DOACs: focus, gestione perioperatoria, strategie di reverse

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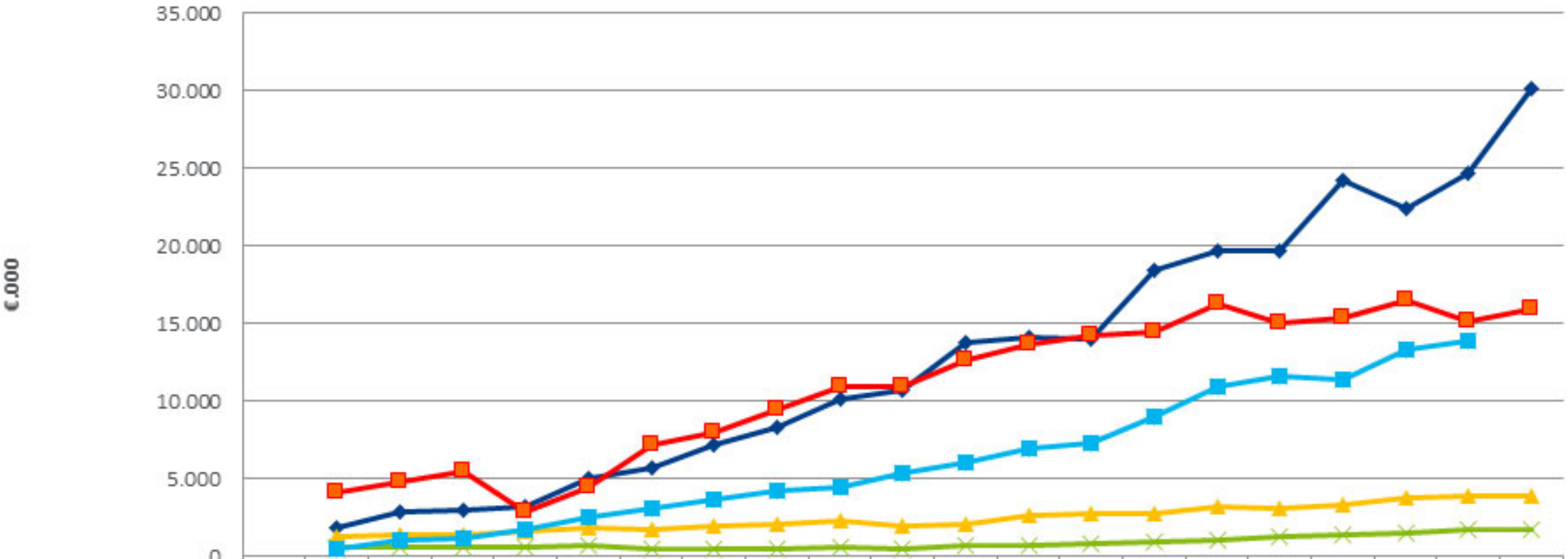
Attuali indicazioni ai farmaci anticoagulanti orali diretti

- Prevenzione dell'ictus nei pazienti con Fibrillazione Atriale non valvolare (tutti)
- Sindromi coronariche acute (rivaroxaban)

- Prevenzione del tromboembolismo venoso in pazienti sottoposti a chirurgia protesica di anca e ginocchio (apixaban, dabigatran, rivaroxaban)
- Terapia acuta e prevenzione secondaria di TVP ed embolia polmonare (tutti)

NOACs Launch Uptake by Country Comparison

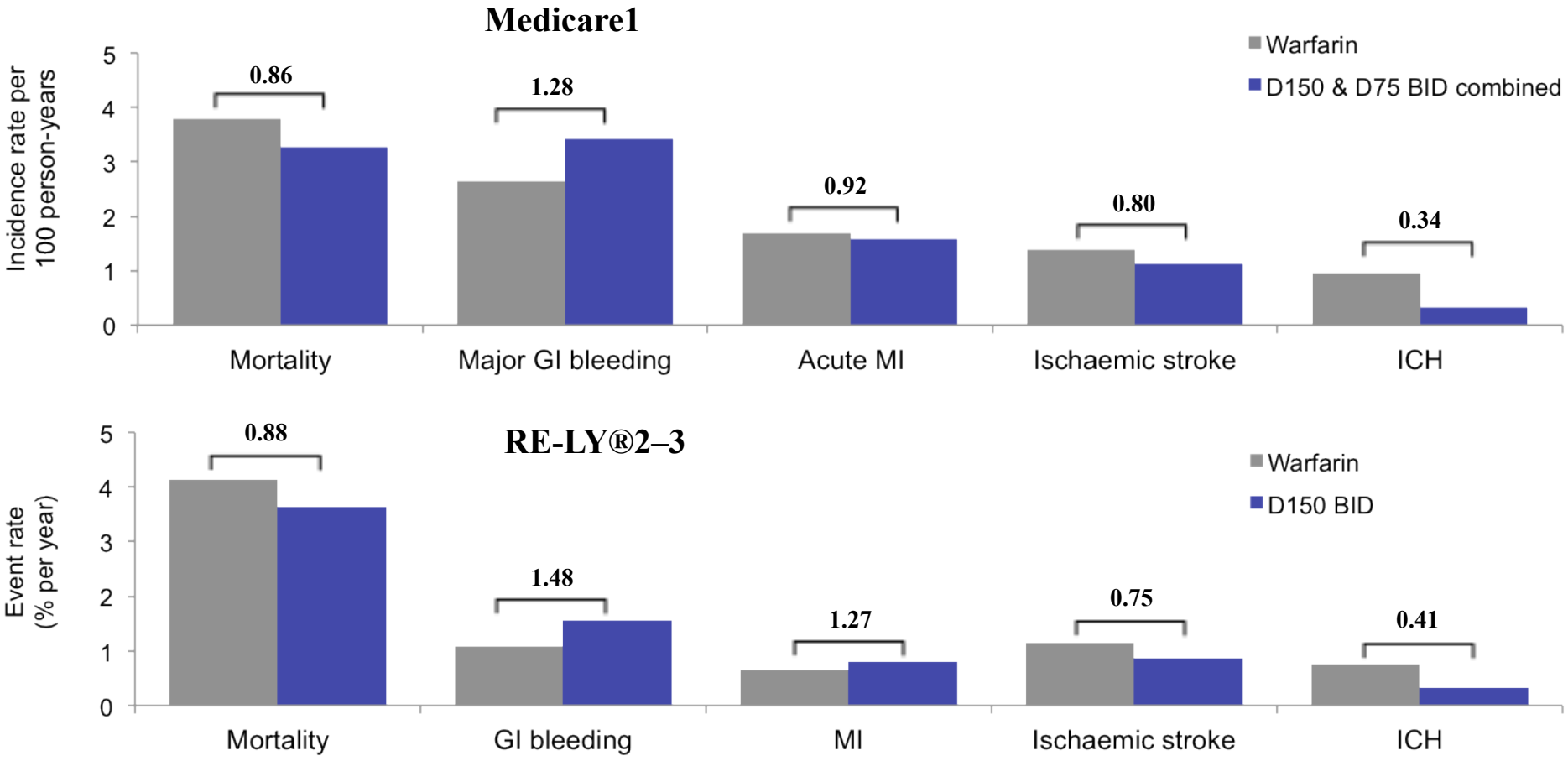
Total NOAC - Cumulative Value (.000 LEU) - SPAF Launch - Total



