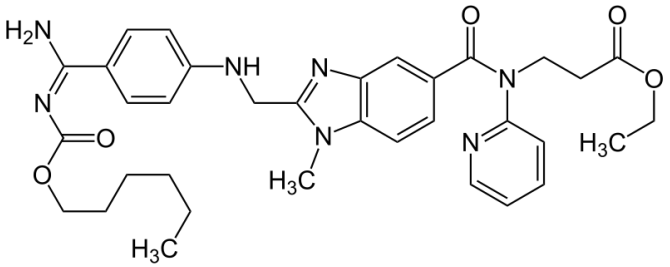
Rivaroxaban



Apixaban



Edoxaban



Dabigatran

Non valvular atrial fibrillation

	Dabi LD	Dabi HD	Riva SD	Apix SD	Edox LD	Edox HD
Stroke/SE	ni*	-33%	ni†	-20%	ni	ni†

*** Non inferior; † -21% on treatment**

Non valvular atrial fibrillation

	Dabi LD	Dabi HD	Riva SD	Apix SD	Edox LD	Edox HD
Stroke/SE	ni*	-33%	ni†	-20%	ni	ni†
Non hemorrh. stroke	ni	-23%	ni	ni	+42%	ni
Hemorrhagic stroke	-69%	-74%	-42%	-49%	-67%	-46%

*** Non inferior; † -21% on treatment**

Non valvular atrial fibrillation

	Dabi LD	Dabi HD	Riva SD	Apix SD	Edox LD	Edox HD
Stroke/SE	ni*	-33%	ni†	-20%	ni	ni†
Non hemorrh. stroke	ni	-23%	ni	ni	+42%	ni
Hemorrhagic stroke	-69%	-74%	-42%	-49%	-67%	-46%
Intracranial bleeding	-69%	-59%	-34%	-58%	-69%	-54%

*** Non inferior; † -21% on treatment**

Non valvular atrial fibrillation

	Dabi LD	Dabi HD	Riva SD	Apix SD	Edox LD	Edox HD
Stroke/SE	ni*	-33%	ni†	-20%	ni	ni†
Non hemorrh. stroke	ni	-23%	ni	ni	+42%	ni
Hemorrhagic stroke	-69%	-74%	-42%	-49%	-67%	-46%
Intracranial bleeding	-69%	-59%	-34%	-58%	-69%	-54%
Fatal bleeding	-42%	-27%	-50%	-38%	-65%	-45%

*** Non inferior; † -21% on treatment**

Non valvular atrial fibrillation

	Dabi LD	Dabi HD	Riva SD	Apix SD	Edox LD	Edox HD
Stroke/SE	ni*	-33%	ni†	-20%	ni	ni†
Non hemorrh. stroke	ni	-23%	ni	ni	+42%	ni
Hemorrhagic stroke	-69%	-74%	-42%	-49%	-67%	-46%
Intracranial bleeding	-69%	-59%	-34%	-58%	-69%	-54%
Fatal bleeding	-42%	-27%	-50%	-38%	-65%	-45%
Vascular death	ni	-15%	ni	ni	-15%	-14%

*** Non inferior; † -21% on treatment**

Non valvular atrial fibrillation

	Dabi LD	Dabi HD	Riva SD	Apix SD	Edox LD	Edox HD
Stroke/SE	ni*	-33%	ni†	-20%	ni	ni†
Non hemorrh. stroke	ni	-23%	ni	ni	+42%	ni
Hemorrhagic stroke	-69%	-74%	-42%	-49%	-67%	-46%
Intracranial bleeding	-69%	-59%	-34%	-58%	-69%	-54%
Fatal bleeding	-42%	-27%	-50%	-38%	-65%	-45%
Vascular death	ni	-15%	ni	ni	-15%	-14%
All-cause death	ni	ni‡	ni	ni	-13%	ni

*** Non inferior; † -21% on treatment; ‡ p = 0.051**

Non valvular atrial fibrillation

	Dabi LD	Dabi HD	Riva SD	Apix SD	Edox LD	Edox HD
Stroke/SE	ni*	-33%	ni†	-20%	ni	ni†
Non hemorrh. stroke	ni	-23%	ni	ni	+42%	ni
Hemorrhagic stroke	-69%	-74%	-42%	-49%	-67%	-46%
Intracranial bleeding	-69%	-59%	-34%	-58%	-69%	-54%
Fatal bleeding	-42%	-27%	-50%	-38%	-65%	-45%
Vascular death	ni	-15%	ni	ni	-15%	-14%
All-cause death	ni	ni‡	ni	ni	-13%	ni

*** Non inferior; † -21% on treatment; ‡ p = 0.051**

Un confronto con i pazienti dei Centri Emostasi e Trombosi

Major bleeding complications

	DABI		EDOX		RIVA	APIX
	LD	HD	LD	HD	SD	SD
	% p-y	% p-y	% p-y	% p-y	% p-y	% p-y
Mean age (yrs)	71.5		72.0		73	70
Major bleeding	2.71	3.11	1.61	2.75	3.60	2.13
Intracranial bleeding	0.35	0.40	0.26	0.41	0.75	0.57
Gastrointestinal bleeding	1.12	1.51	0.82	1.51	3.20	0.76
Fatal bleeding	0.19	0.23	0.13	0.21	0.20	0.40

Major bleeding complications

	DABI		EDOX		RIVA	APIX	AVK
	LD	HD	LD	HD	SD	SD	Poli et al
	% p-y	% p-y	% p-y	% p-y	% p-y	% p-y	% p-y
Mean age (yrs)	71.5		72.0		73	70	83
Major bleeding	2.71	3.11	1.61	2.75	3.60	2.13	1.73
Intracranial bleeding	0.35	0.40	0.26	0.41	0.75	0.57	0.55
Gastrointestinal bleeding	1.12	1.51	0.82	1.51	3.20	0.76	0.67
Fatal bleeding	0.19	0.23	0.13	0.21	0.20	0.40	0.27

Ma…

Major bleeding complications

Vascular Medicine

Bleeding Risk in Very Old Patients on Vitamin K Antagonist Treatment

Results of a Prospective Collaborative Study on Elderly Patients Followed by Italian Centres for Anticoagulation

Daniela Poli, MD; Emilia Antonucci, MD; Sophie Testa, MD; Alberto Tosetto, MD; Walter Ageno, MD; Gualtiero Palareti, MD; for the Italian Federation of Anticoagulation Clinics (FCSA)

Table 3. Bleeding Events

Total, n (rate per 100 patient-y)	179 (1.87)
Mean age (range), y	85 (80–94)
Time elapsed from start of VKA treatment, mo	14.2 (1–109)
Median INR (range)	2.5 (1.0–13.8)
Bleeds with INR of 2.0–3.0, n (%)	147 (82.1)
Patients <85 y, n (rate per 100 patient-y)	115 (1.71)
Patients ≥85 y, n (rate per 100 patient-y)	64 (2.22)*

VKA indicates vitamin K antagonist; INR, international normalized ratio.
*Patients ≥85 versus <85 years of age: relative risk, 1.3; 95% confidence interval, 1.0 to 1.65; P=0.048.

Table 4. Distribution of Bleeding Events in Relation to Indication to Vitamin K Antagonist Treatment

	All	AF	VTE
n (rate per 100 patient-y)	179 (1.87)	132 (1.73)	47 (2.4)*
Type of bleeding, n (rate per 100 patient-y)			
Cerebral	53 (0.55)	42 (0.55)	11 (0.56)
Gastrointestinal	65 (0.68)	51 (0.67)	14 (0.71)
Retroperitoneal	2 (0.02)	1 (0.01)	1 (0.05)
Ocular causing blindness	4 (0.04)	2 (0.03)	2 (0.1)
Blood transfusion ≥2 U	13 (0.13)	7 (0.1)	6 (0.30)
Loss of hemoglobin ≥2 g/dL	33 (0.34)	24 (0.31)	9 (0.46)
Articular bleeding	9 (0.09)	5 (0.06)	4 (0.2)

AF indicates atrial fibrillation; VTE, venous thromboembolism.
*VTE versus AF: relative risk, 1.4; 95% confidence interval, 1.02 to 1.85; P=0.032.

Perché meno emorragie intracraniche ?

Proteine vitamina K-dipendenti

Matrix Gla-protein ed osteocalcina

Minor numero
di emorragie cerebrali

Osteoporosi

Vantaggi dei nuovi farmaci anticoagulanti orali

- Riduzione delle emorragie intracraniche
- Risparmio del sistema della proteina C
- Scompare la necrosi cutanea da AVK

Vantaggi dei nuovi farmaci anticoagulanti orali

- Riduzione delle emorragie intracraniche
- Risparmio del sistema della proteina C
- Scompare la necrosi cutanea da AVK
- Si riducono gli stroke cardioembolici ad inizio di trattamento ?

Increased risk of stroke and of bleeding events on transitioning from Rivaroxaban or Apixaban to Warfarin

	Rivaroxaban to W*	Apixaban to W
HR for ischemic stroke/embolism	3.72	4.06
HR for major bleeding events	3.62	2.52

* less than 50% of patients had a therapeutic INR 30 days after last dose of rivaroxaban

4045 **Events after discontinuation of randomized treatment at the end of the ARISTOTLE trial**

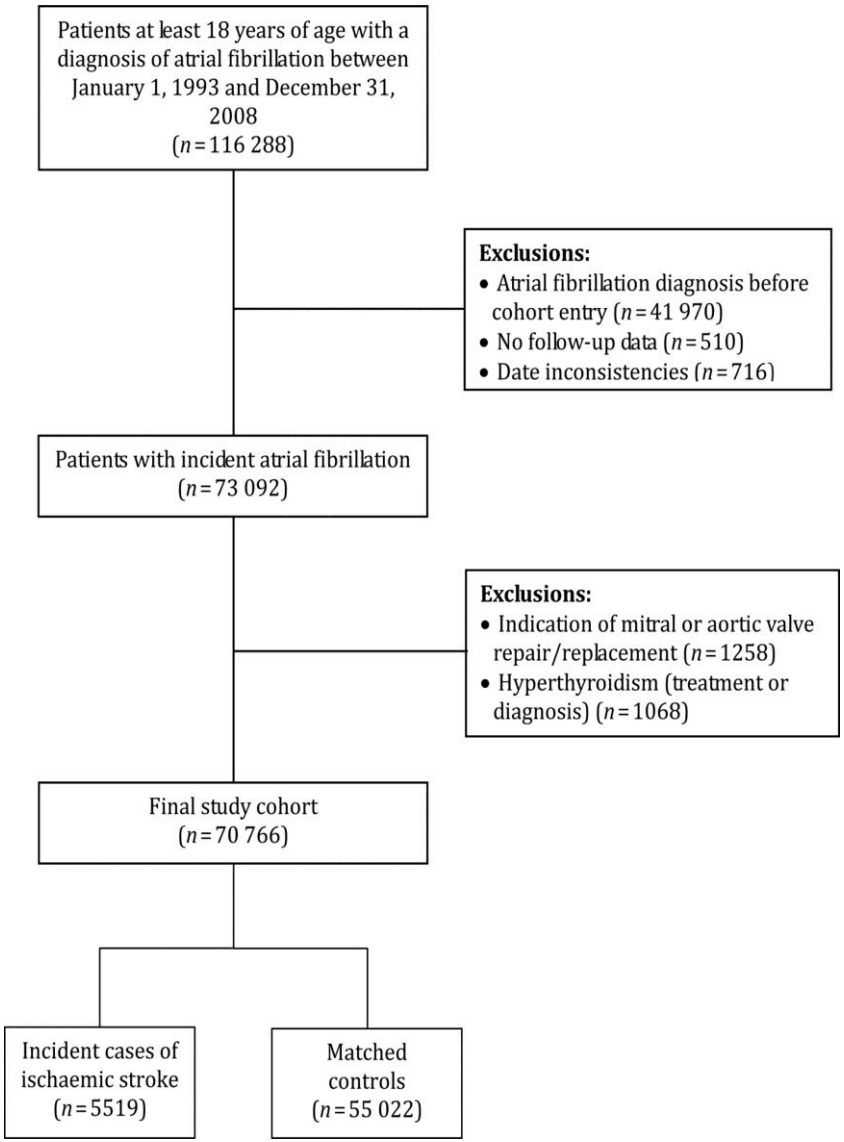
C.B. Granger[1], J.H. Alexander[1], M. Hanna[2], J. Wang[2], P. Mohan[2], J. Lawrence[2], E. Hylek[3], J.E. Ansell[4], L. Wallentin[5] on behalf of ARISTOTLE Investigators and Committees. [1]*Duke Clinical Research Institute, Duke University Medical Center, Durham, United States of America;* [2]*Bristol Myers Squibb, Princeton, NJ, United States of America;* [3]*Boston University, Boston, United States of America;* [4]*Lenox Hill Heart and Vascular Institute, New York, United States of America;* [5]*Uppsala University, UCR-Uppsala Clinical Research Center, Uppsala, Sweden*

This pattern mirrored the first 30 days of the trial where warfarin-naive patients starting warfarin had a higher rate of stroke or systemic embolism (5.41 % pat-y) than warfarin-experienced patients (1.41 % pat-y).

Azoulay L, et al. Eur Heart J, December 18, 2013

- Using the UK Clinical Practice Research Datalink, a nested case–control analysis was conducted within a cohort of 70,766 patients with AF between 1993 and 2008.
- Stroke cases were randomly matched with up to 10 controls on age, sex, date of AF diagnosis, and time since AF diagnosis. Conditional logistic regression was used to estimate adjusted rate ratios (RRs) with 95% confidence intervals (CIs) of stroke associated with current warfarin use classified according to time since initiation of treatment (<30 days, 31–90 days, and >90 days), when compared with non-use.

