GESTIONE DEL SANGUINAMENTO NEL PAZIENTE IN TERAPIA ANTIAGGREGANTE / ANTICOAGULANTE

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Il sottoscritto Giancarlo Antonucci

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

dichiara

che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

AGENDA

1. Introduzione e scenari clinici
2. Misure aspecifiche
3. Reversione:

➔Farmaci antipiastrinici

➔Farmaci anticoagulanti

4. Conclusioni

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Sanguinamenti pericolosi per la vita

Una o più delle seguenti caratteristiche:

1. ***Instabilità emodinamica.*** ***shock***, iperlattacidemia, confusione mentale, ischemia….(POLITRAUMA)
2. Sanguinamento **in un organo o un area critica**.
   - Retroperitoneale
   - Intra-articolare
   - Pericardico
   - Epidurale
   - Intramuscolare con sindrome compartimentale
   - ***Intracranico***
3. Calo di Emoglobina di almeno **2 g/dl** (o Hb **≤8** g/dl in assenza di valori basali) o richiedenti **emotrasfusioni** (almeno 2). (???)
   - l'anemia può non essere evidente in acuto,
   - il sanguinamento cronico può non essere severo

N Engl J Med 2019;380:1326-35

Class of Hemorrhagic shock

Post 2000 cc cristalloid sol.

Shock Index (SI)= FC/PAS	>1 e <1,4	≥ 1,4
Base excess (BE):	tra -6 e -10	< -10

PARAMETER	CLASS I	CLASS II (MILD)	CLASS III (MODERATE)	CLASS IV (SEVERE)
Approximate blood loss	<15%	15–30%	31–40%	>40%
Heart rate	↔	↔/↑	↑	↑/↑↑
Blood pressure	↔	↔	↔/↓	↓
Pulse pressure	↔	↓	↓	↓
Respiratory rate	↔	↔	↔/↑	↑
Urine output	↔	↔	↓	↓↓
Glasgow Coma Scale score	↔	↔	↓	↓
Base deficit[a]	0 to –2 mEq/L	–2 to –6 mEq/L	–6 to –10 mEq/L	–10 mEq/L or less
Need for blood products	Monitor	Possible	Yes	Massive Transfusion Protocol