	Mth 1	Mth 2	Mth 3	Mth 4	Mth 5	Mth 6	Mth 7	Mth 8	Mth 9	Mth 10	Mth 11	Mth 12	Mth 13	Mth 14	Mth 15	Mth 16	Mth 17	Mth 18	Mth 19	Mth 20
Germany 09/2011	1.862	2.872	3.001	3.181	4.969	5.727	7.193	8.285	10.17	10.64	13.72	14.10	14.03	18.41	19.67	19.66	24.22	22.39	24.70	30.09
France 05/2012	4.099	4.821	5.452	2.820	4.446	7.194	8.007	9.398	10.90	10.92	12.63	13.64	14.16	14.38	16.20	15.05	15.39	16.52	15.09	15.88
Spain 11/2011	1.231	1.380	1.402	1.580	1.803	1.738	1.938	2.113	2.274	1.926	2.090	2.642	2.724	2.793	3.150	3.097	3.312	3.715	3.867	3.870
UK 07/2011	638	560	591	616	704	433	436	479	575	491	682	683	853	961	1.028	1.255	1.396	1.485	1.700	1.753
Italy 06/2013	426	1.055	1.102	1.708	2.499	3.084	3.655	4.180	4.449	5.371	6.022	6.911	7.332	8.956	10.97	11.63	11.41	13.27	13.90	

Source: IMS Medical Audit

Independent FDA Medicare analysis and findings from RE-LY®

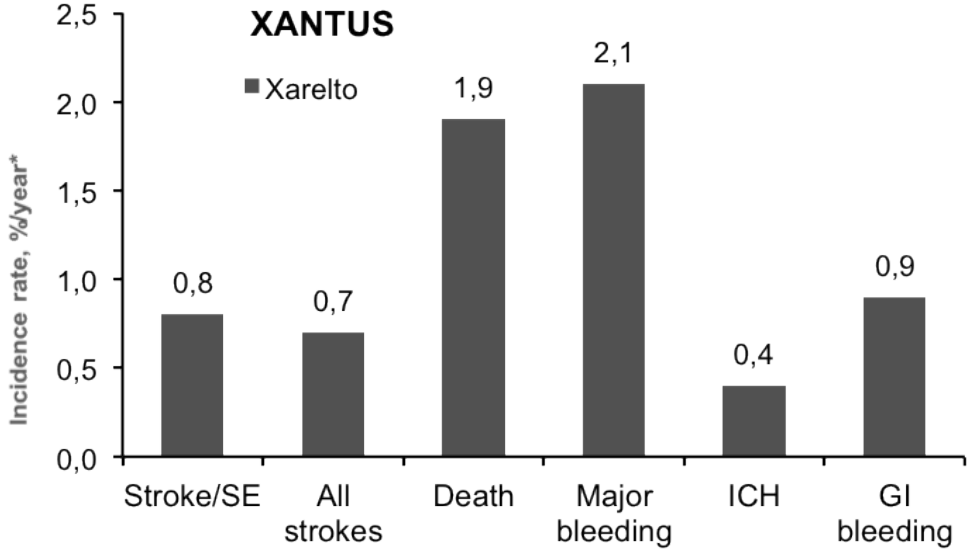


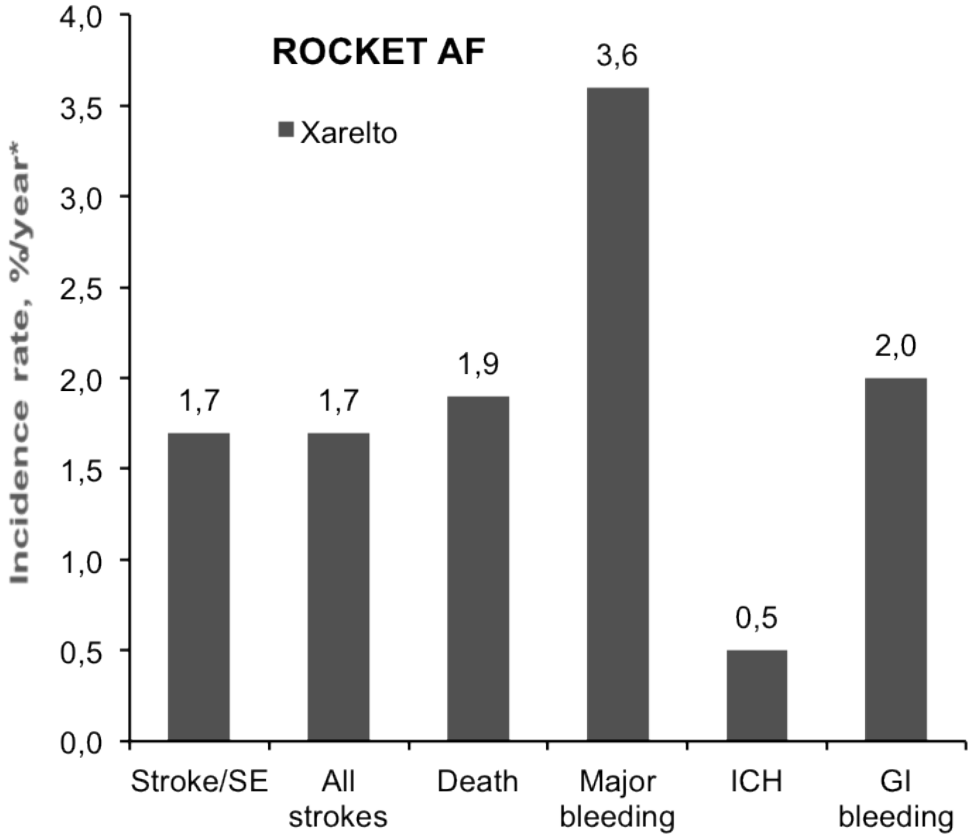
Numbers on bars denote HRs vs warfarin. D75 = dabigatran 75 mg; D150 = dabigatran 150 mg

1. Graham DJ et al Circulation 2014; 2. Connolly SJ et al. N Engl J Med 2009;361:1139–51; 3. Connolly SJ et al. N Engl J Med 2010;363:1875–6