Azoulay L, et al. Eur Heart J, December 18, 2013



European Heart Journal

Azoulay L, et al. Eur Heart J, December 18, 2013

Table I Characteristics of cases of ischaemic stroke and matched controls overall and across the primary warfarin exposure duration groups

Characteristics at index date	Cases of ischaemic stroke				Controls			
		Warfarin				Warfarin		
	Overall (n = 5519)	First 30 days (n = 117)	≥30 days (n = 637)	Non-use[a] (n = 1513)	Overall (n = 55 022)	First 30 days (n = 732)	≥30 days (n = 10 689)	Non-use[a] (n = 15 499)
Age, years, mean (SD)	79.5 (9.2)	74.8 (8.9)	77.1 (8.9)	79.0 (10.1)	79.5 (9.1)	73.9 (9.1)	77.9 (8.2)	79.0 (10.3)
Males, n (%)	2503 (45.4)	58 (49.6)	359 (56.4)	661 (43.7)	24 979 (45.4)	388 (53.0)	5429 (50.8)	6500 (41.9)
Excessive alcohol use, n (%)	76 (1.4)	0 (0.0)	13 (2.0)	19 (1.3)	643 (1.2)	9 (1.2)	104 (1.0)	154 (1.0)
Smoking status, n (%)								
Ever	2253 (40.8)	46 (39.3)	313 (49.1)	495 (32.7)	22 044 (40.1)	304 (41.5)	4765 (44.6)	5004 (32.3)
Never	2709 (49.1)	58 (49.6)	283 (44.4)	791 (52.3)	28 181 (51.2)	373 (51.0)	5372 (50.3)	8312 (53.6)
Unknown	557 (10.1)	13 (11.1)	41 (6.4)	227 (15.0)	4797 (8.7)	55 (7.5)	552 (5.2)	2183 (14.1)
Obesity, n (%)								
BMI <30 kg/m^2	3407 (61.7)	69 (59.0)	410 (64.4)	841 (55.6)	34 630 (62.9)	443 (60.5)	7058 (66.0)	8968 (57.9)
BMI ≥30 kg/m^2	810 (14.7)	19 (16.2)	112 (17.6)	190 (12.6)	8716 (15.8)	151 (20.6)	2045 (19.1)	1982 (12.8)
Unknown	1302 (23.6)	29 (24.8)	115 (18.1)	482 (31.9)	11 676 (21.2)	138 (18.9)	1586 (14.8)	4549 (29.4)
$CHADS_2$ score, n (%)								
0	390 (7.1)	20 (17.1)	44 (6.9)	181 (12.0)	5593 (10.2)	137 (18.7)	1055 (9.9)	2373 (15.3)
1	1301 (23.6)	28 (23.9)	124 (19.5)	494 (32.7)	16 626 (30.2)	298 (40.7)	3043 (28.5)	5636 (36.4)
≥2	3828 (69.4)	69 (59.0)	469 (73.6)	838 (55.4)	32 803 (59.6)	297 (40.6)	6591 (61.7)	7490 (48.3)
Peripheral artery disease, n (%)	297 (5.4)	2 (1.7)	44 (6.9)	45 (3.0)	2275 (4.1)	15 (2.1)	432 (4.0)	389 (2.5)
Myocardial infarction, n (%)	696 (12.6)	5 (4.3)	93 (14.6)	90 (6.0)	6554 (11.9)	30 (4.1)	1255 (11.7)	721 (4.7)
Previous cancer, n (%)	1003 (18.2)	20 (17.1)	133 (20.9)	237 (15.7)	10 605 (19.3)	114 (15.6)	2109 (19.7)	2744 (17.7)
History of bleeds, n (%)	1304 (23.6)	21 (18.0)	194 (30.5)	269 (17.8)	12 358 (22.5)	111 (15.2)	2789 (26.1)	2875 (18.6)
Venous thromboembolism, n (%)	421 (7.6)	10 (8.6)	77 (12.1)	83 (5.5)	4094 (7.4)	62 (8.5)	1255 (11.7)	680 (4.4)
Valvular disease	388 (7.0)	4 (3.4)	96 (15.1)	64 (4.2)	3946 (7.2)	42 (5.7)	1389 (13.0)	615 (4.0)
ACE inhibitors, n (%)	1738 (31.5)	21 (18.0)	288 (45.2)	244 (16.1)	18 237 (33.1)	216 (29.5)	4614 (43.2)	2837 (18.3)
Angiotensin receptor blockers, n (%)	397 (7.2)	7 (6.0)	58 (9.1)	53 (3.5)	4572 (8.3)	54 (7.4)	1268 (11.9)	606 (3.9)
Antidepressants, n (%)	706 (12.8)	12 (10.3)	76 (11.9)	162 (10.7)	5404 (9.8)	56 (7.7)	879 (8.2)	1390 (9.0)
Antipsychotics, n (%)	555 (10.1)	9 (7.7)	52 (8.2)	144 (9.5)	3858 (7.0)	33 (4.5)	508 (4.8)	1177 (7.6)
NSAIDs, n (%)	981 (17.8)	15 (12.8)	59 (9.3)	291 (19.2)	9102 (16.5)	171 (23.4)	882 (8.3)	2996 (9.3)
Statins, n (%)	1294 (23.4)	16 (13.7)	218 (34.2)	100 (6.6)	12 503 (22.7)	110 (15.0)	3243 (30.3)	936 (6.0)

SD, standard deviation; BMI, body mass index; ACE, angiotensin-converting enzyme; NSAIDs, non-steroidal anti-inflammatory drugs.
[a]Defined as no use of any antithrombotic therapy for at least one year before index date.

Azoulay L, et al. Eur Heart J, December 18, 2013

Table 2 Timing of warfarin initiation and the risk of ischaemic stroke

Current use of warfarin monotherapy	Cases ($n = 5519$)	Controls[a] ($n = 55\,022$)	Crude RR	Adjusted RR (95% CI)[b]
No use of any antithrombotic therapy for at least 1 year, *n* (%)	1513 (27.4)	15 499 (28.2)	1.00	1.00 (reference)
Time since initiation of warfarin, *n* (%)				
≤30 days	117 (2.1)	732 (1.3)	1.74	1.71 (1.39–2.12)
31–90 days	27 (0.5)	544 (1.0)	0.52	0.50 (0.34–0.75)
≥90 days	610 (11.1)	10 145 (18.4)	0.57	0.55 (0.49–0.61)

RR, rate ratio; CI, confidence interval.

Current users of warfarin monotherapy who had used aspirin and/or clopidogrel in the year prior to index date, current users of aspirin or clopidogrel monotherapy, current users of antithrombotic combinations (including warfarin), and past users of any of these drugs in the year before index date are not displayed in the table, but were considered in the regression model for proper estimation of treatment effects (representing 3252 cases and 28 102 controls).

[a]Cases and controls were matched on age, sex, and date of atrial fibrillation diagnosis, and time since atrial fibrillation diagnosis.

[b]Adjusted for excessive alcohol use, smoking status, obesity, $CHADS_2$ score, peripheral artery disease, myocardial infarction, previous cancer, prior bleeds, venous thromboembolism, valvular disease, and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antidepressants, antipsychotics, non-steroidal anti-inflammatory drugs, and statins.

Azoulay L, et al. Eur Heart J, December 18, 2013

- A total of 5519 patients experienced a stroke during follow-up.
- Warfarin was associated with a 71% increased risk of stroke in the first 30 days of use:

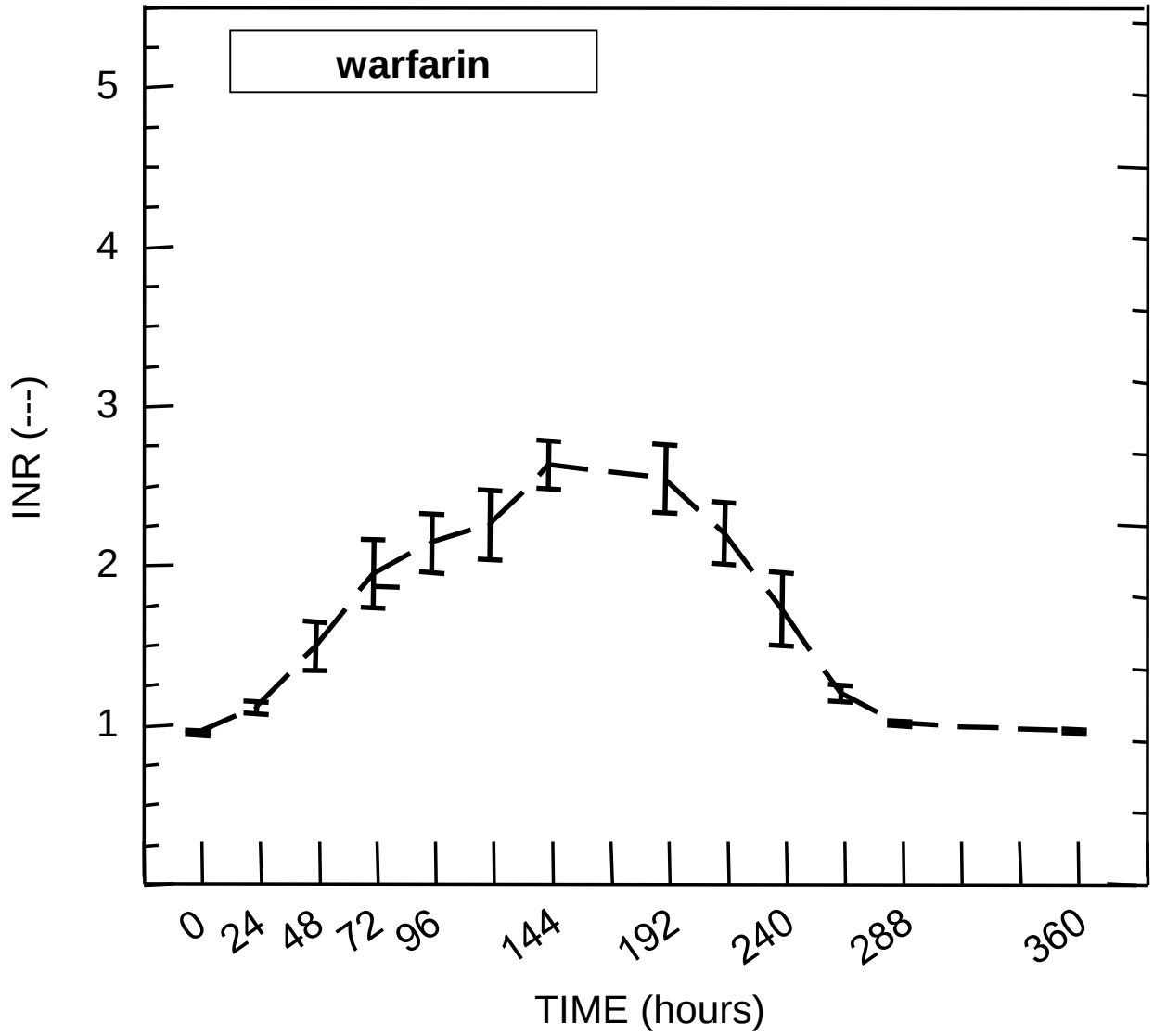
  RR: 1.71, 95% CI: 1.39–2.12),

  while decreased risks were observed with initiation >30 days before the event

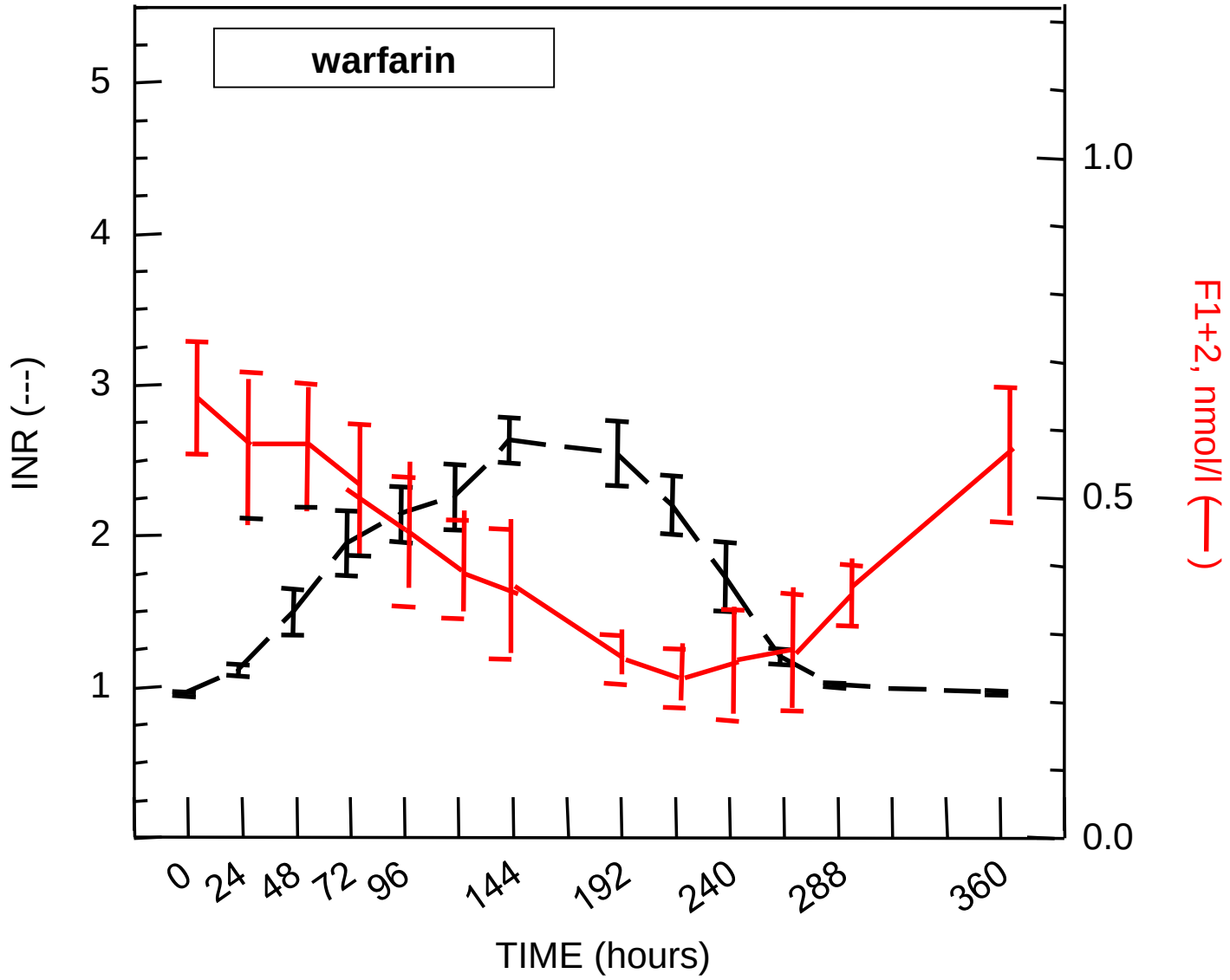
  31–90 days: RR: 0.50, 95% CI: 0.34–0.75

  >90 days: RR: 0.55, 95% CI: 0.50–0.61.