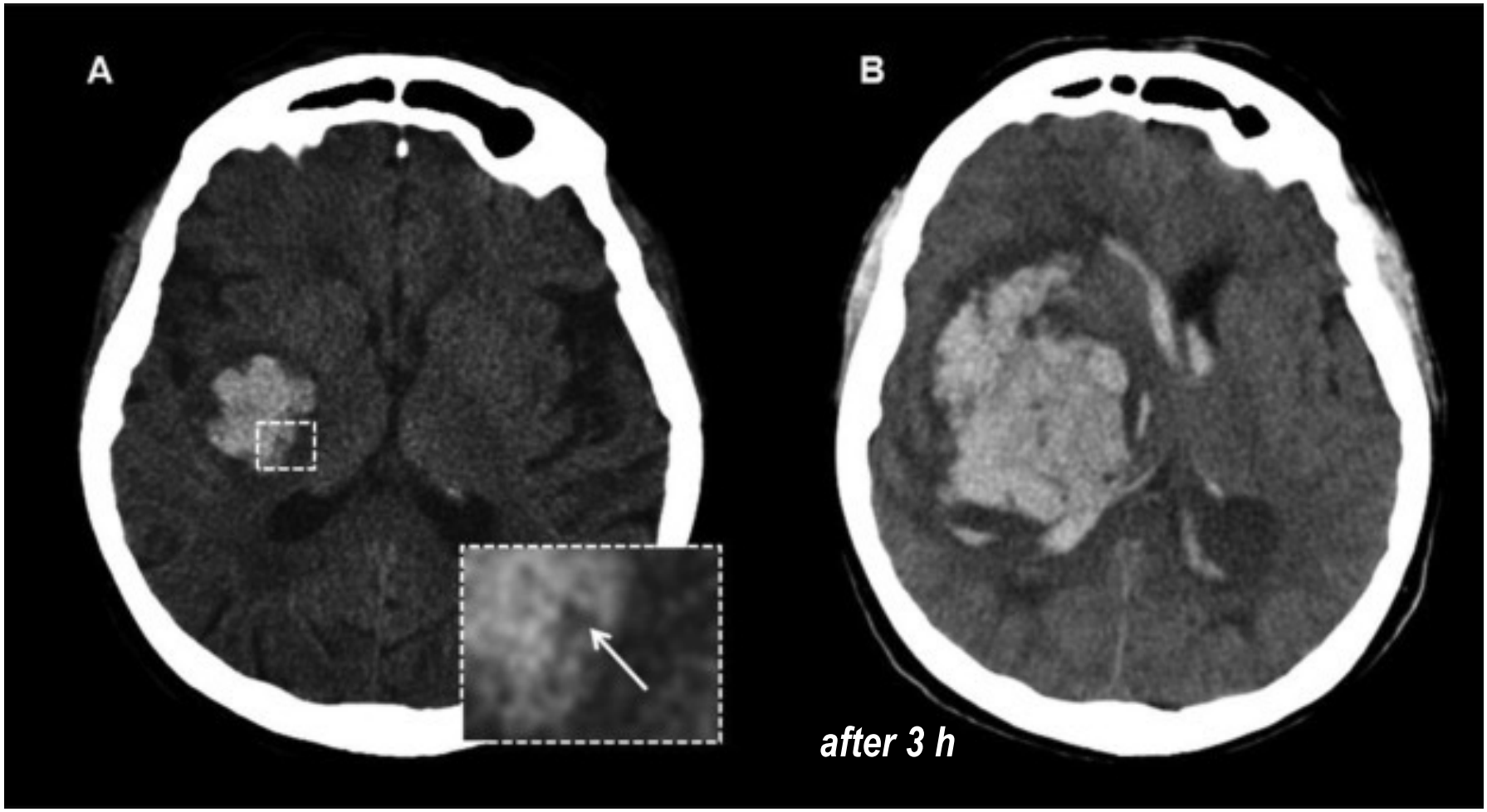
[a] Base excess is the quantity of base (HCO_3^-, in mEq/L) that is above or below the normal range in the body. A negative number is called a base deficit and indicates metabolic acidosis.

Data from: Mutschler A, Nienaber U, Brockamp T, et al. A critical reappraisal of the ATLS classification of hypovolaemic shock: does it really reflect clinical reality? *Resuscitation* 2013,84:309–313.

ATLS guidelines

Le *emorragie intracraniche*

- *Circa la meta dei decessi si verificano nelle prime 48 h dall'esordio*
- *L'espansione dell'ematoma è una complicanza che peggiora l'outcome ed è tipica dei pazienti in terapia antiaggregante e anticoagulante*



Scenari clinici

Sanguinamento pericoloso per la vita in corso

Rischio elevato di eventi emorragici maggiori (chirurgia non differibile)

Scenari diversi

1)Interruzione immediata del famaco antitrombotico

2)Misure di supporto standard

3)Terapia di reversione

Bilancio rischio emorragico / rischio trombotico

1)sospensione della protezione antitrombotica
2)“rebound” procoagulante (emorragia, trauma, chirurgia…)
3)agente reversore

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Pacchetto emorragia massiva politrauma

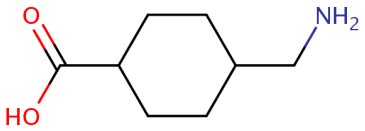
- 4 unità **GRC**
- 2-4 unità **PFC**
- 1 unità **PLT** / **Fibrinogeno** 2g → 3-5g
  - ➔ Test viscoelastici e dosaggi FBG
- **Acido tranexamico**: 10-15 mg/Kg in bolo + 10/15 mg/kg infusione 8 ore