Comparison of Main Outcomes: XANTUS versus ROCKET AF

	CHADS2	Prior stroke#
ROCKET AF1	3.5	55%
XANTUS2	2.0	19%

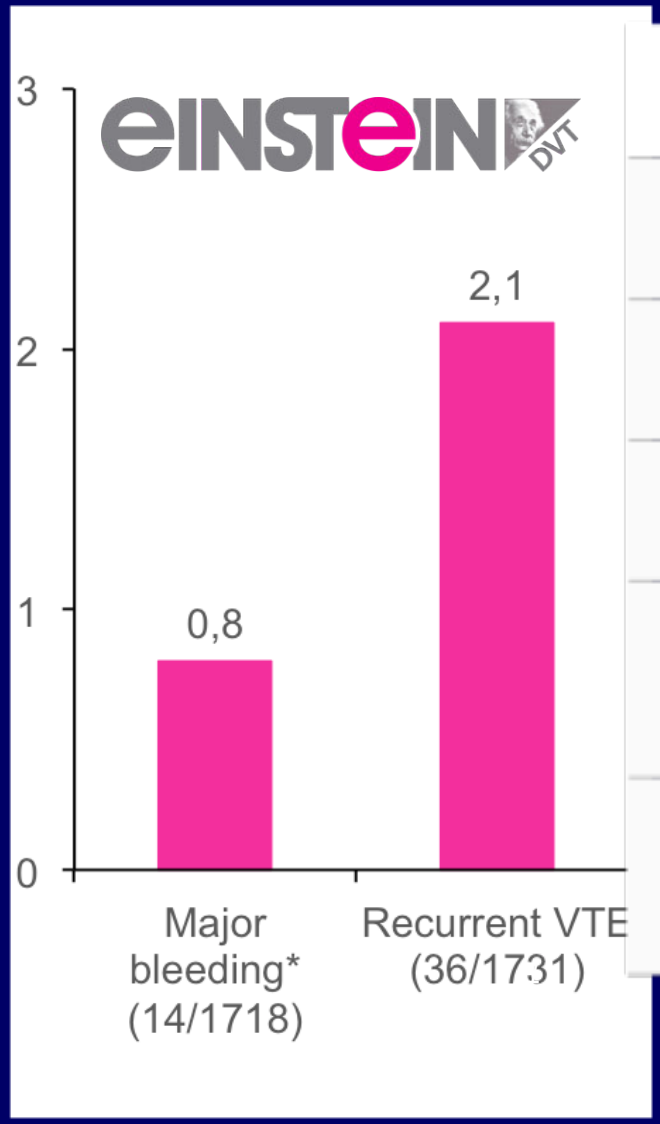




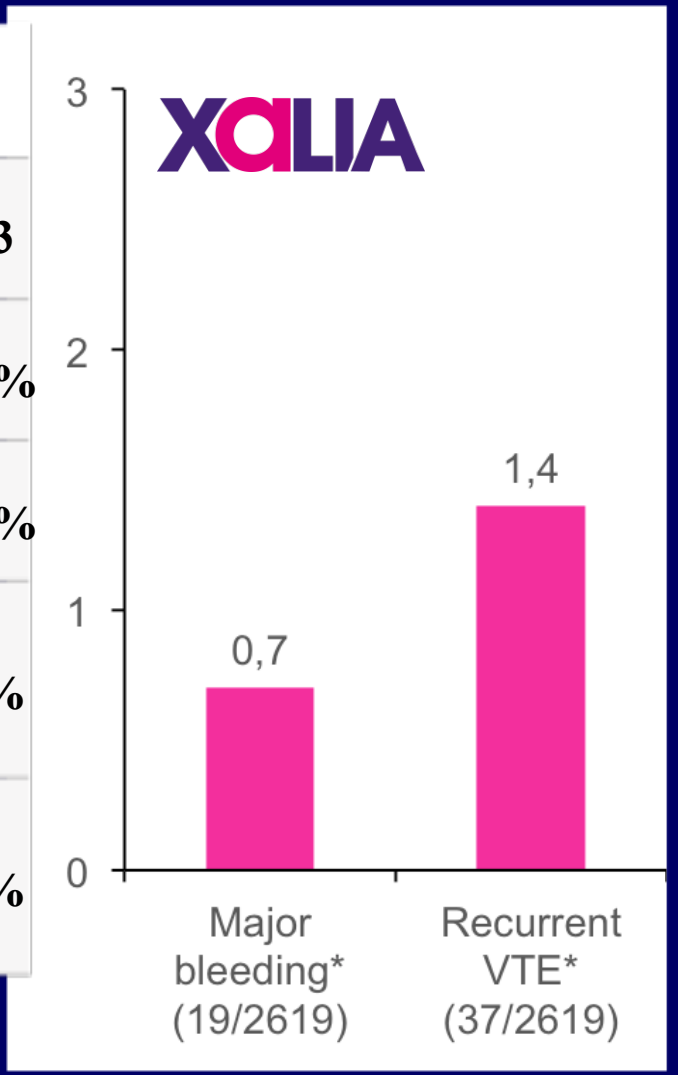
#Includes prior stroke, SE or TIA; *Events per 100 patient-years

1. Patel MR *et al, N Engl J Med* 2011;365:883–891; 2. Camm AJ *et al*, *Eur Heart J* 2015*;* doi: 10.1093/eurheartj/ehv4(

EINSTEIN DVT and XALIA: Rivaroxaban Outcomes



	Characteristic	
55.8	Age (years)	57.3
57.4%	Male	54.5%
19.4%	Previous VTE	24.1%
6.8%	Baseline active cancer	5.6%
6.2%	Known thrombophilia	6.0%



Incidence (% of patients)

Ageno W et al Lancet Haematol 2015

Sospensione periprocedurale elettiva degli anticoagulanti orali diretti

- La tempistica dipende dal farmaco
- La funzionalità renale è determinante
- I test di laboratorio pre-procedura non sono necessari (se utilizzati, meglio quelli specifici: tempo di trombina diluito, attività anti fattore Xa)
- Non utilizzare mai EBPM come bridging
- La tempistica della ripresa dipende dal rischio emorragico, ricordare che l'effetto anticoagulante è immediato

Caratteristiche farmacocinetiche e farmacodinamiche dei nuovi farmaci

	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Target	IIa (trombina)	Xa	Xa	Xa
Ore al Cmax	0.5-2.0	3.0-4.0	2.0-4.0	1.0-2.0
Interazioni	P-gp	P-gp and CYP3A4	P-gp and CYP3A4	P-gp
Emivita	14-17 h	12-15h	9-13h	8-10h
Eliminazione renale	80%	27%	33%	50%

Estimated drug half lives and effect on AUC NOAC plasma concentrations in different stages of CKD compared to healthy controls

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
CrCl >80 mL/min	12–17 h[61]	12 h	10–14 h[51,65]	5–9 h (young) 11–13 h (elderly)
CrCl 50–80 mL/min	~17 h[122]	~14.6 h[123]	~8.6 h[124]	~8.7 h[125]
CKD Stages I and II	(+50%)	(+16%)	(+32%)[SmPC]	(+44%)[126]
CrCl 30–50 mL/min	~19 h[122]	~17.6 h	~9.4 h[124]	~9.0 h
CKD Stage III	(+320%)	(+29%)	(+74%)[SmPC]	(+52%)[126]
CrCl 15–30 mL/min	~28 h[122]	~17.3 h	~16.9 h[124]	~9.5 h
CKD Stage IV	(+530%)	(+44%)	(72%)[SmPC]	(+64%)[126]
CrCl ≤ 15 mL/min	No data	–	–	–
CKD Stage V; off-dialysis		(+36%)	(+93%)[SmPC]	(+70%)[127]