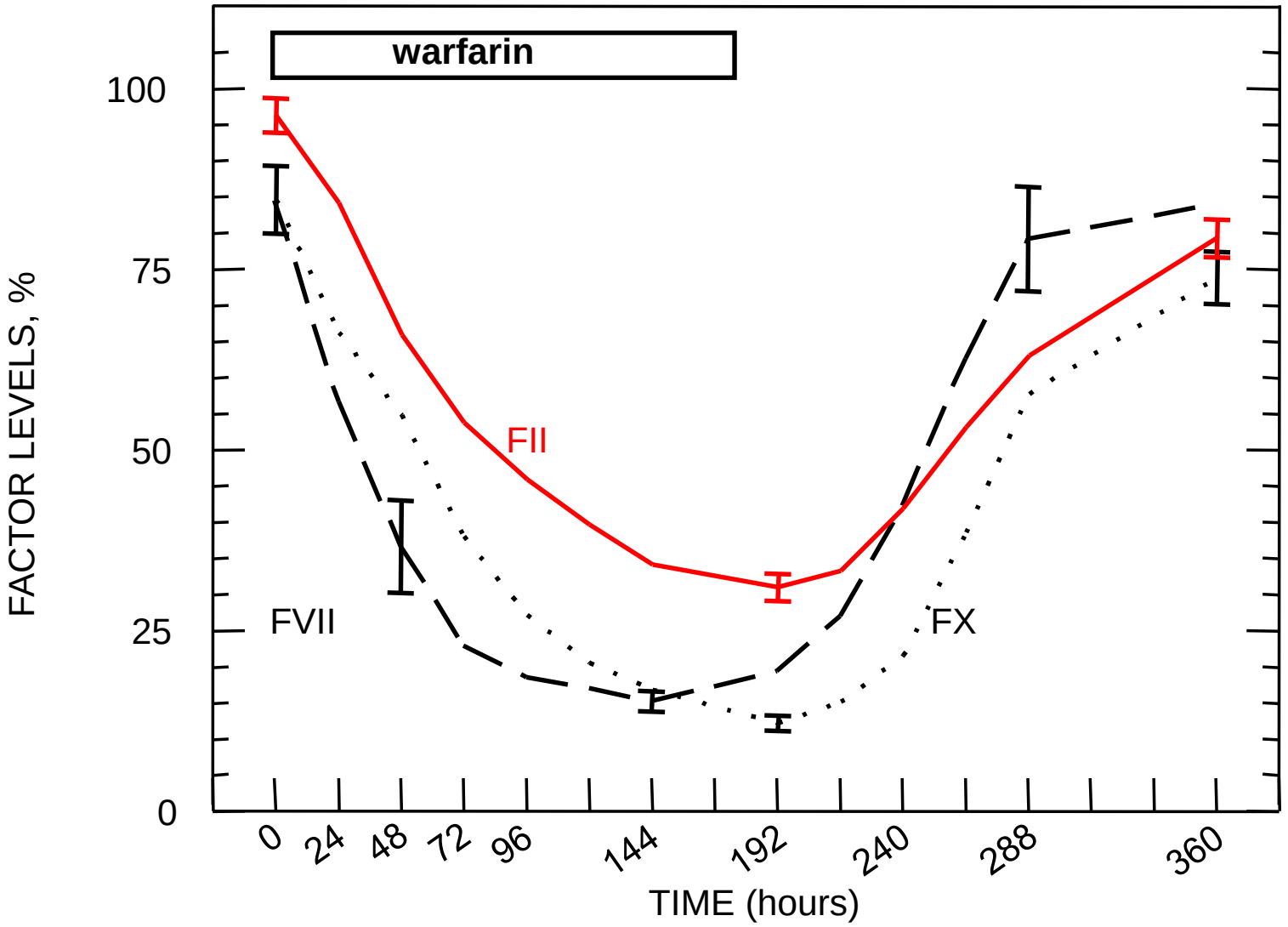
L’inizio della terapia con VKA



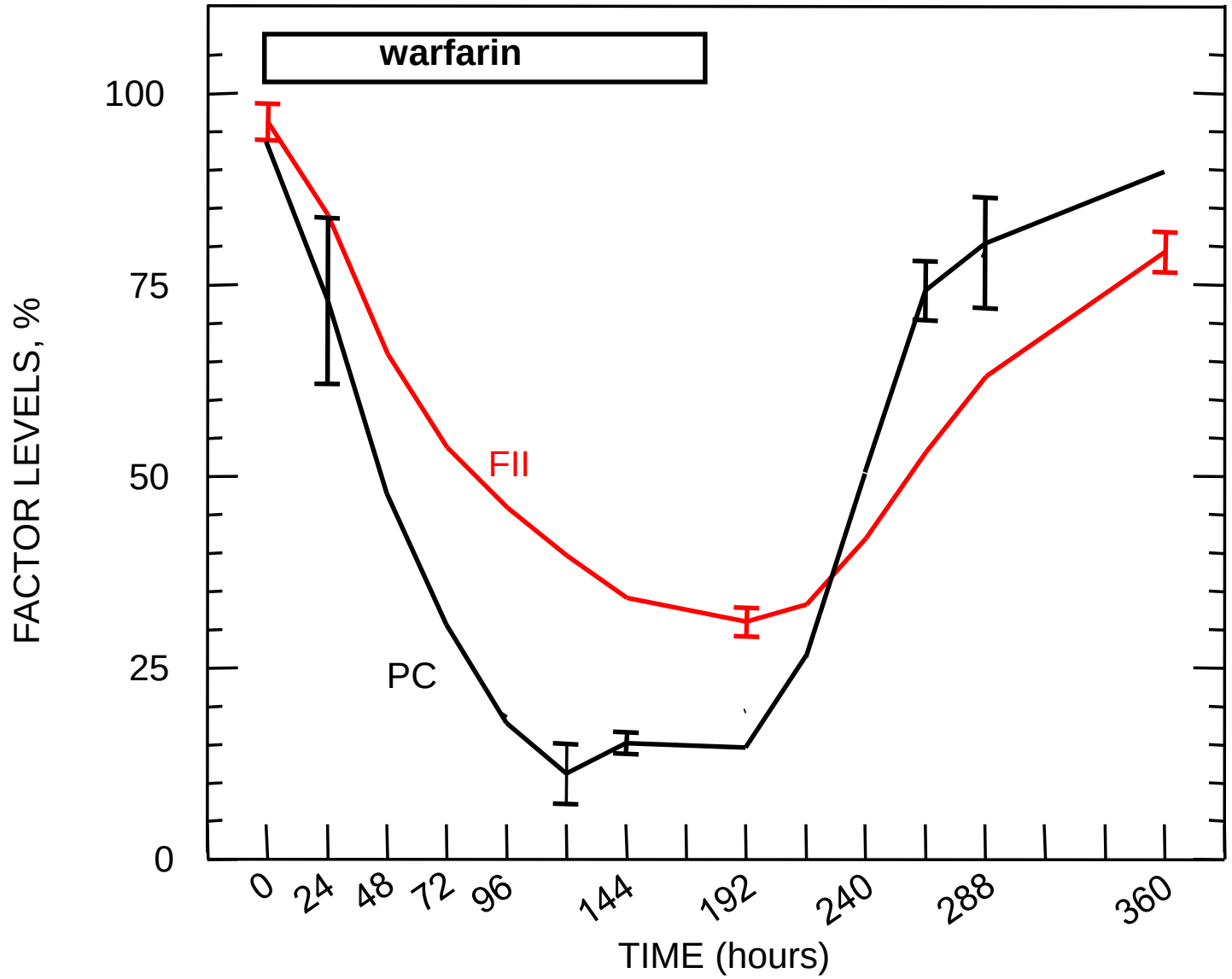
L’inizio della terapia con VKA



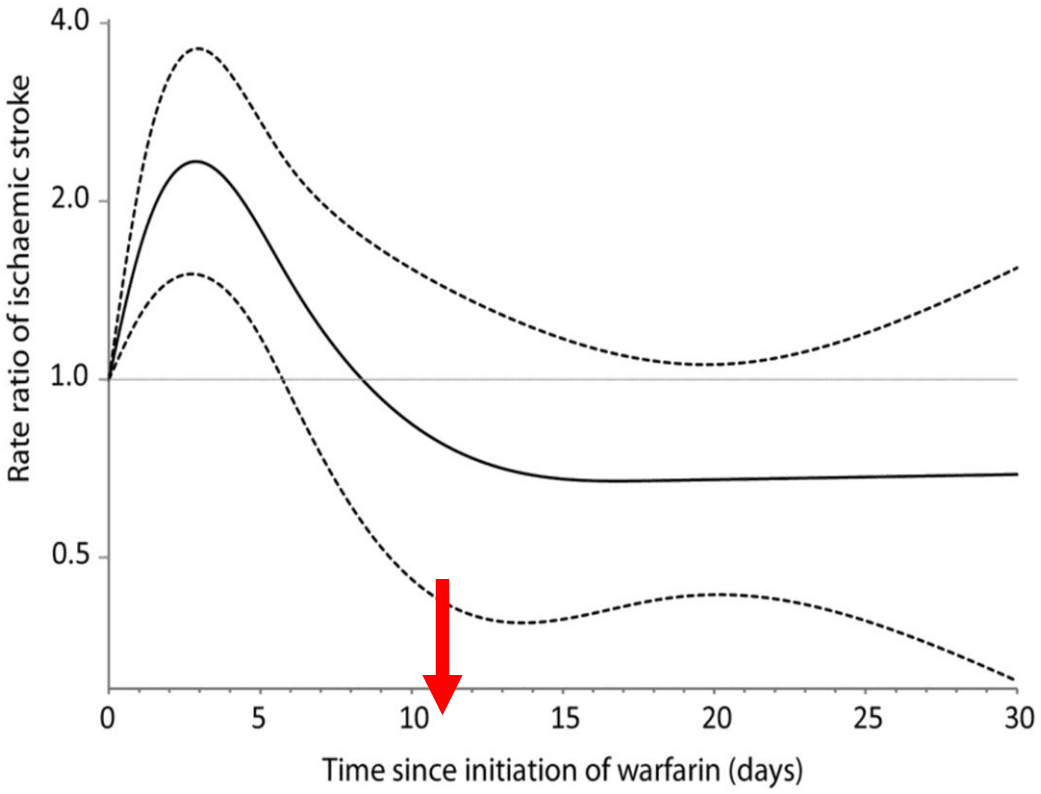
L’inizio della terapia con VKA



L’inizio della terapia con VKA



Azoulay L, et al. Eur Heart J, December 18, 2013



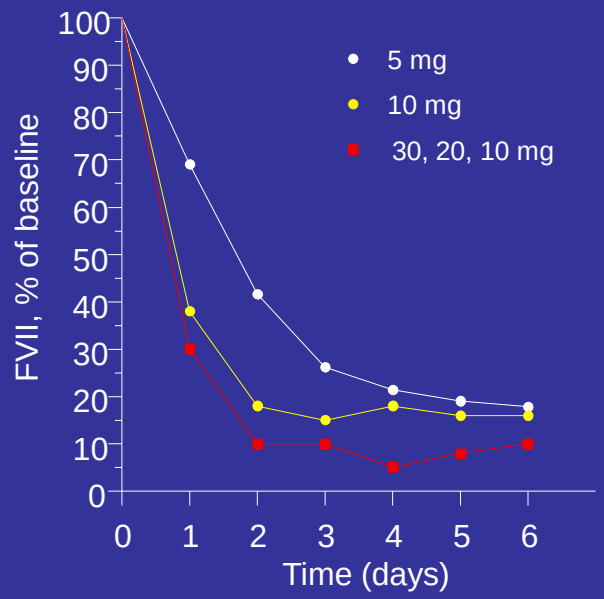
Smooth cubic spline curve of the adjusted rate ratio of ischaemic stroke (solid line) and 95% confidence limits (dashed lines) as a function of the time since initiation of warfarin.

European Heart Journal

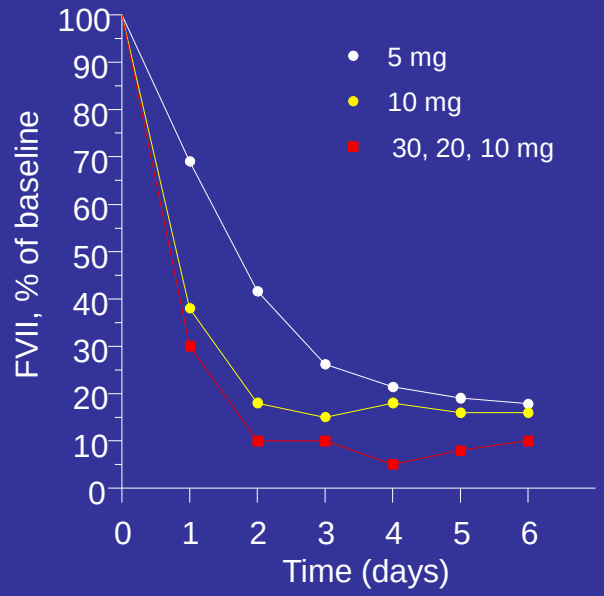
Azoulay L, et al. Eur Heart J, December 18, 2013

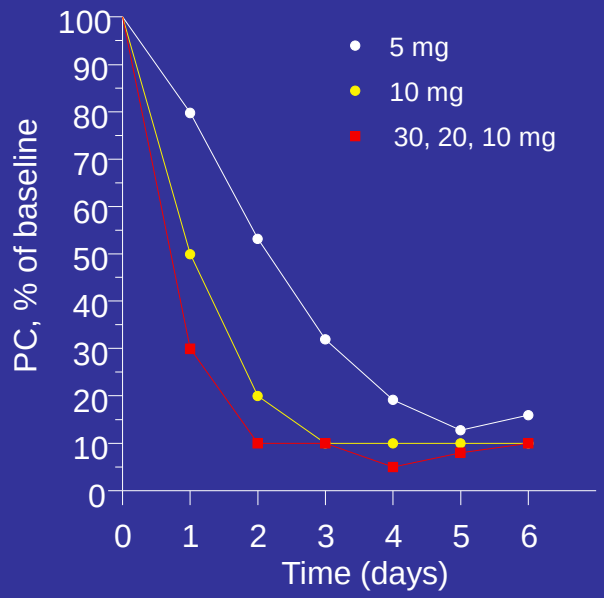
- Patients initiating warfarin may be at an increased risk of stroke during the first 30 days of treatment, supporting the biological plausibility of a transient hypercoagulable state at the start of the treatment, although additional studies are needed to confirm these findings.