Se persiste sanguinamento:

- Se antiaggregante in corso o noto deficit di aggregazione o vWF: **desmopressina** 0,3 µg/kg
- Concentrati di complesso protrombinico **PCC**: 50 UI/Kg
- **rFVIIa**: 90 µcg/kg ripetibile dopo 30 min (off-label)

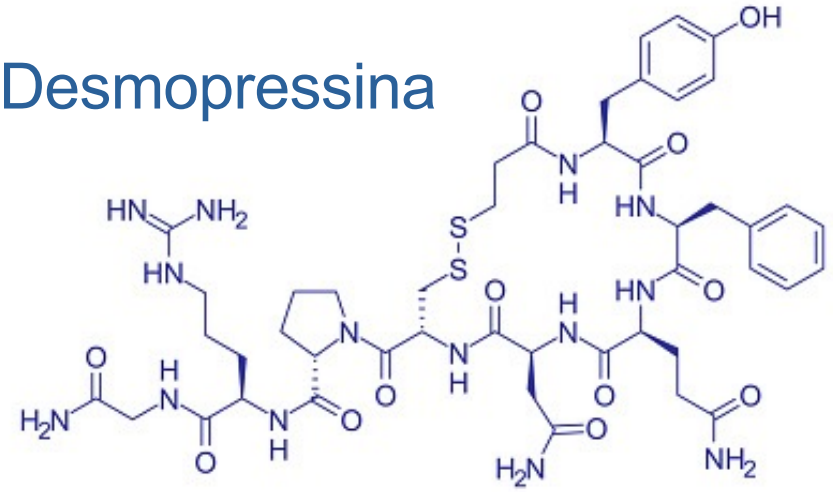
Agenti emostatici aspecifici

Acido tranexamico



- Antifibrinolitico
- Via sistemica o topica
- Buoni risultati su pazienti chirurgici

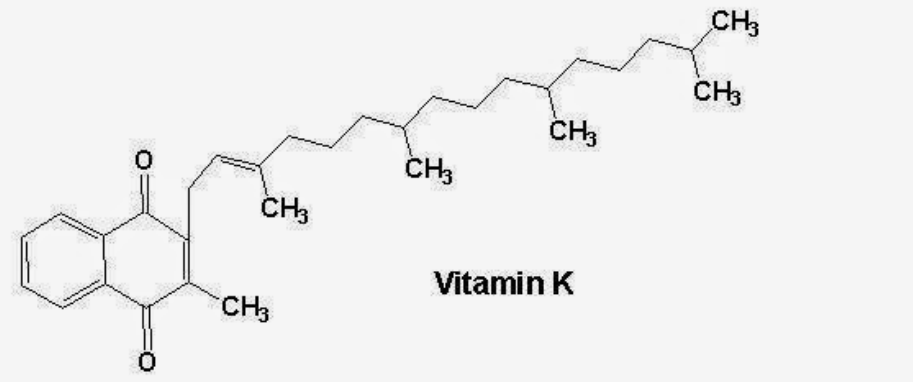
Desmopressina

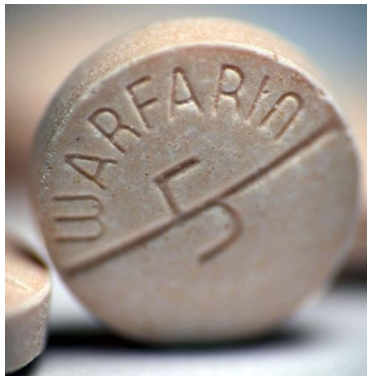


- Arginin-vasopressina
- ↑ Fatt. VIII, von Willebrand →↑aggregazione piastrinica

Concentrati di complesso protrombinico (PCC)
Concentrati di complesso protrombinico attivato (aPCC)