19 h +320%

17.6 h +29%

9.4 h +74%

9.0 h +52%

28 h +530%

17.3 h +44%

16.9 h +72%

9.5 h +64%

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

Guidance on perioperative management of DOACs

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

CrCl, creatinine clearance
Heidbuchel et al. Europace 2015

Prospective studies of DOACs in the real world for elective surgery

	Dresden registry (n=2179)1	Canadian cohort study (n=541)2
OAC	All DOACs	Dabigatran
Interruptions (n)	863	541
Perioperative protocol	Non-standard	Standard*
Major bleeding	1.2% (CI: 0.6–2.1)	1.8% (CI: 0.7–3.0)

Dabigatran stopped 1–4 days preprocedure and resumed 24–72 hours postprocedure (when haemostasis secured) without bridging

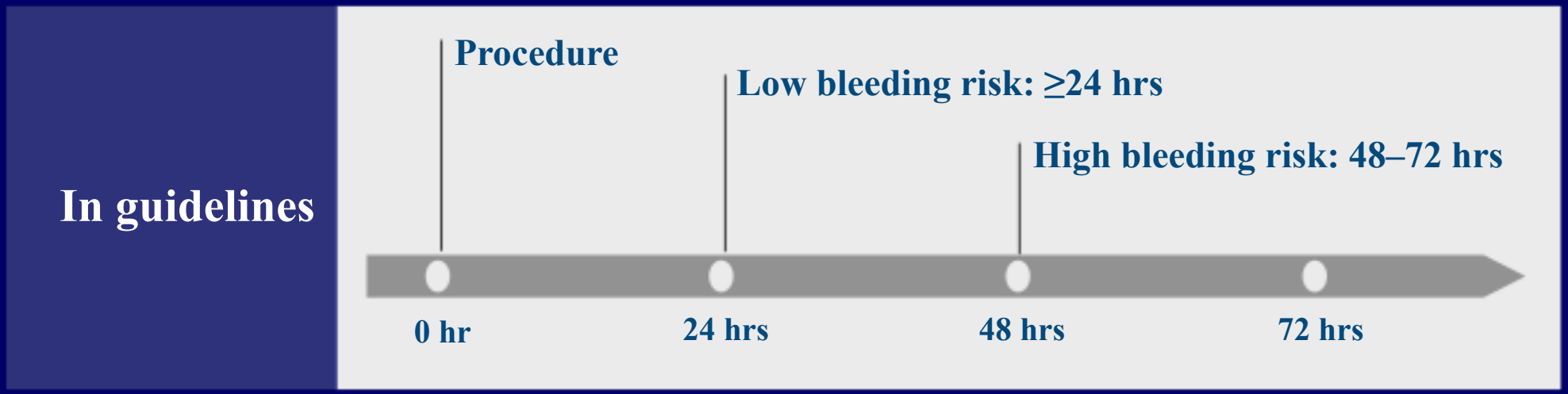
1. Beyer-Westendorf et al. Eur Heart J 2014; 2. Schulman et al. Circulation 2015

Perioperative bridging sub-analysis of RE-LY

Dabigatran	**2709 patients; treatment interruption for elective surgery/procedure** **Heparin bridging vs no bridging** • **Increased major bleeding 6.5% vs 1.8% (P<0.001)** • **Any thromboembolism 1.2% vs 0.6% (P=0.16)**

- **Douketis et al. Thromb Haemost 2015**

Guidance on restarting DOACs



Verma et al. Can J Cardiol 2014

PAUSE study design

Objective
Assess safety of standardized protocol for perioperative management of patients with AF on DOACs

- **Assess rates of major bleeding and atrial thromboembolism**
- **Assess level of residual anti-coagulation using routine coagulation tests and DOAC-specific tests**

N=3291; 15–20 centres in Canada, 2 centres in USA
Estimated primary completion date: May 2018

- **Perioperative Anticoagulant Use for Surgery Trial (PAUSE) trial; ClinicalTrials.gov Identifier: NCT02228798**

PAUSE Patient Population

Inclusion criteria

- age 18 years
- receiving a NOAC for SPAF
- assessed 4 days before an elective surgery/procedure

Exclusion criteria

- CrCl <30 mL/min for dabigatran/rivaroxaban patients and <25 mL/min for apixaban patients
- cognitive impairment or psychiatric illness that precludes collection of follow-up data
- inability or unwillingness to provide informed consent
- previous participation in this study

Follow-up and Outcomes

- **<u>Observation period</u>: starts the day of NOAC interruption and ends 30 days post-procedure.**
- **Timing (date/hour/min) of NOAC doses (including last pre- and first post-procedure) and blood sample documented.**
- **Patients will be assessed on the procedure day and contacted weekly (telephone) for 1 month to assess for outcomes. Hospitalized patients will be seen daily.**

- **Outcomes:**
  - **Primary: MB, ATE (ischemic stroke, systemic embolism, TIA)**
  - **Secondary: death, VTE, ACS, minor bleeding**