Warfarin treatment

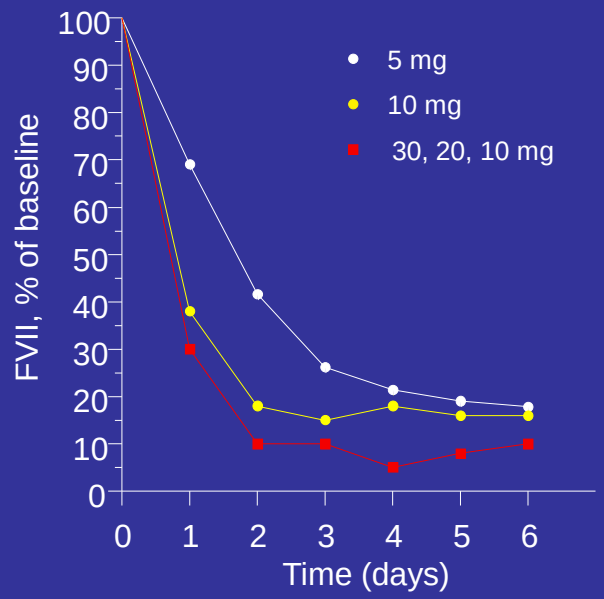


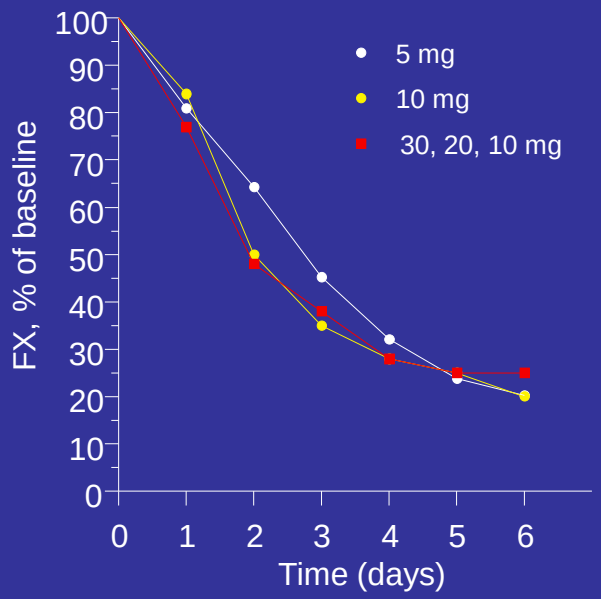
Warfarin treatment

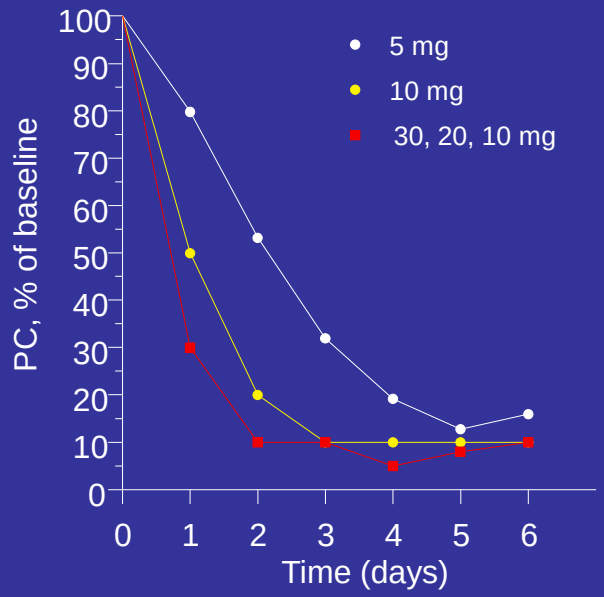




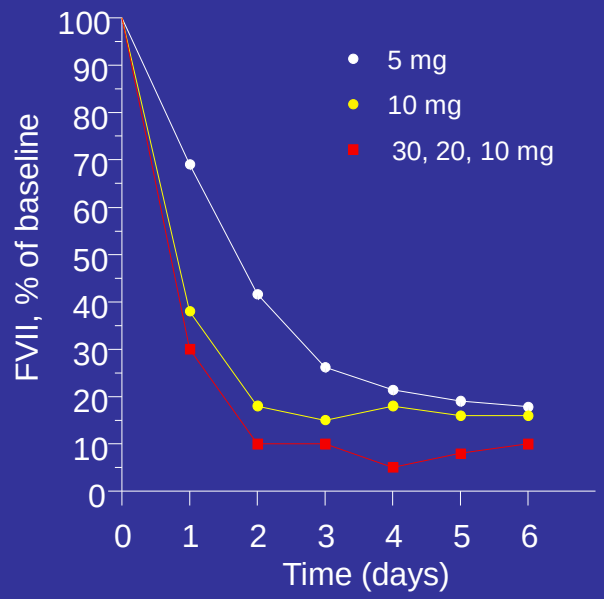
Warfarin treatment

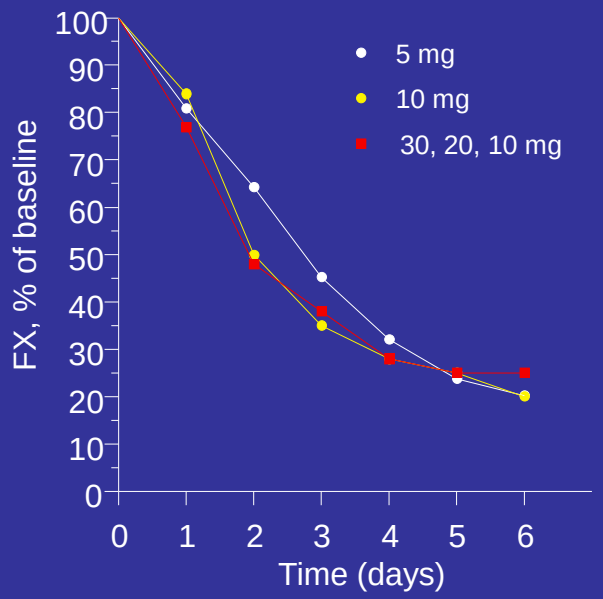


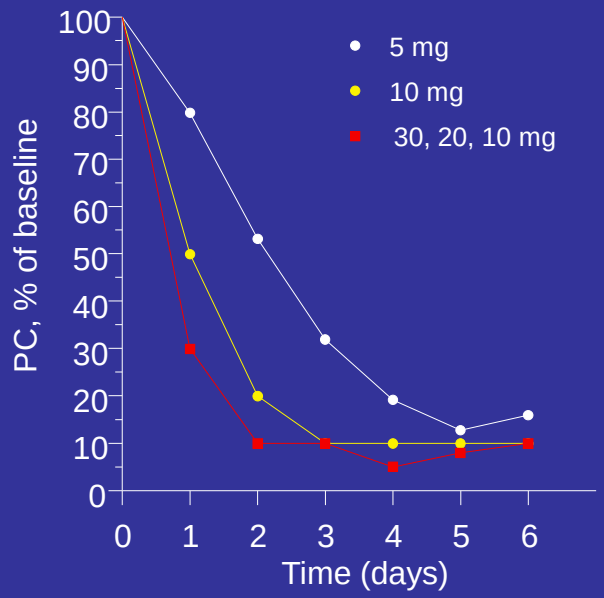


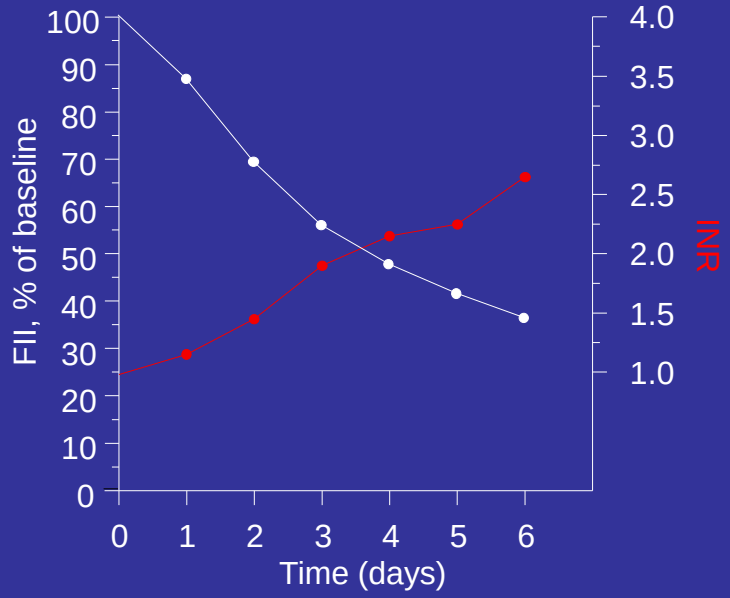


Warfarin treatment









D’Angelo A, et al. Eur Heart J, January 15, 2014

- The INR is a valid monitoring tool in patients on stable VKA treatment because it adjusts for the different sensitivity of thromboplastin reagents to the reduction in factor II, but this is not true at initiation of VKA treatment because of the much faster reduction in factor VII levels.
- Hence, the faster obtainment of "therapeutic" INRs with a loading dose is meaningless with respect to antithrombotic activity.

D'Angelo A, et al. Eur Heart J, January 15, 2014

- The INR is a valid monitoring tool in patients on stable VKA treatment because it adjusts for the different sensitivity of thromboplastin reagents to the reduction in factor II, but this is not true at initiation of VKA treatment because of the much faster reduction in factor VII levels.
- Hence, the faster obtainment of "therapeutic" INRs with a loading dose is meaningless with respect to antithrombotic activity.
- Based on data from patients with acute VTE - and heparin bridging -, the 2012 ACCP guidelines suggest (grade 2C) initiating therapy with warfarin 10 mg for the first two days rather than starting with the estimated maintenance dose.

D’Angelo A, et al. Eur Heart J, January 15, 2014

- The INR is a valid monitoring tool in patients on stable VKA treatment because it adjusts for the different sensitivity of thromboplastin reagents to the reduction in factor II, but this is not true at initiation of VKA treatment because of the much faster reduction in factor VII levels.
- Hence, the faster obtainment of "therapeutic" INRs with a loading dose is meaningless with respect to antithrombotic activity.
- Based on data from patients with acute VTE - and heparin bridging -, the 2012 ACCP guidelines suggest (grade 2C) initiating therapy with warfarin 10 mg for the first two days rather than starting with the estimated maintenance dose.
- The implication of a 2C suggestion is that higher-quality research may well change the estimate: isn't it time for a change ?

D’Angelo A, et al. Eur Heart J, January 15, 2014

- The INR is a valid monitoring tool in patients on stable VKA treatment because it adjusts for the different sensitivity of thromboplastin reagents to the reduction in factor II, but this is not true at initiation of VKA treatment because of the much faster reduction in factor VII levels.
- Hence, the faster obtainment of "therapeutic" INRs with a loading dose is meaningless with respect to antithrombotic activity.
- Based on data from patients with acute VTE - and heparin bridging -, the 2012 ACCP guidelines suggest (grade 2C) initiating therapy with warfarin 10 mg for the first two days rather than starting with the estimated maintenance dose.
- The implication of a 2C suggestion is that higher-quality research may well change the estimate: isn't it time for a change ?

Ostacoli potenziali ai nuovi farmaci

- Aderenza e persistenza senza monitoraggio di laboratorio

Ostacoli potenziali ai nuovi farmaci

Table 2. Major Predictors of Poor Adherence to Medication, According to Studies of Predictors.

Predictor	Study
Presence of psychological problems, particularly depression	van Servellen et al.,[51] Ammassari et al.,[52] Stilley et al.[53]
Presence of cognitive impairment	Stilley et al.,[53] Okuno et al.[54]
Treatment of asymptomatic disease	Sewitch et al.,[55]
Inadequate follow-up or discharge planning	Sewitch et al.,[55] Lacro et al.[56]
Side effects of medication	van Servellen et al.[51]
Patient's lack of belief in benefit of treatment	Okuno et al.,[54] Lacro et al.[56]
Patient's lack of insight into the illness	Lacro et al.,[56] Perkins[57]
Poor provider–patient relationship	Okuno et al.,[54] Lacro et al.[56]
Presence of barriers to care or medications	van Servellen et al.,[51] Perkins[57]
Missed appointments	van Servellen et al.,[51] Farley et al.[58]
Complexity of treatment	Ammassari et al.[52]
Cost of medication, copayment, or both	Balkrishnan,[59] Ellis et al.[60]

Osterberg L, Blaschke T. Adherence to medication NEJM 2005;353;487

Assessment of an **E**ducation and **G**uidance program
for **E**liquis **A**dherence in **N**on-valvular atrial fibrillation

Ostacoli potenziali ai nuovi farmaci

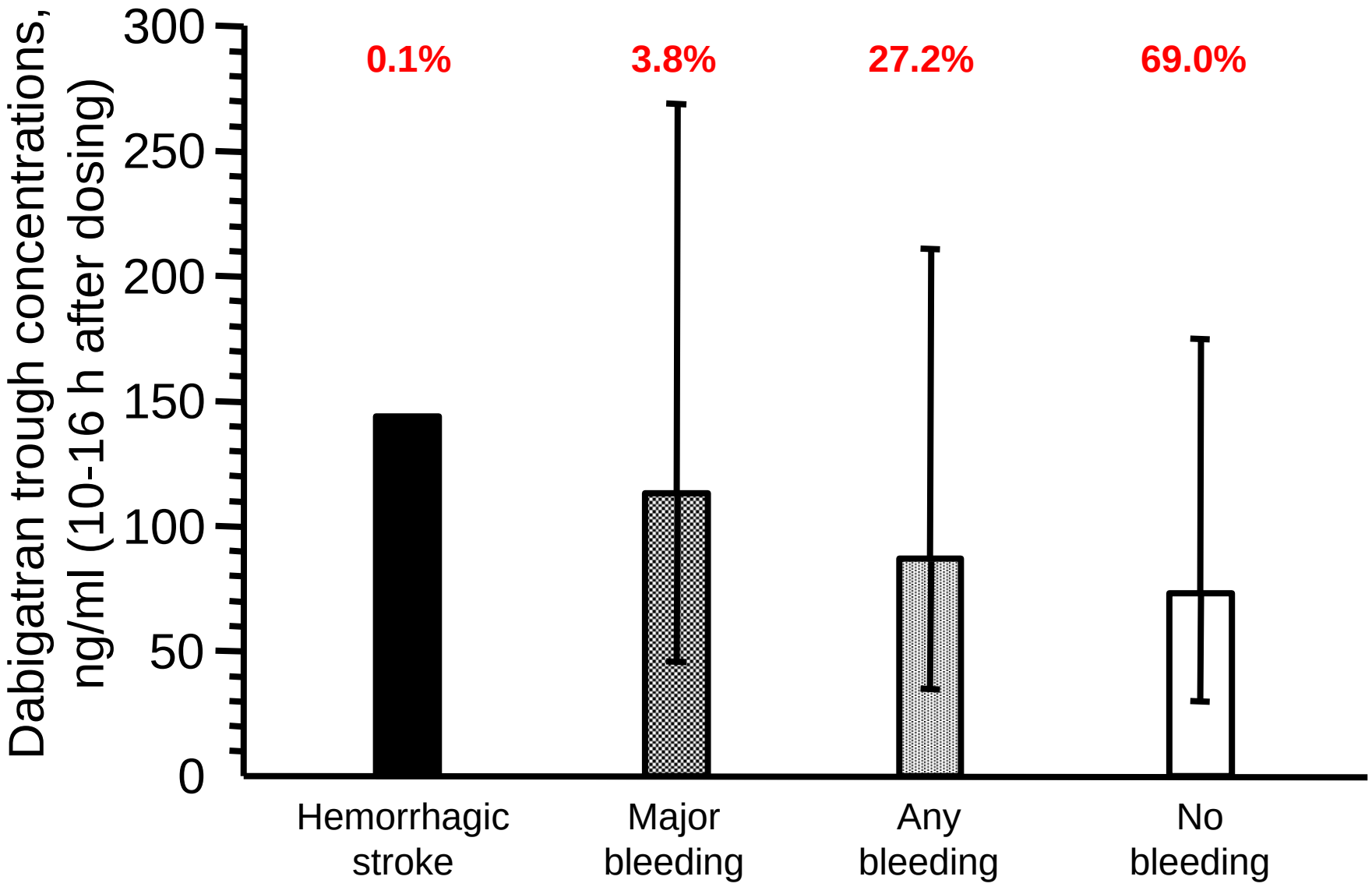
- Aderenza e persistenza senza monitoraggio di laboratorio
- Il paradigma dell'ampio range terapeutico non è piuttosto solo ampia variabilità interindividuale ?