Tipo PCC		Fattori Coagulazione	note
Non -attivato	3-fattori	II-IX-X	Tracce trascurabili VII-Proteina C-S
	4-fattori	II-**VII**-IX-X	+ Proteina C-S
Attivato aPCC	4-fattori "agente by-passante"	II-**VIIa**-IX-X	**Grandi quantità di VIIa** Piccole quantità IXa-Xa-II Alto potenziale protrombotico





4-factor PCC intravenously

25-50 units/kg

A stepwise increase in dose is recommended with INR prolongation

Overuse of PCC (giving further PCC when INR is in normal range) will produce a prothrombotic state which may lead to further thrombosis

4 Factor PCC Dosing

	INR 2 to <4	INR 4 to <6	INR≥6 or DOAC
Dose	25U/kg	35U/kg	50U/kg
Max Dose	2500U	3500U	5000U

	INR 2 to <4	INR 4 to <6	INR≥6 or DOAC
30 - 49kg	1000U	1500U	2000U
50 - 69kg	1500U	2000U	3000U
70 - 89kg	2000U	3000U	4000U
≥90kg	2500U	3500U	5000U

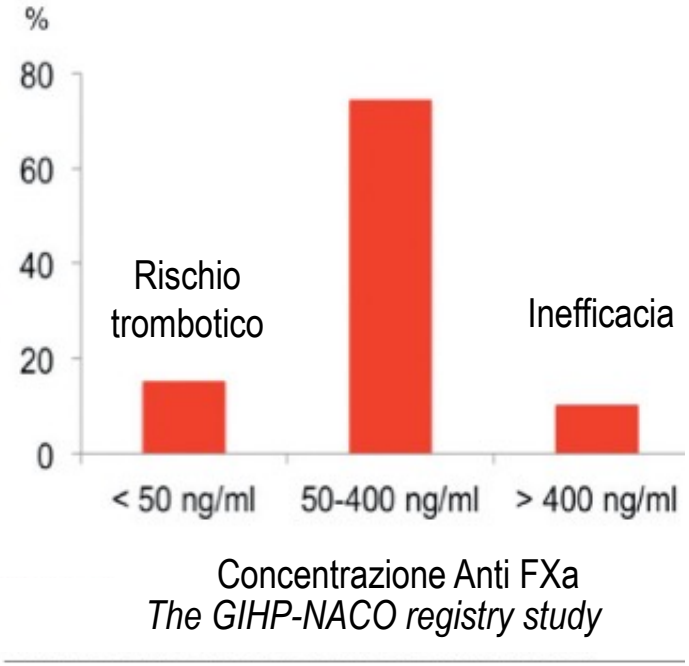
Use actual body weight and round dose to nearest vial size