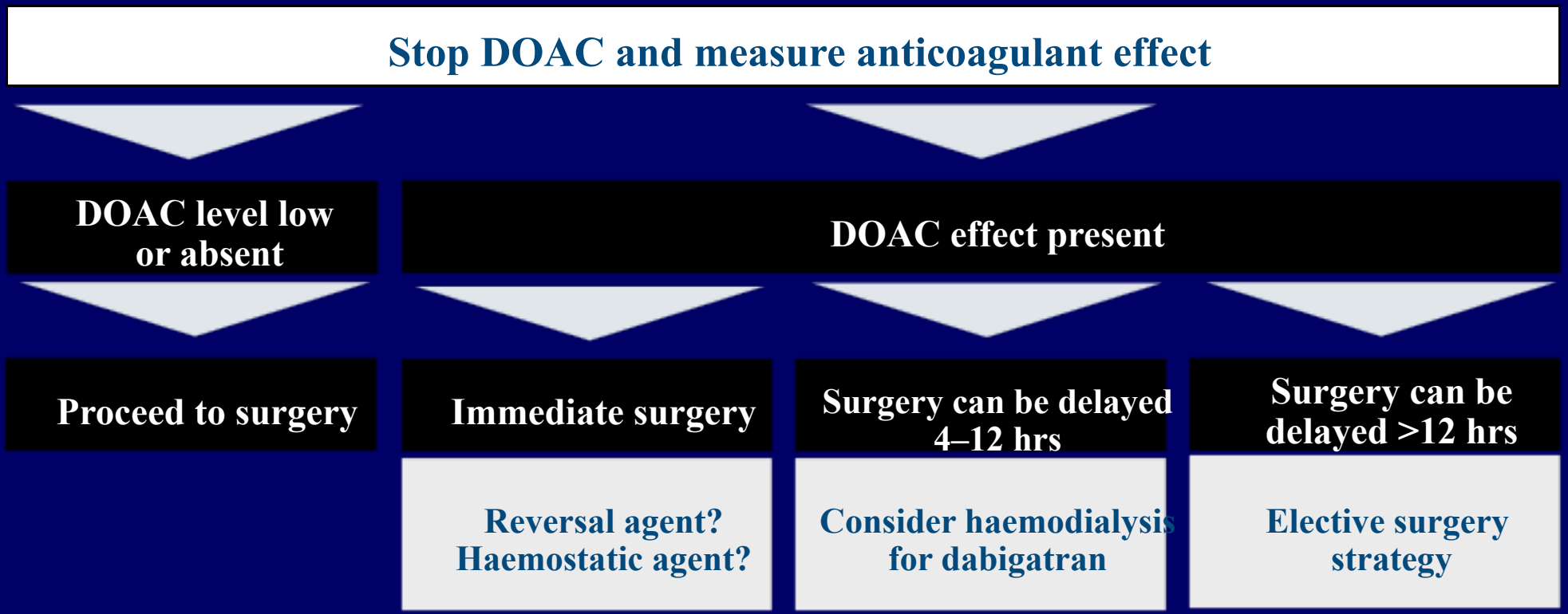
Laboratory Component

All patients will have pre-procedure CBC (for Hgb), and serum creatinine (for CrCl).

Patients may have additional pre- /post-operative blood tests as per usual practice (e.g., INR, trop) but these tests will not affect the management unless indicated (e.g., post-op myocardial injury).

<u>One study blood sample</u> obtained pre-procedure but will not be for clinical use. Plasma will be shipped to core laboratory for PT/INR, aPTT, TT, dilute TT (dabigatran), anti-Xa (rivarox/apix-aban).

Balancing risk of bleeding vs urgency of intervention



Adapted from Tran et al. Intern Med J 2014

Management strategies for the bleeding patient

- Inquire about last NOAC intake
- Blood sample to determine CrCl, haemoglobin, white blood cells
- Inquire with lab about possibility of rapid coagulation assessment

Mild bleeding

- Delay or discontinue next dose
- Reconsider concomitant medication

Moderate/severe bleeding

Supportive measures

- Mechanical compression
- Endoscopic haemostasis if GI bleed
- Surgical haemostasis
- Fluid replacement (colloids if needed)
- RBC transfusion if needed
- FFP (as plasma expander)
- Platelet transfusion (if platelet count ≤60×109/L)

For dabigatran-treated patients

- Idarucizumab 5 g IV (when available)
- Maintain adequate diuresis
- Consider haemodialysis

Life-threatening bleeding

For dabigatran-treated patients

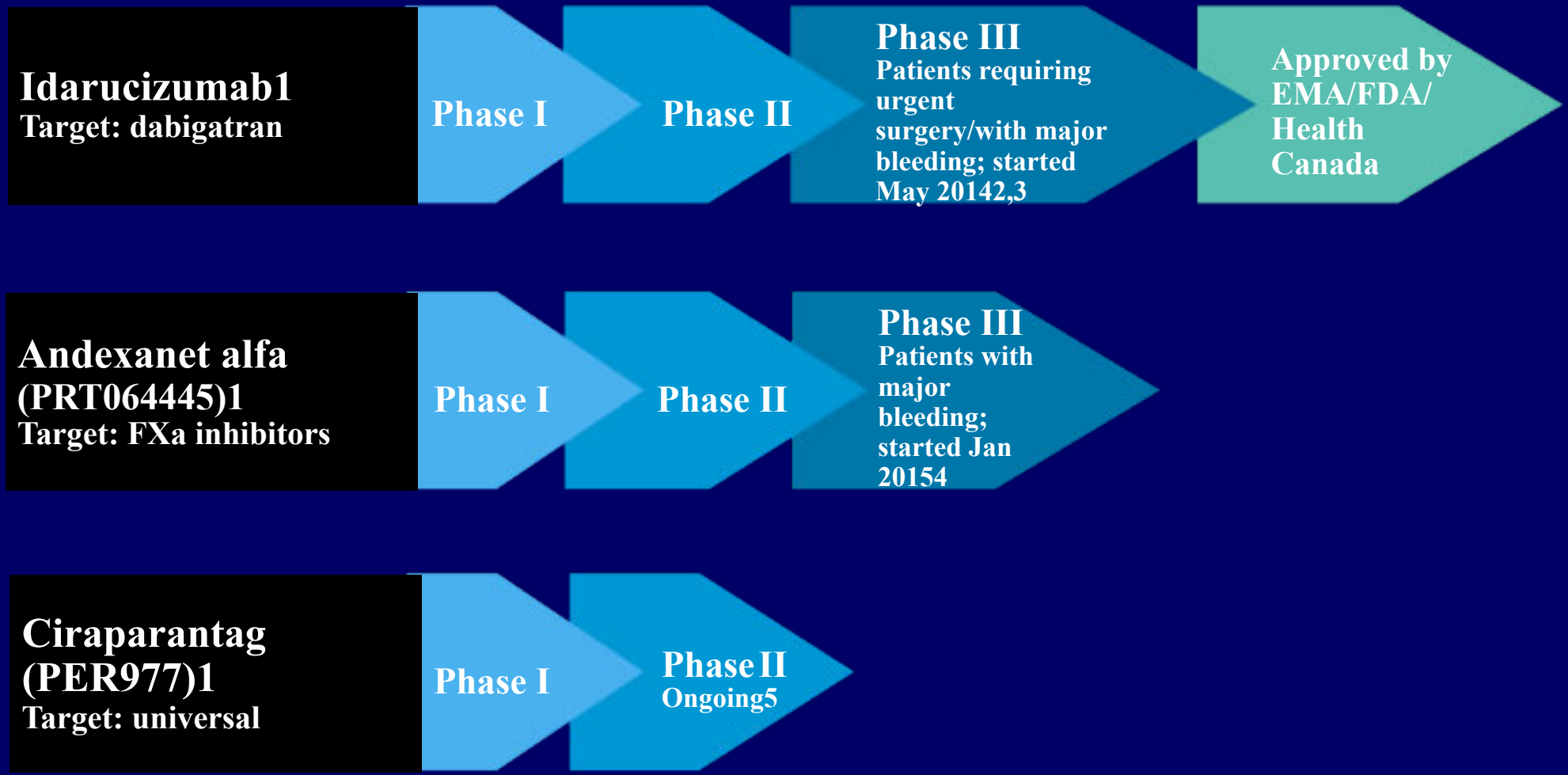
- Idarucizumab 5 g IV (when available)

For all NOACs, consider:

- PCC 50 U/kg + 25 U/kg if indicated
- aPCC 50 U/kg; max 200 U/kg/day
- rFVIIa 90 µg/kg

FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; RBC, red blood cell; rFVIIa, activated Factor VII; Figure adapted from Heidbuchel et al. Europace 2015

DOAC reversal agents in development



DOAC reversal agents are investigational compounds under development and have not been approved for use in the EU.