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

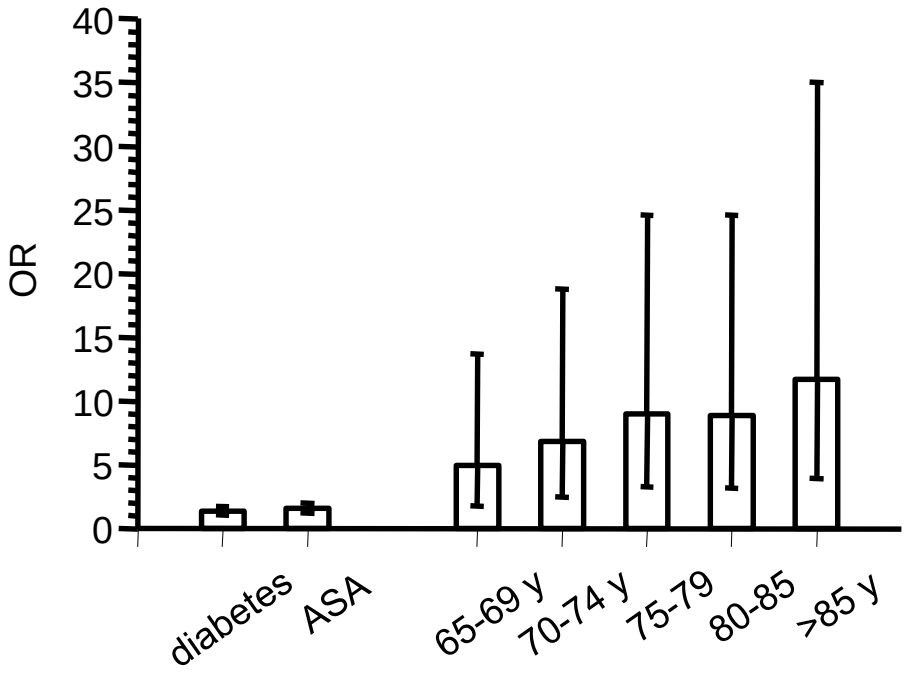
10-90° percentile
5-95° percentile
interquartile

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

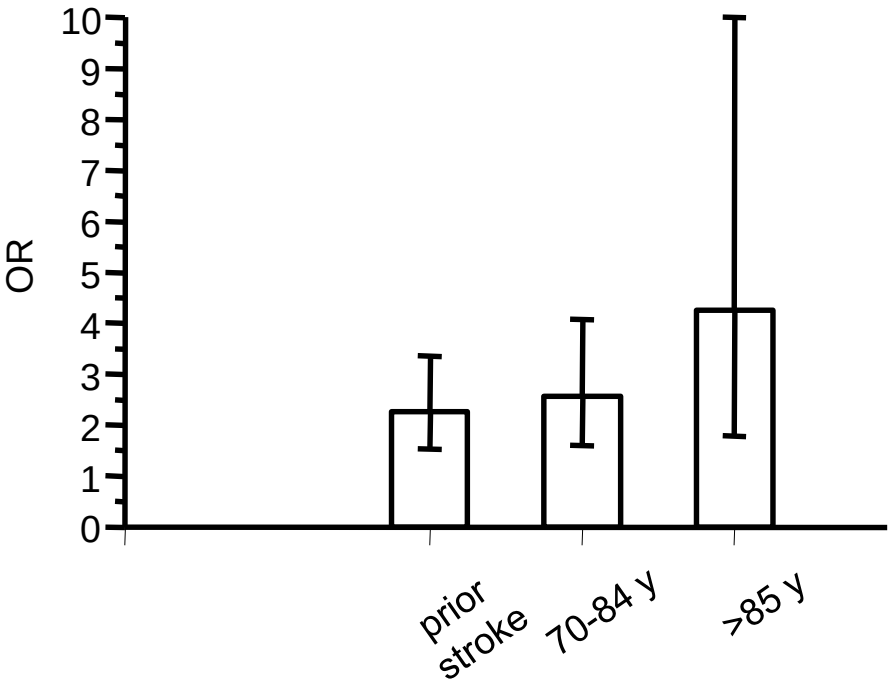


Reilly PA, et al. JACC 2014;63:321-8

Major Bleeding

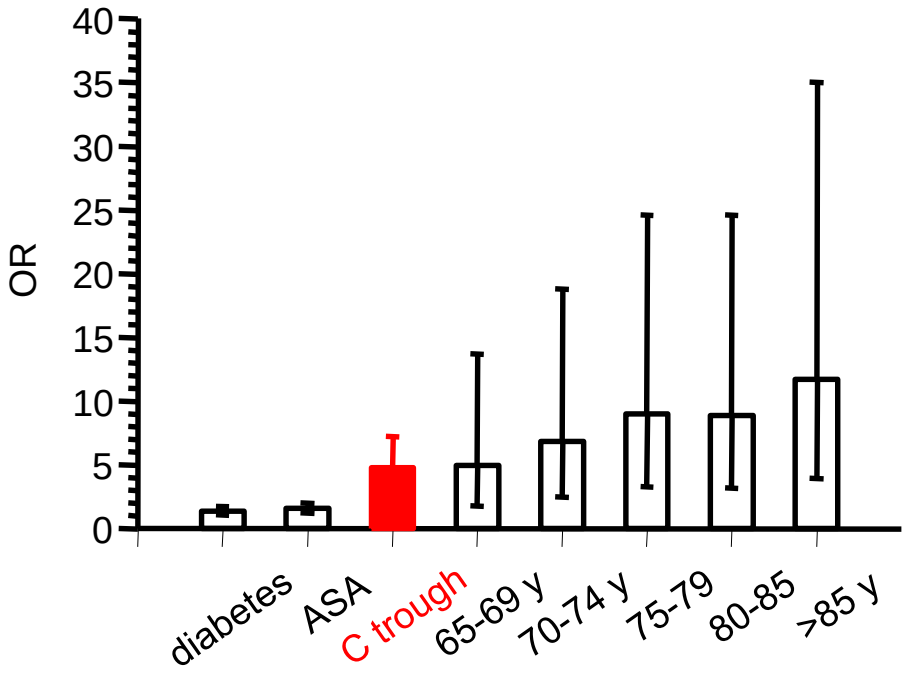


Stroke/SE

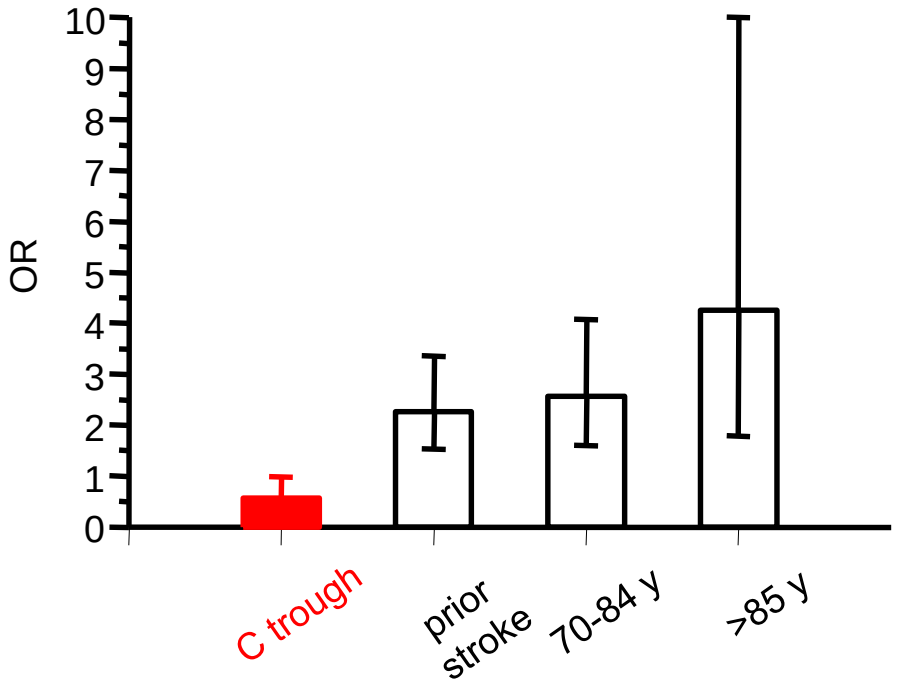


Reilly PA, et al. JACC 2014;63:321-8

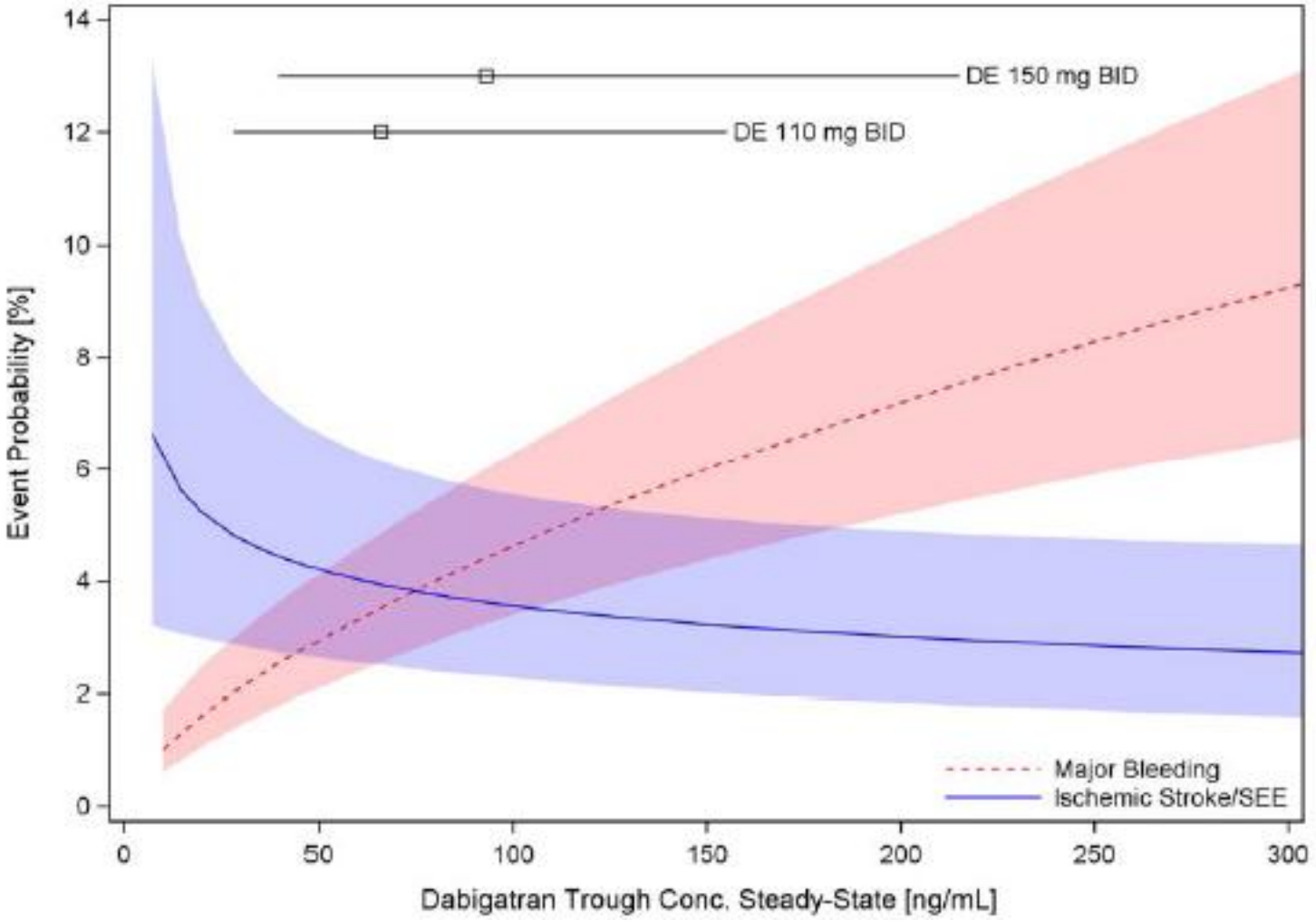
Major Bleeding



Stroke/SE

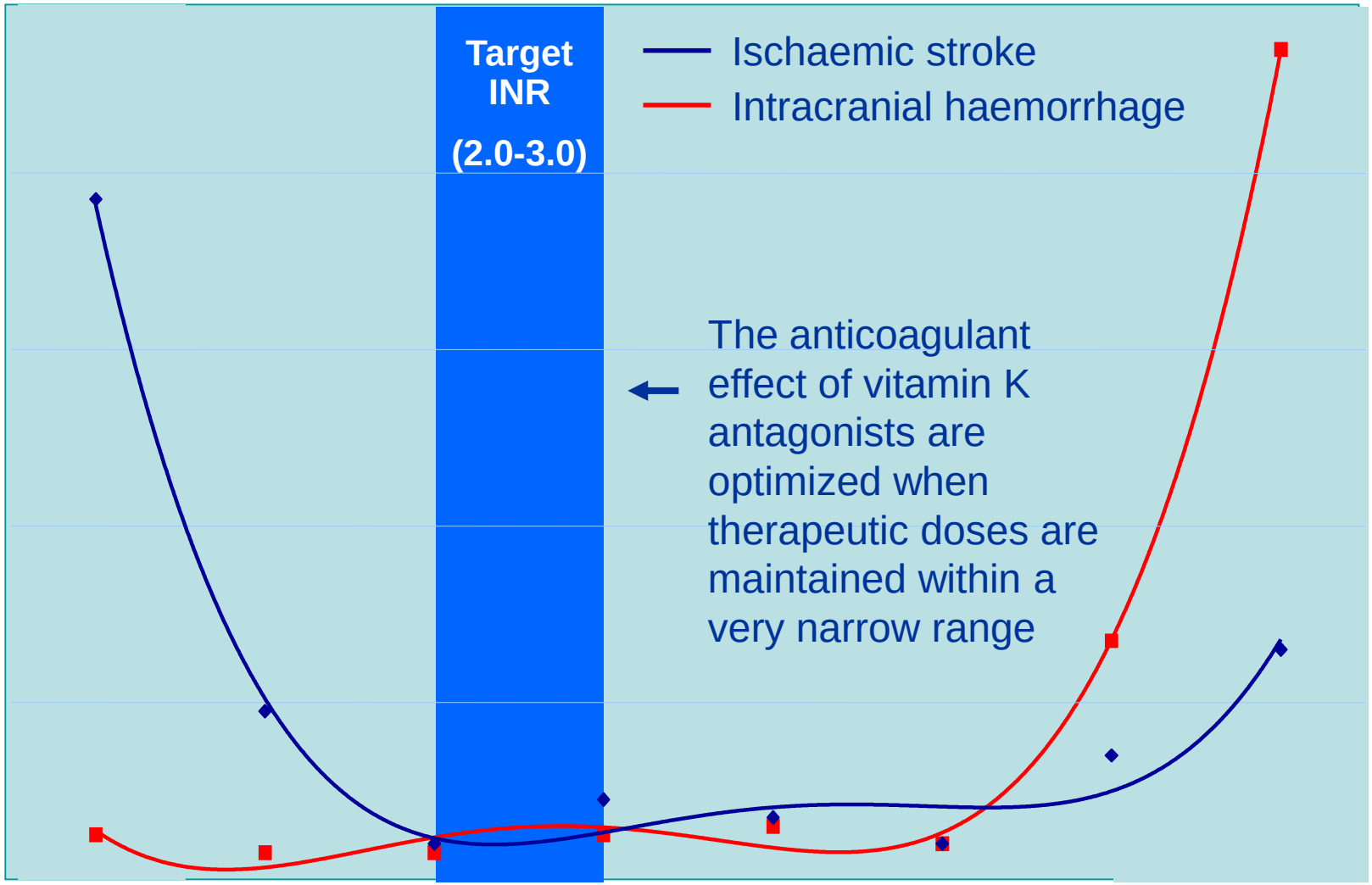


Reilly PA, et al. JACC 2014;63:321-8



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

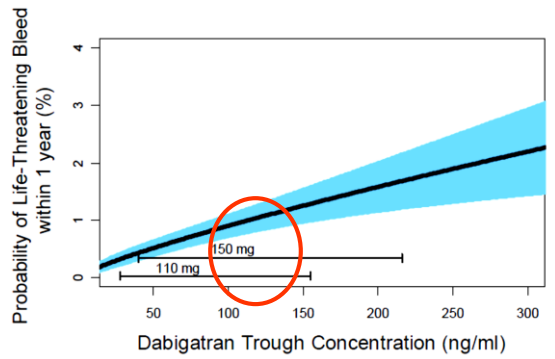
Narrow therapeutic range with VKA in AF/VTE



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

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.