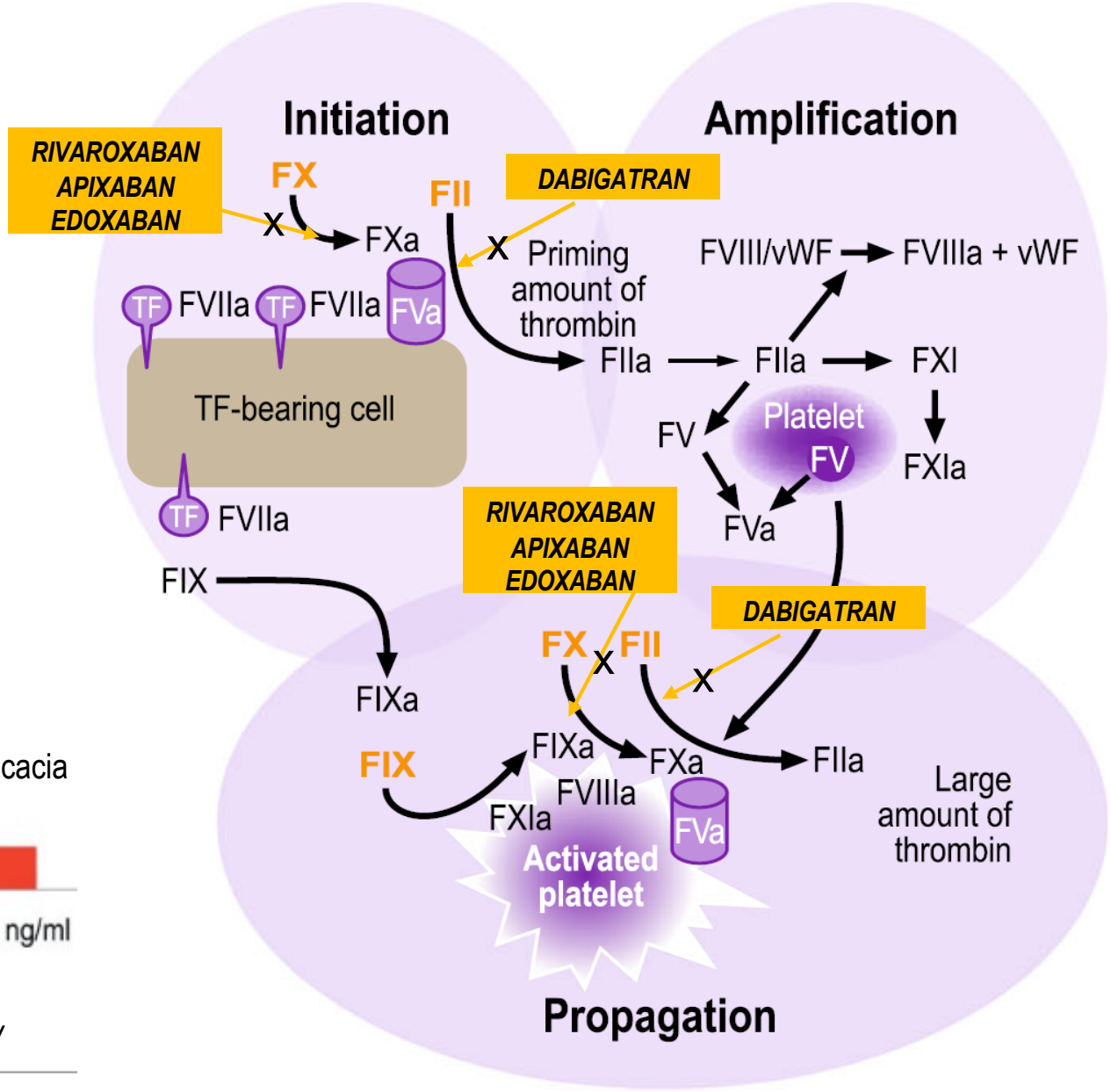
JACC 2017 PMID: 29203195

+ K vitamin e.v. (every 12 hrs)

Hunt BJ, Levi M. Urgent reversal of vitamin K antagonists. *BMJ* 2018; **360**:j5424.

DOACs ?????





The GIHP-NACO registry study

Concentrati di complesso protrombinico ***OFF-LABEL*** nell'emorragia pericolosa per la vita in corso di DOACs come reversore aspecifico

Tipo PCC		**Fattori Coagulazione**	**note**	***Se non disponibile agente reversore specifico****
Non - attivato	3-fattori	II-IX-X	Tracce trascurabili VII-Proteina C-S	
	4-fattori	II-**VII**-IX-X	+ Proteina C-S	Anti Fatt. X
Attivato aPCC	4-fattori "agente by-passante"	II-**VIIa**-IX-X	**Grandi quantità di VIIa** Piccole quantità IXa-Xa-II Alto potenziale protrombotico	Dabigatran

*Un solo studio di confronto randomizzato (ANNEXa-I 2024)
Studi real world a favore della reversione con antidoto