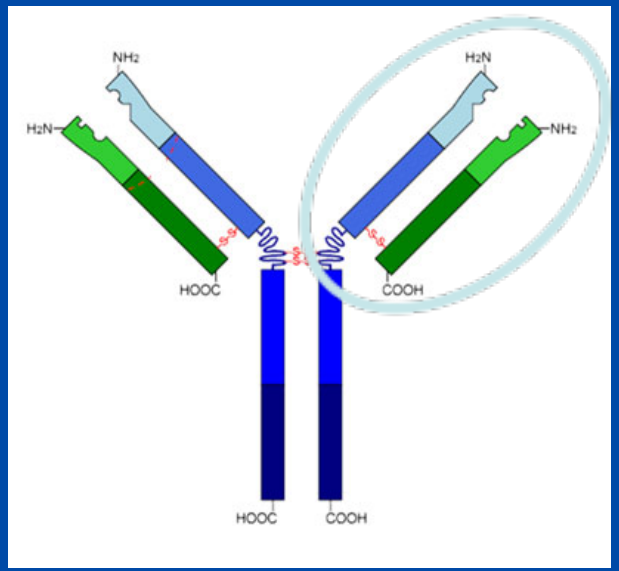
1. Adapted from Greinacher A et al. Thromb Haemost 2015;113:931–42;
2. Clinicaltrials.gov: NCT02104947; 3. Pollack CV et al. Thromb Haemost. 2015;114:198–205;
4. ClinicalTrials.gov Identifier: NCT02329327; 5. ClinicalTrials.gov Identifier: NCT02207257

Idarucizumab

Potente affinità di legame (~350 volte maggiore di quella di dabigatran con la trombina)

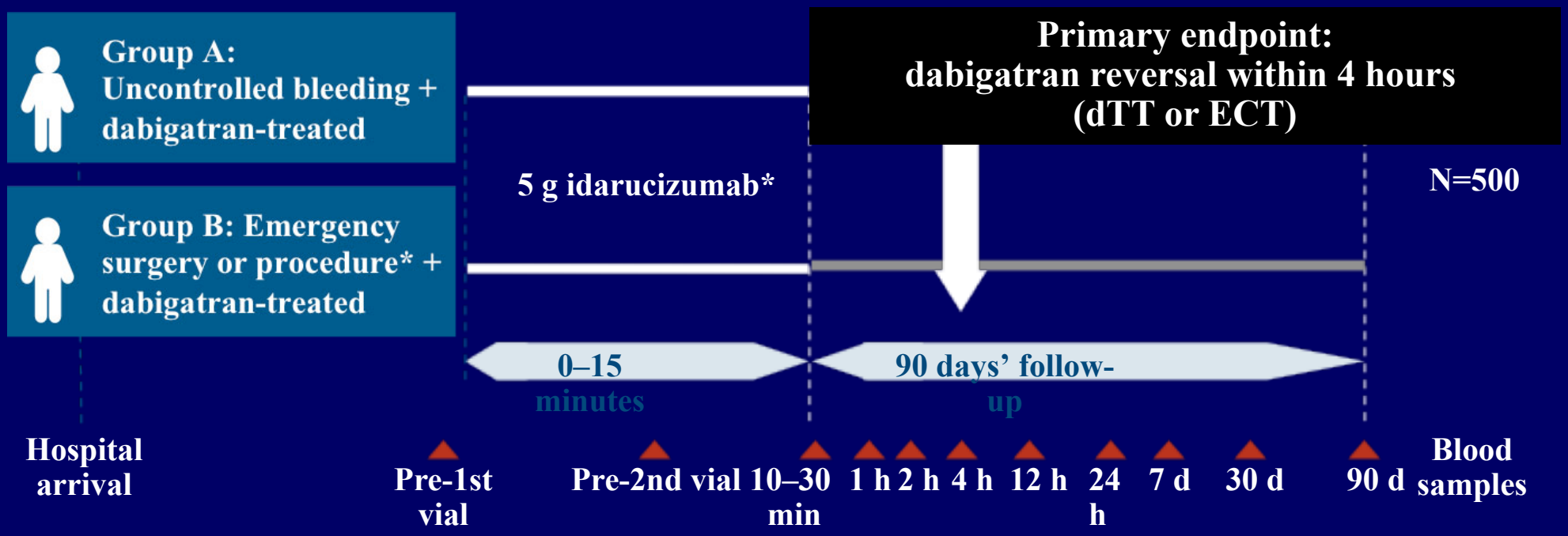
- **Somministrazione endovenosa**
  - **Inizio di azione immediato**
  - **Emivita breve (45 minuti circa)**
  - **Eliminazione prevalentemente renale**

Humanized antibody fragment (Fab)



Glund S et al. AHA 2013; abstract 17765; van Ryn J. AHA 2012; abstract 9928; van Ryn J et al. Circulation 2012;126:A9928