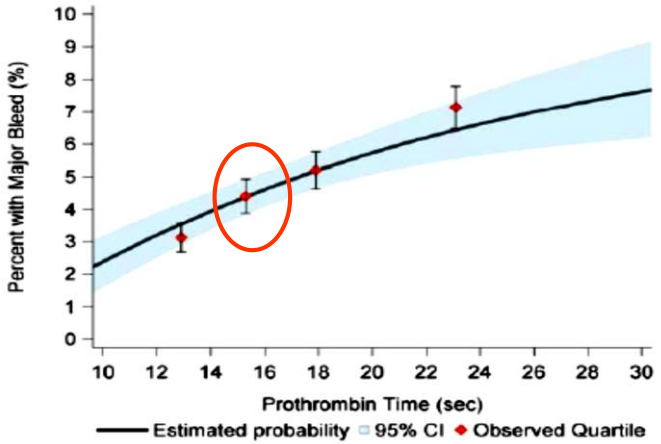


Figure 5. Probability of ischemic stroke within 1 year vs. dabigatran trough concentration. The blue shaded region represents the 95% confidence interval. The bars on the bottom on the plot region represent the 10th to 90th percentiles of observed dabigatran pre-dose concentrations in the RE-LY trial.

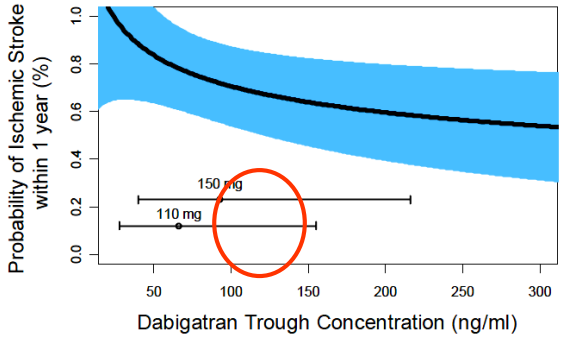
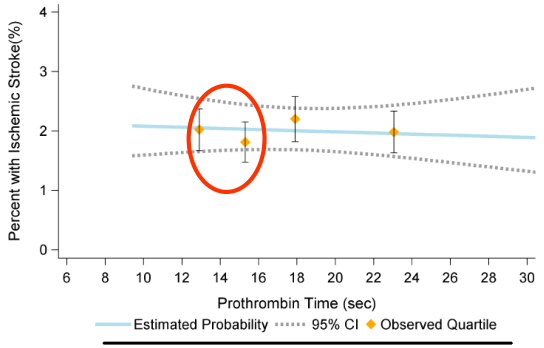


Figure 7. ROCKET ischemic stroke vs. PT (LD+2, pp pop)



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

Ruf et al, Lancet 2015

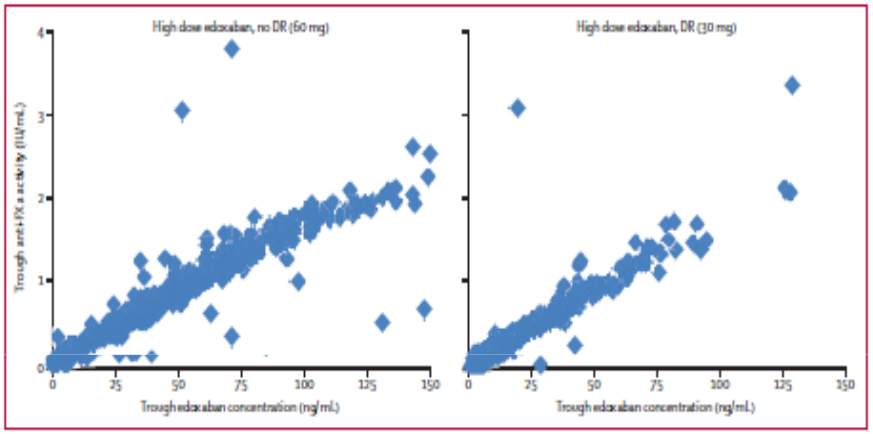


Figure 1: Correlation between edoxaban concentration and anti-FXa Activity
Trough edoxaban plasma concentration and anti-FXa activity at 1 month after randomisation. Spearman correlation: overall, r=0·96, 95% CI 0·95–0·96; low-dose edoxaban, dose reduced, r=0·92, 95% CI 0·89–0·94; low-dose edoxaban, 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.

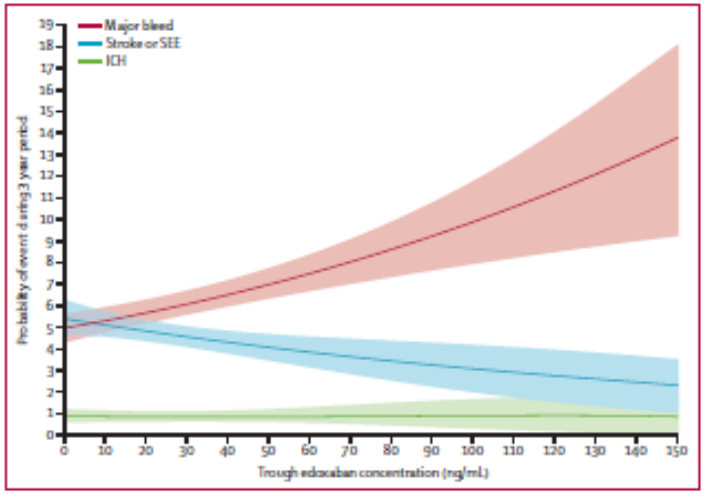


Figure 2: Probability of clinical outcomes versus edoxaban concentration
Trough edoxaban plasma concentration at 1 month after randomisation versus probability of efficacy and safety outcomes (median follow-up 2·8 years). ICH=intracranial haemorrhage. SEE=systemic embolic event.

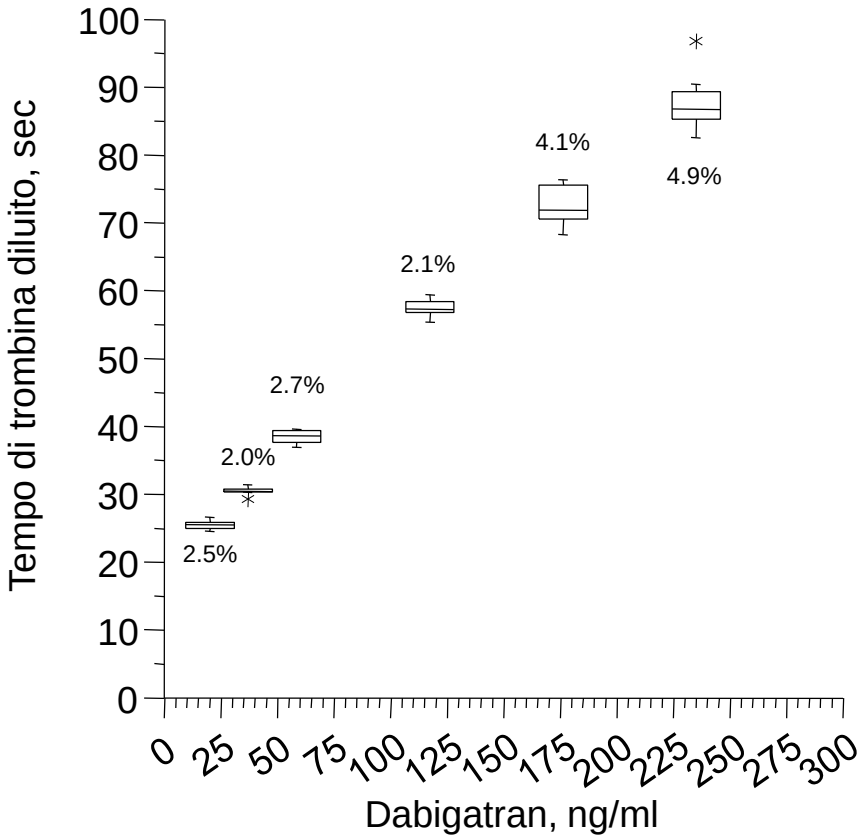
Non è difficile…

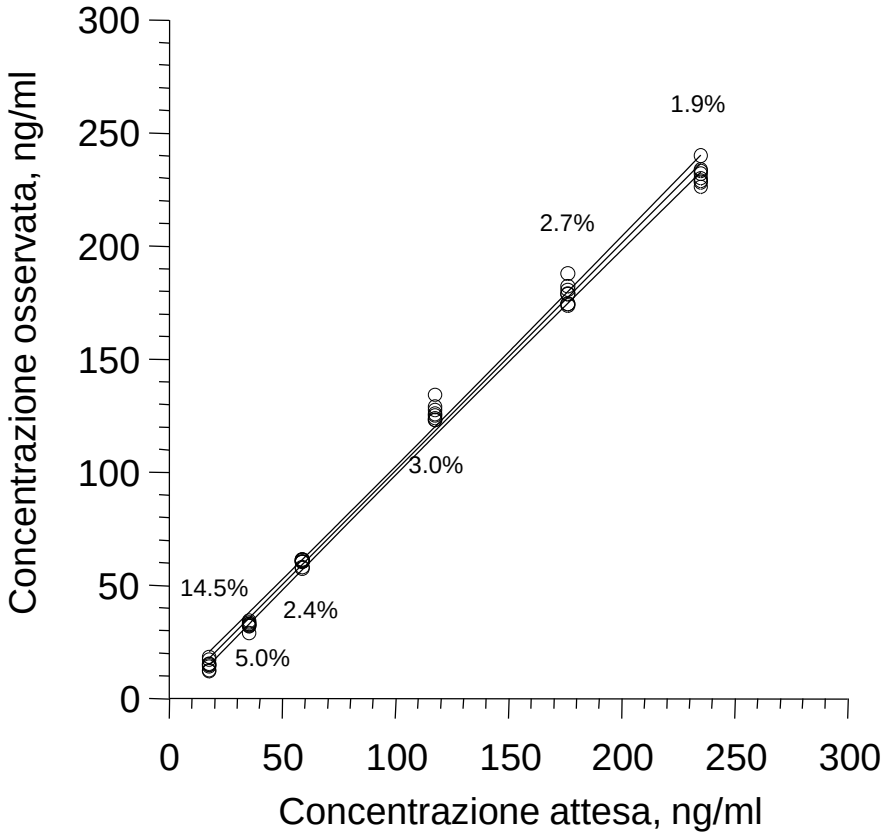
DOA: QUALI TEST?

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

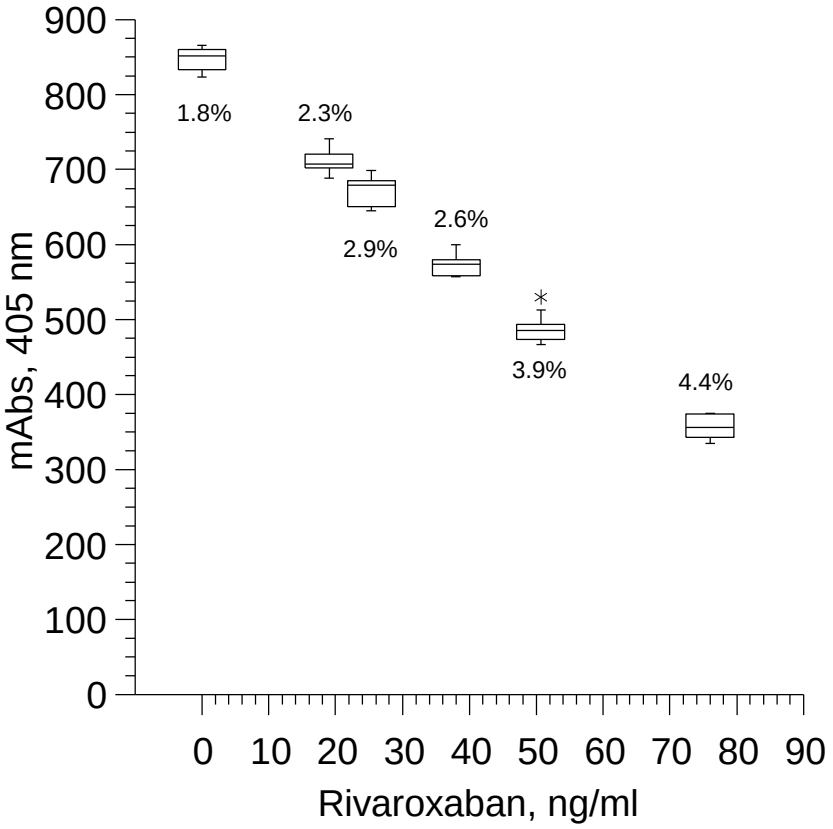
Pengo V et al, T&H 2011; Douxfils J et al, T&H 2012, 2013; Baglin T, JT&H 2013.

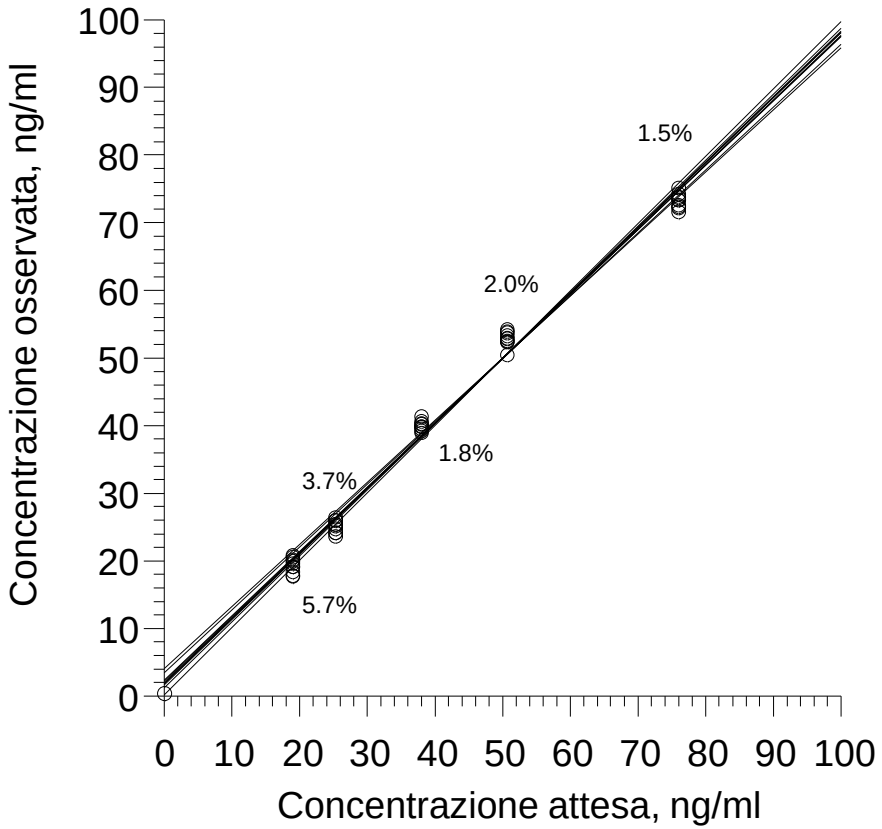
Misurare la concentrazione plasmatica di dabigatran con il tempo di trombina diluito (mediana di concentrazione attesa a valle 91 ng/mL)