RE-VERSE AD: multicentre, ongoing, single-arm, open-label Phase III study

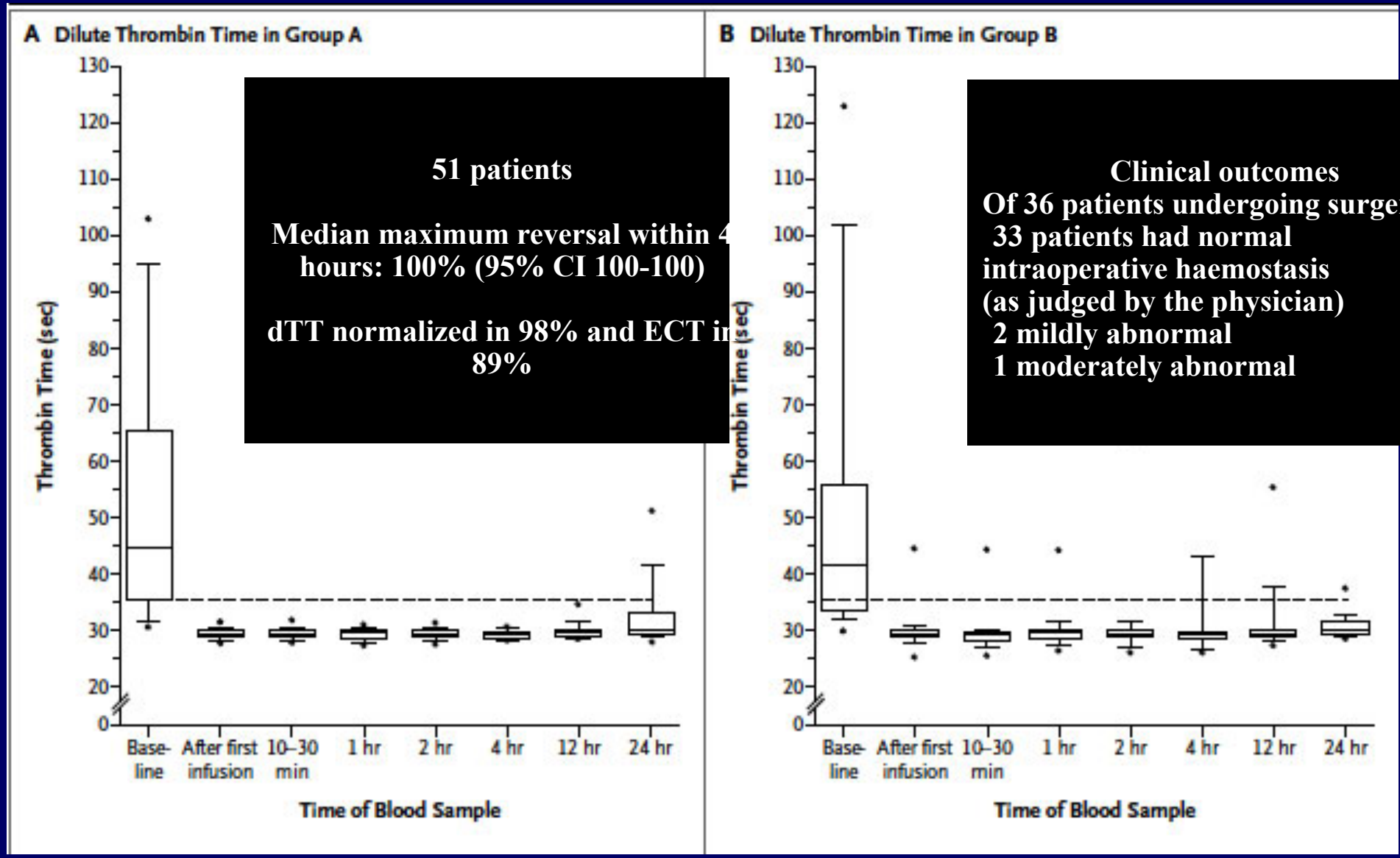


* Two 50-mL bolus infusions, no more than 15 minutes apart

*Other than bleeding. dTT, diluted thrombin time; ECT, ecarin clotting time

Pollack et al. N Engl J Med 2015

REVERSE-AD: dTT prima e dopo la somministrazione di idarucizumab



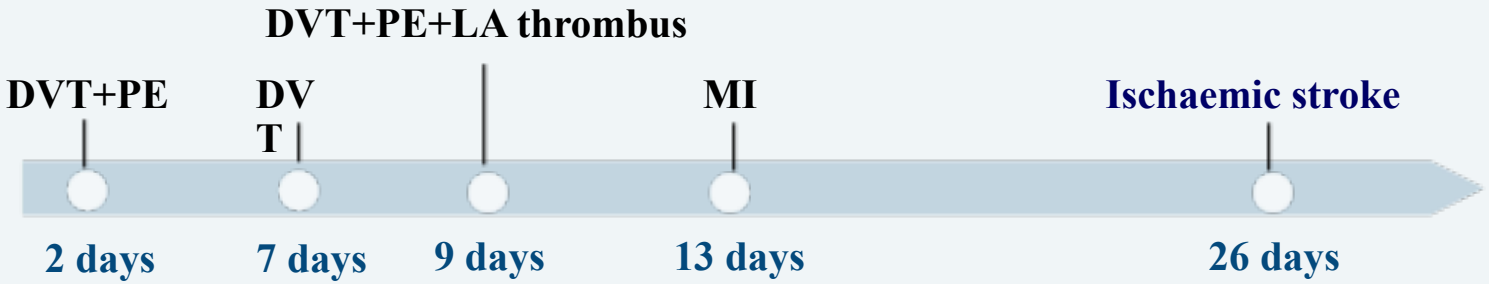
Pollack CV et al NEJM 2015

RE-VERSE AD: Safety

No cases of hypersensitivity observed

5 thrombotic events

- 1 early event (DVT+PE) 2 days after idarucizumab administration
- 4 events after >6 days of idarucizumab administration



- None of these 5 patients were receiving any antithrombotic therapy when the events occurred

18 deaths (9 in each Group)

- RE-VERSE AD™ allows even severely ill patients into the study
- All deaths related to presenting index event and comorbidities

Pollack et al; NEJM 2016

Andexanet alfa

Fattore Xa umano ricombinante

- **Agisce come "esca" per gli inibitori del fattore Xa legandoli con affinità simile a quella del fattore Xa nativo.**