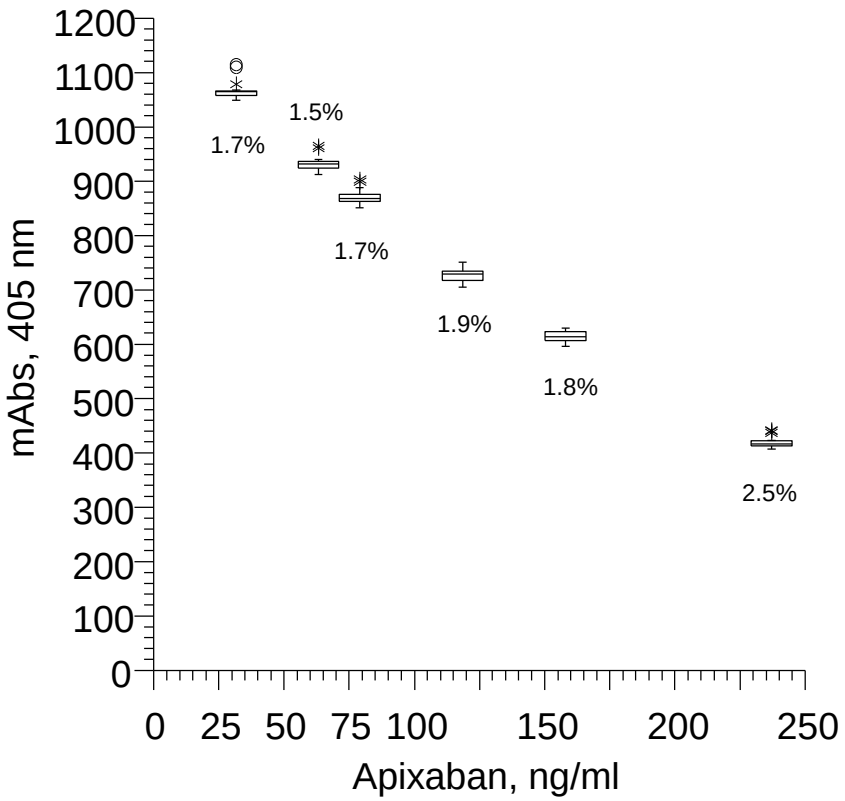


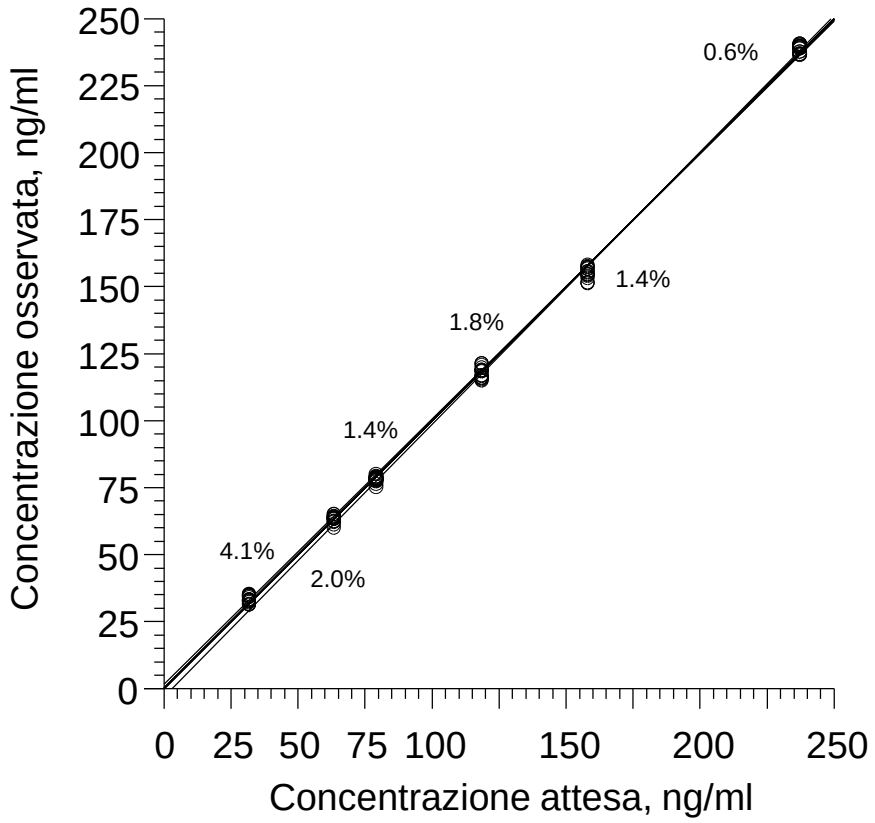
Misurare la concentrazione plasmatica di rivaroxaban con il test anti-Xa (mediana di concentrazione attesa a valle 32 ng/mL)



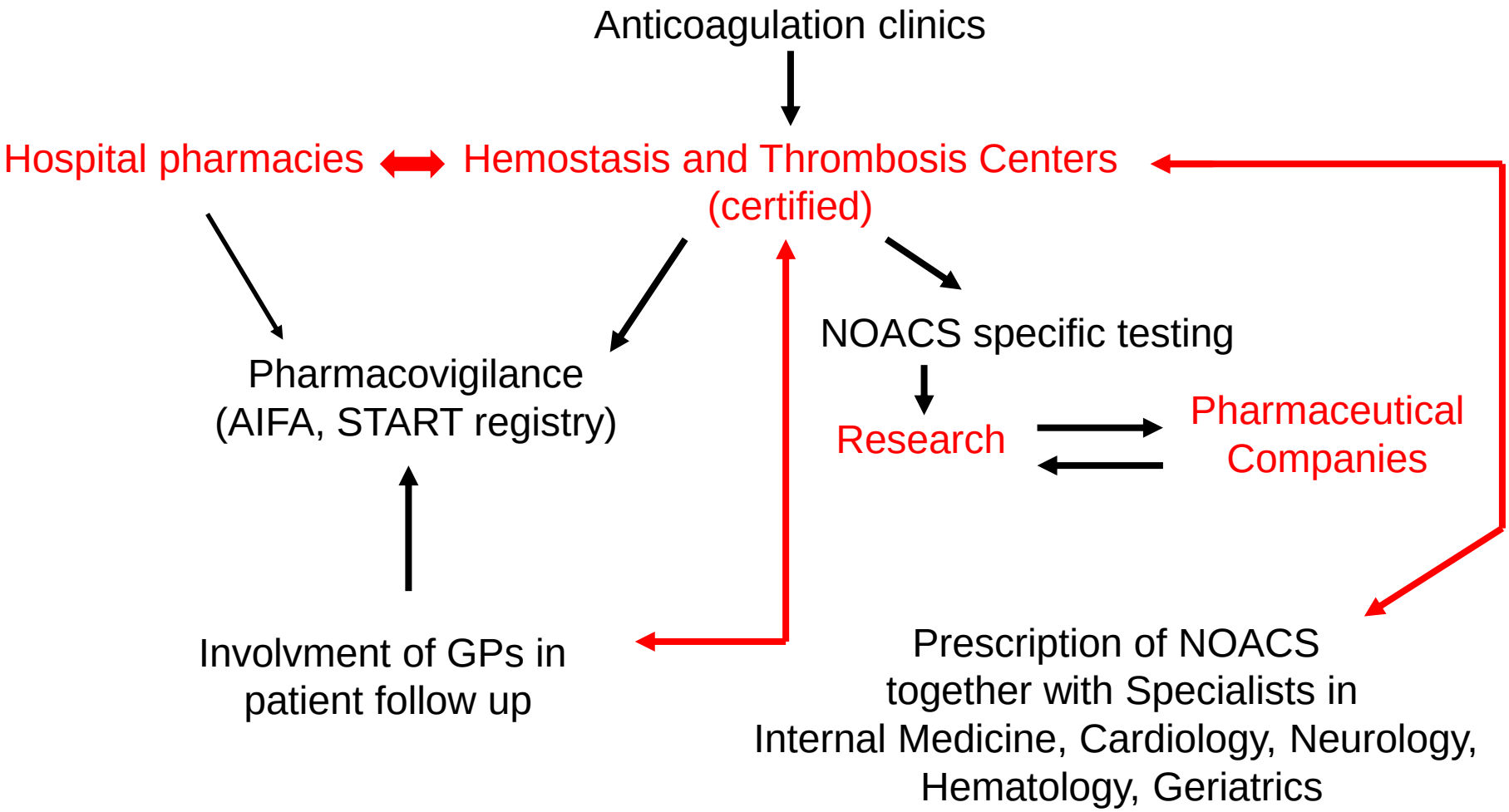


Misurare la concentrazione plasmatica di apixaban con il test anti-Xa
(mediana di concentrazione attesa a valle ?)





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


Anticoagulation clinics
Hospital pharmacies
Hemostasis and Thrombosis Centers
(certified)
Pharmacovigilance
(AIFA, START registry)
NOACS specific testing
Research
Pharmaceutical
Companies
Involvment of GPs in
patient follow up
Prescription of NOACS
together with Specialists in
Internal Medicine, Cardiology, Neurology,
Hematology, Geriatrics

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

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

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

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

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)
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

Table 1. Clinical Characteristics of the Patients.*

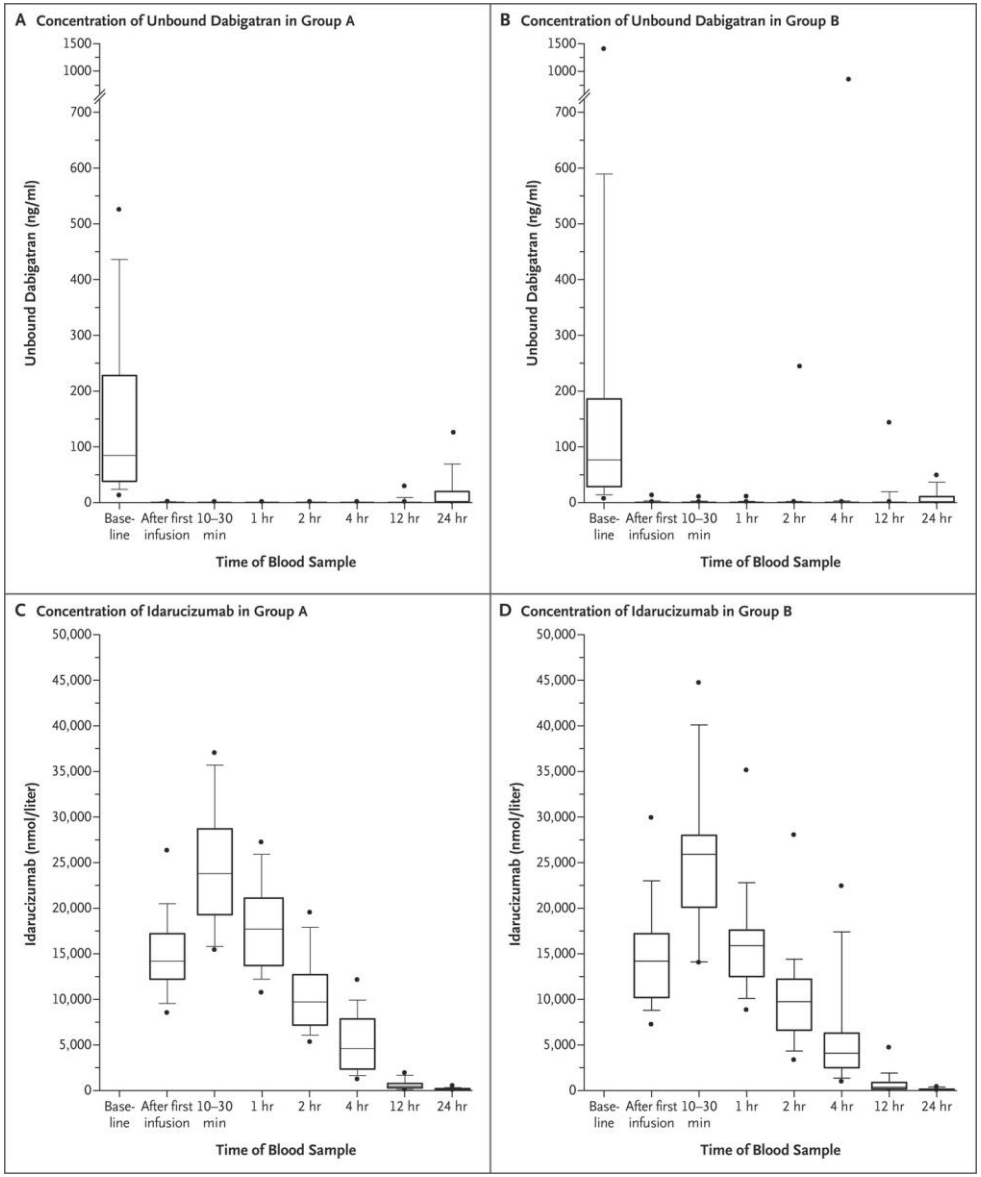
Characteristic	Group A (N=51)	Group B (N=39)	Total (N=90)
Age — yr			
Median	77.0	76.0	76.5
Range	48–93	56–93	48–93
Male sex — no. (%)	32 (63)	18 (46)	50 (56)
Race or ethnic group — no. (%)†			
Asian	5 (10)	1 (3)	6 (7)
Hawaiian or Pacific Islander	3 (6)	3 (8)	6 (7)
White	43 (84)	35 (90)	78 (87)
Weight — 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

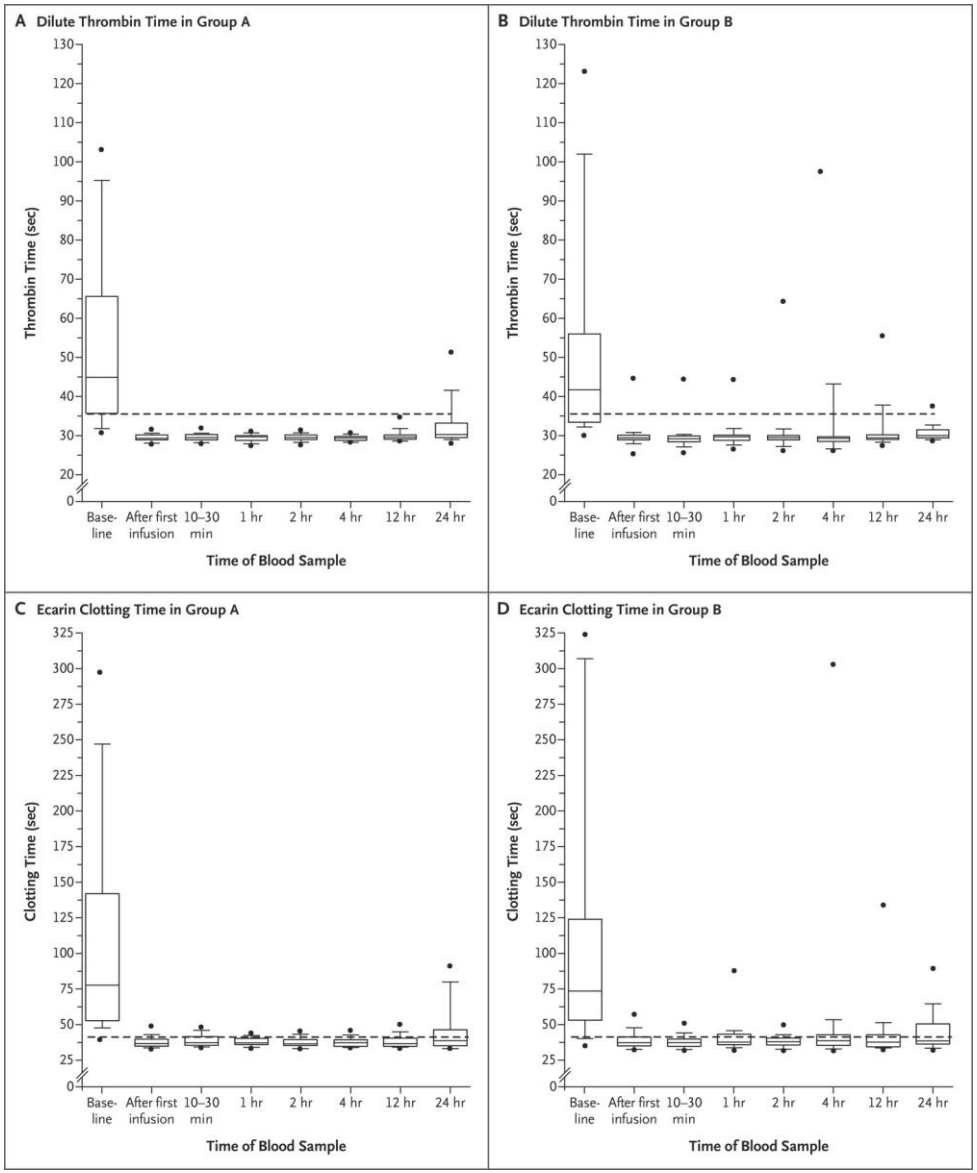
Idarucizumab



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

The NEW ENGLAND JOURNAL of MEDICINE

Idarucizumab



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

The NEW ENGLAND JOURNAL of MEDICINE

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.

The NEW ENGLAND JOURNAL of MEDICINE

Idarucizumab

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

The NEW ENGLAND JOURNAL of MEDICINE

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.

The NEW ENGLAND JOURNAL of MEDICINE

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.

The NEW ENGLAND JOURNAL of MEDICINE

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.

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.

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)	19.5 (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.

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	10.7 (10.2–23.5)	19.5 (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.

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 487.1 ng per milliliter (interquartile range, 298.7 to 505.8) at baseline

The NEW ENGLAND JOURNAL of MEDICINE

Andexanet

Table 2. Characteristics of Acute Major Bleeding Episodes and Clinical Outcomes.*

Characteristic	Safety Population (N=67)	Efficacy Population (N=47)
Gastrointestinal bleeding — no./total no. (%)	33/67 (49)	25/47 (53)
Patients receiving rivaroxaban	20/33 (61)	16/25 (64)
Patients receiving apixaban	11/33 (33)	8/25 (32)
Site of bleeding		
Upper gastrointestinal tract	9/33 (27)	7/25 (28)
Lower gastrointestinal tract	10/33 (30)	8/25 (32)
Unknown	14/33 (42)	10/25 (40)
Baseline hemoglobin ≤10 g/dl	20/33 (61)	16/25 (64)
Pretreatment red-cell transfusion	21/33 (64)	19/25 (76)
Intracranial bleeding — no./total no. (%)	28/67 (42)	20/47 (43)
Patients receiving rivaroxaban — no./total no. (%)	10/28 (36)	8/20 (40)
Patients receiving apixaban — no./total no. (%)	17/28 (61)	12/20 (60)
Baseline score on Glasgow Coma Scale†	14.1±1.7	14.1±1.7
Intracerebral site — no./total no. (%)	14/28 (50)	12/20 (60)
Baseline score on modified Rankin scale‡	3.0±1.8	2.8±1.9
Hematoma volume — no./total no. (%)		
≤10 ml	8/14 (57)	8/12 (67)
11 to 60 ml	6/14 (43)	4/12 (33)
Subdural site — no./total no. (%)	11/28 (39)	7/20 (35)
Baseline score on modified Rankin scale	2.1±1.6	1.4±1.5
Maximal thickness — no./total no. (%)		
≤10 mm	8/11 (73)	5/7 (71)
>10 mm	3/11 (27)	2/7 (29)
Subarachnoid site — no./total no. (%)	3/28 (11)	1/20 (5)
Other bleeding site — no./total no. (%)	6/67 (9)	2/47 (4)
Patients receiving rivaroxaban	2/6 (33)	2/2 (100)
Patients receiving apixaban	4/6 (67)	0
Site of bleeding		
Nasal	1/6 (17)	0
Pericardial, pleural, or retroperitoneal	3/6 (50)	1/2 (50)
Genital or urinary	1/6 (17)	1/2 (50)
Articular	1/6 (17)	0
Pretreatment red-cell transfusion	3/6 (50)	1/2 (50)
Clinical outcome — no./total no. (%)		
Death	10/67 (15)	7/47 (15)
Thromboembolic event	12/67 (18)	7/47 (15)

* Plus–minus values are means ±SD.
† Scores on the Glasgow Coma Scale range from 15 (normal) to 3 (deep coma).
‡ Scores on the modified Rankin scale for global disability and handicap range from 0 (no symptoms or disability) to 6 (death).

Characteristics of Acute Major Bleeding Episodes and Clinical Outcomes.

The NEW ENGLAND JOURNAL of MEDICINE

Andexanet

Table 2. Characteristics of Acute Major Bleeding Episodes and Clinical Outcomes.*

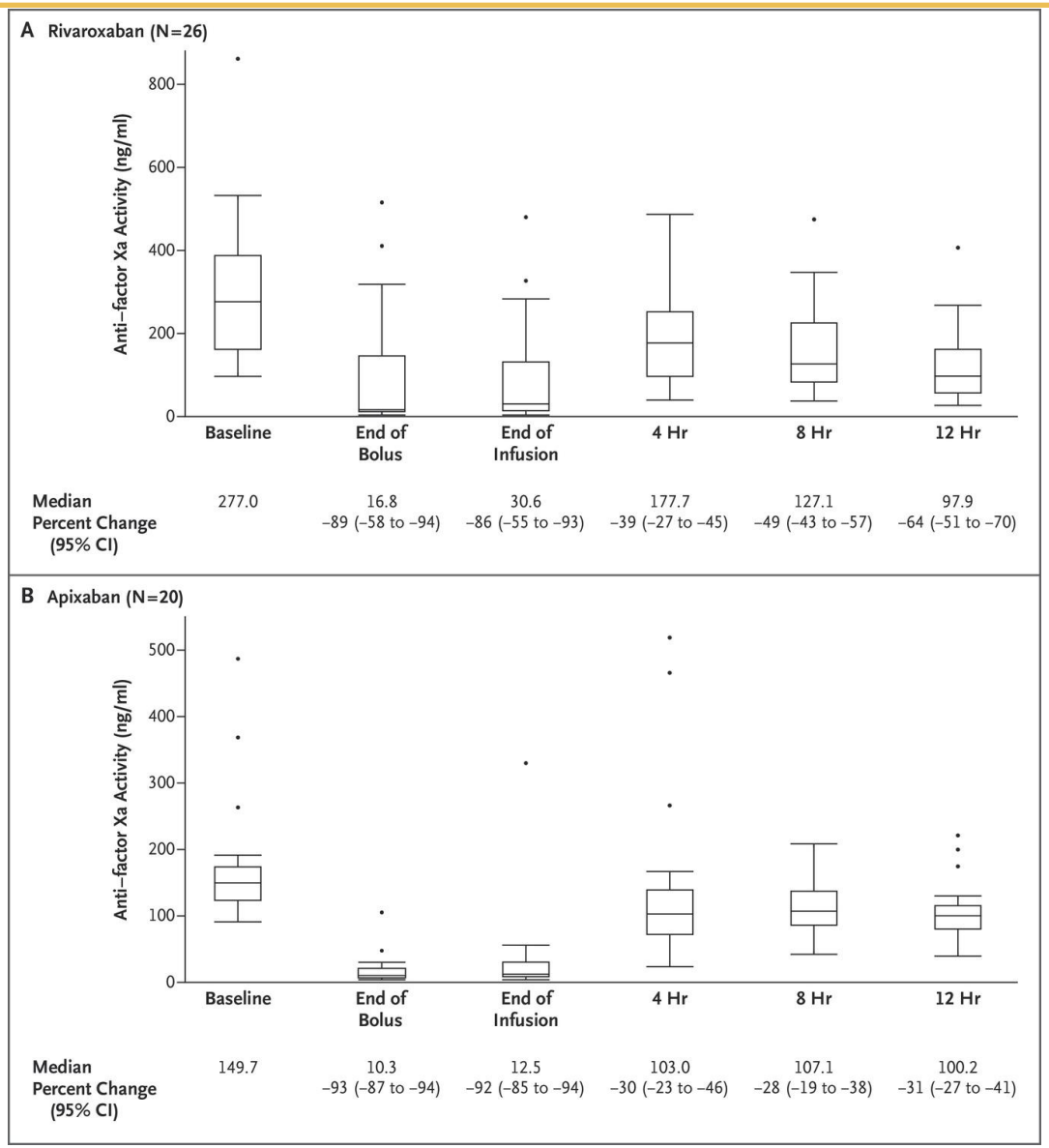
Characteristic	Safety Population (N=67)	Efficacy Population (N=47)
Gastrointestinal bleeding — no./total no. (%)	33/67 (49)	25/47 (53)
Patients receiving rivaroxaban	20/33 (61)	16/25 (64)
Patients receiving apixaban	11/33 (33)	8/25 (32)
Site of bleeding		
Upper gastrointestinal tract	9/33 (27)	7/25 (28)
Lower gastrointestinal tract	10/33 (30)	8/25 (32)
Unknown	14/33 (42)	10/25 (40)
Baseline hemoglobin ≤10 g/dl	20/33 (61)	16/25 (64)
Pretreatment red-cell transfusion	21/33 (64)	19/25 (76)
Intracranial bleeding — no./total no. (%)	28/67 (42)	20/47 (43)
Patients receiving rivaroxaban — no./total no. (%)	10/28 (36)	8/20 (40)
Patients receiving apixaban — no./total no. (%)	17/28 (61)	12/20 (60)
Baseline score on Glasgow Coma Scale†	14.1±1.7	14.1±1.7
Intracerebral site — no./total no. (%)	14/28 (50)	12/20 (60)
Baseline score on modified Rankin scale‡	3.0±1.8	2.8±1.9
Hematoma volume — no./total no. (%)		
≤10 ml	8/14 (57)	8/12 (67)
11 to 60 ml	6/14 (43)	4/12 (33)
Subdural site — no./total no. (%)	11/28 (39)	7/20 (35)
Baseline score on modified Rankin scale	2.1±1.6	1.4±1.5
Maximal thickness — no./total no. (%)		
≤10 mm	8/11 (73)	5/7 (71)
>10 mm	3/11 (27)	2/7 (29)
Subarachnoid site — no./total no. (%)	3/28 (11)	1/20 (5)
Other bleeding site — no./total no. (%)	6/67 (9)	2/47 (4)
Patients receiving rivaroxaban	2/6 (33)	2/2 (100)
Patients receiving apixaban	4/6 (67)	0
Site of bleeding		
Nasal	1/6 (17)	0
Pericardial, pleural, or retroperitoneal	3/6 (50)	1/2 (50)
Genital or urinary	1/6 (17)	1/2 (50)
Articular	1/6 (17)	0
Pretreatment red-cell transfusion	3/6 (50)	1/2 (50)
Clinical outcome — no./total no. (%)		
Death	10/67 (15)	7/47 (15)
Thromboembolic event	12/67 (18)	7/47 (15)

* Plus–minus values are means ±SD.
† Scores on the Glasgow Coma Scale range from 15 (normal) to 3 (deep coma).
‡ Scores on the modified Rankin scale for global disability and handicap range from 0 (no symptoms or disability) to 6 (death).

Characteristics of Acute Major Bleeding Episodes and Clinical Outcomes.

The NEW ENGLAND JOURNAL of MEDICINE

Andexanet



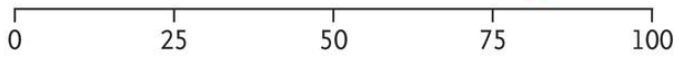
Anti–Factor Xa Activity and Percent Change from Baseline in Patients Receiving Rivaroxaban and Apixaban (Efficacy Population).

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.

The NEW ENGLAND JOURNAL of MEDICINE

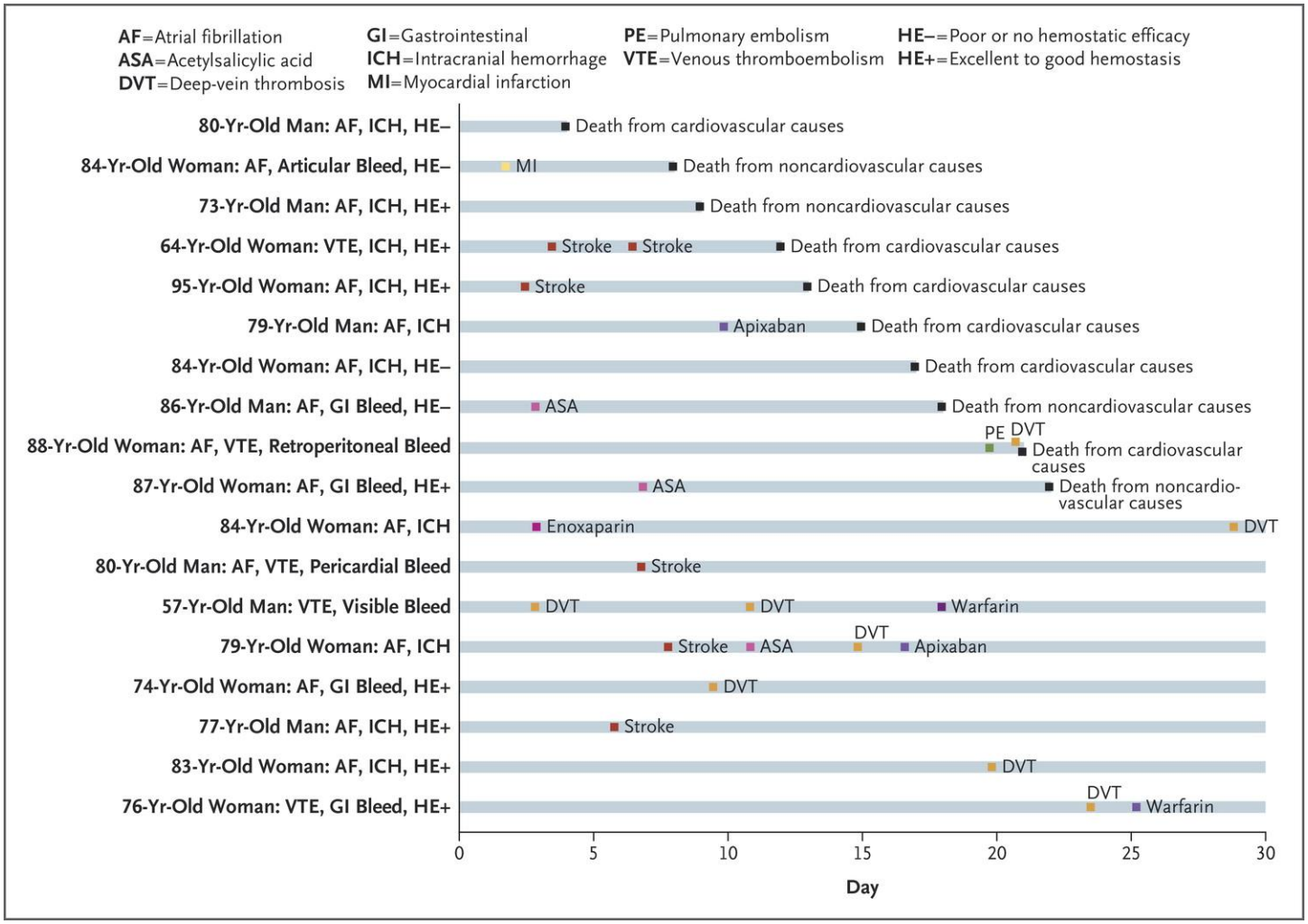
Andexanet

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)



The NEW ENGLAND JOURNAL of MEDICINE

Andexanet



The NEW ENGLAND JOURNAL of MEDICINE