Nature Medicine 2013,19(4): 446-51

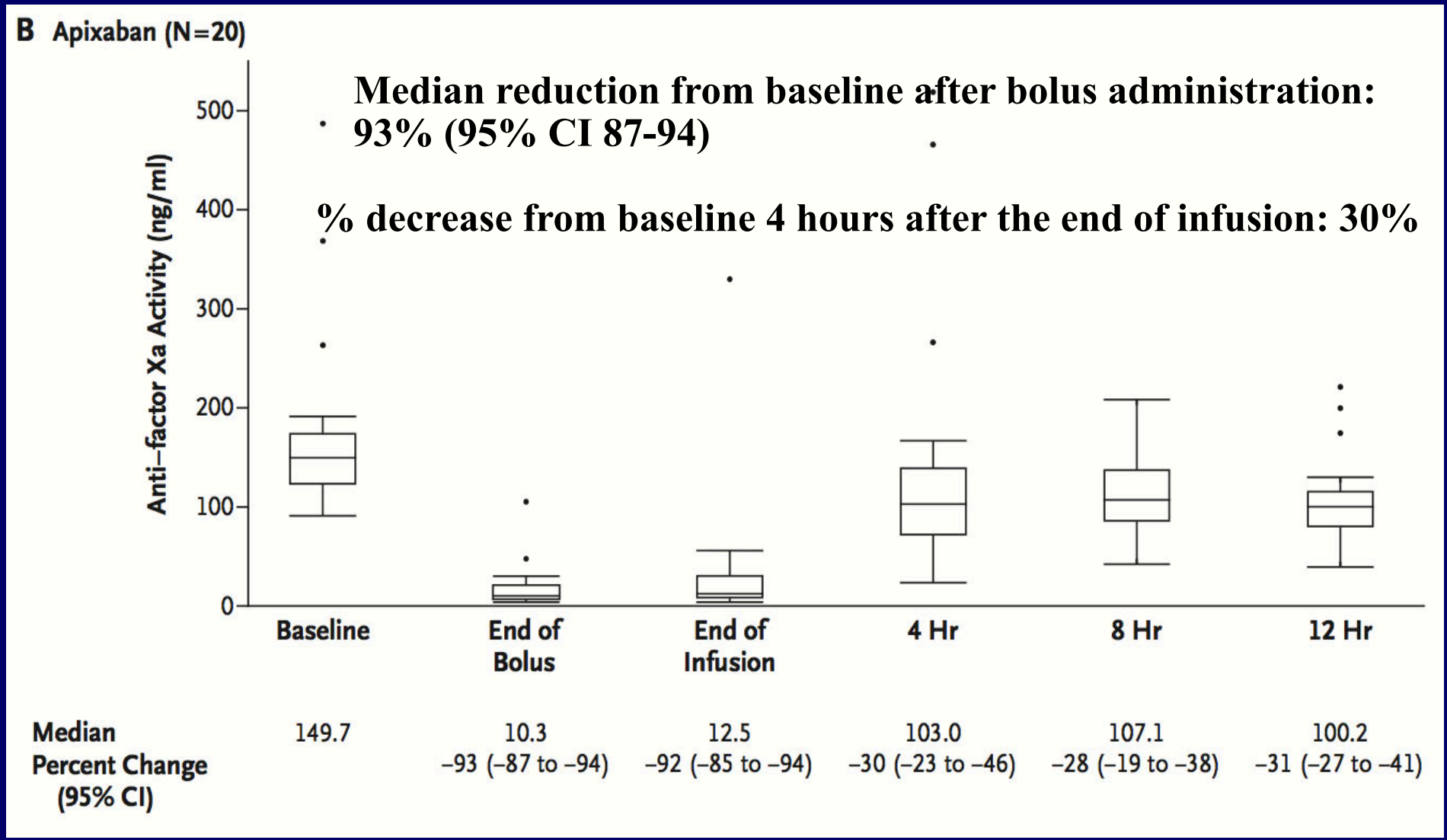
ORIGINAL ARTICLE

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

ANDEXANET DOSES	**Bolus followed by 2-hour infusion:** **Apixaban or rivaroxaban >7 h: 400 mg b + 480 mg infusion** **Enoxa/edoxaban or riva <7 h: 800 mg b + 960 mg infusion**
PRIMARY ENDPOINT	**Percent change in the anti–factor Xa activity**
COPRIMARY ENDPOINT	**The rate of excellent or good hemostatic efficacy 12 hours after the andexanet infusion.**

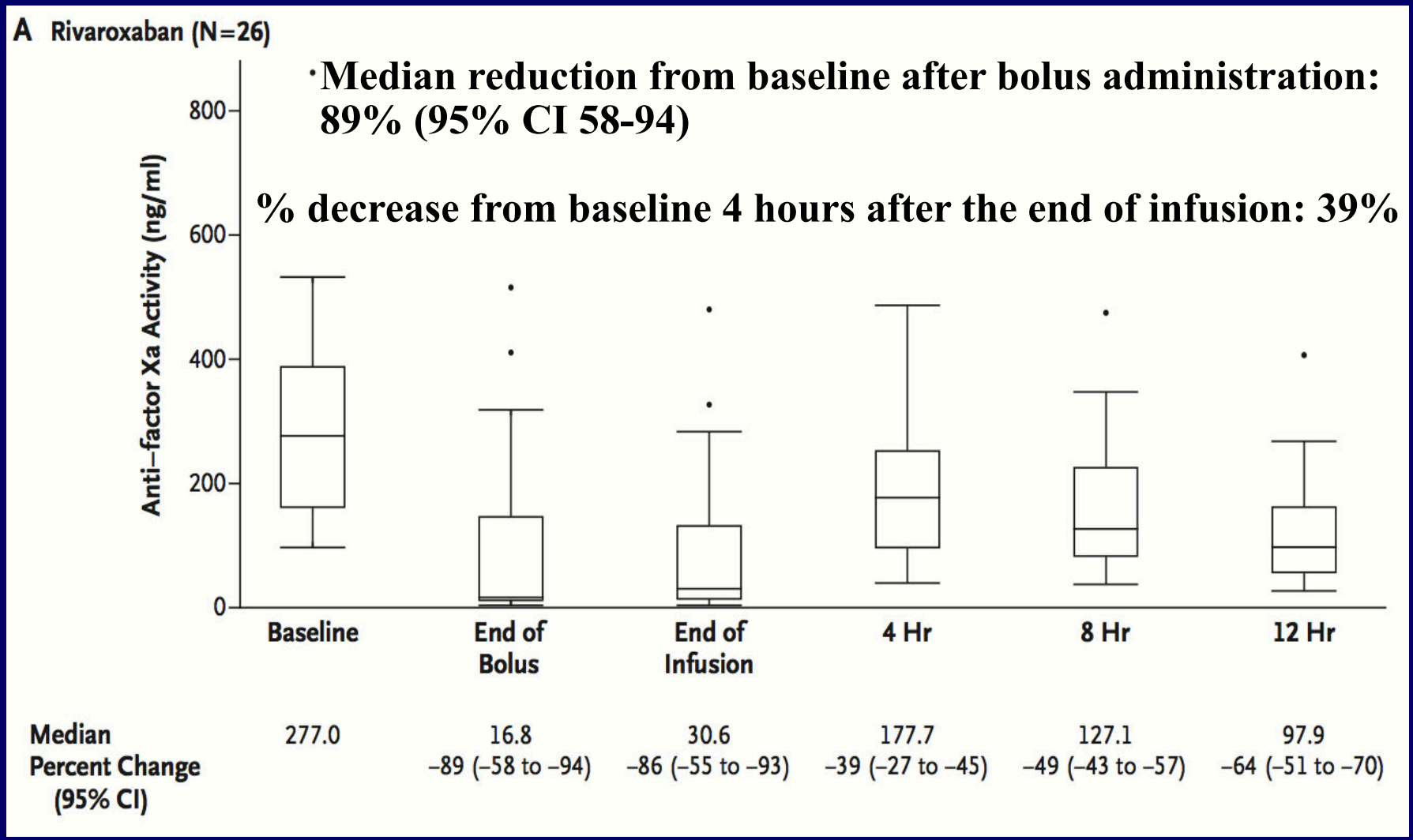
Connolly et al; NEJM 2016

Anti–Factor Xa Activity: apixaban



Connolly et al; NEJM 2016

Anti–Factor Xa Activity: rivaroxaban



Connolly et al; NEJM 2016

ANNEXA-4: secondary outcomes

- Clinical haemostasis 12 hours after infusion adjudicated as excellent or good: 79% (95% CI 64-89)
- Thrombotic events at 30 days: 12 (18%)
- Mortality: 10 (15%), 6 CV, 4 non CV

Connolly et al; NEJM 2016

When and how to use antidotes for the reversal of DOACs: guidance from the ISTH

Clinical situation	Definite need for a reversal agent
Life-threatening bleeding	YES
Bleeding in a closed space or critical organ	YES
Persistent major bleeding despite local haemostatic measures or delayed DOAC clearance or DOAC overdose	YES
Need for urgent intervention with high risk of bleeding and that cannot be delayed	YES
Emergency surgery or intervention and high risk for procedural bleeding	YES
Urgent surgery or intervention and acute renal failure	POSSIBLE

Levy J et al J Thromb Haemost 2016