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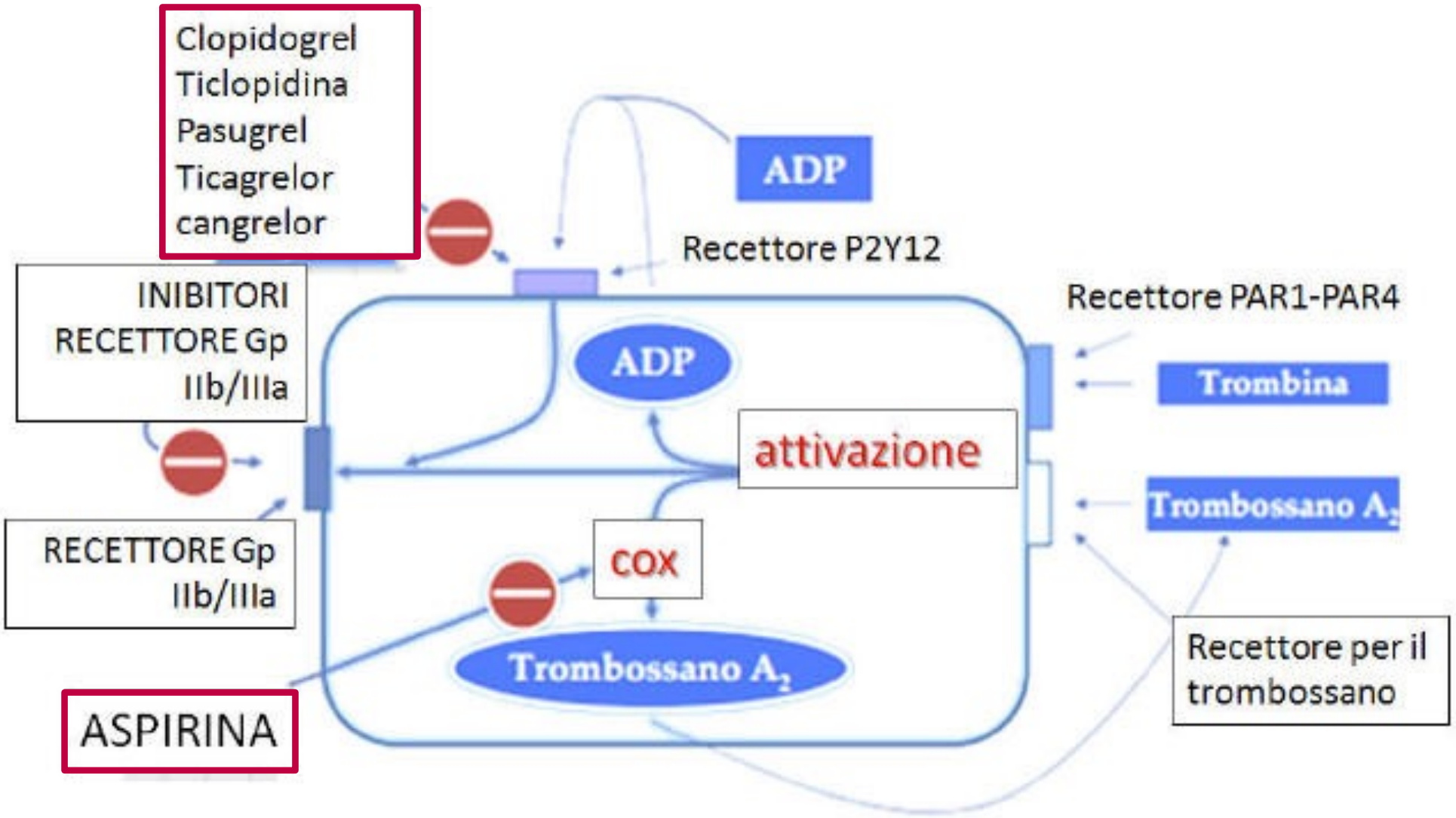
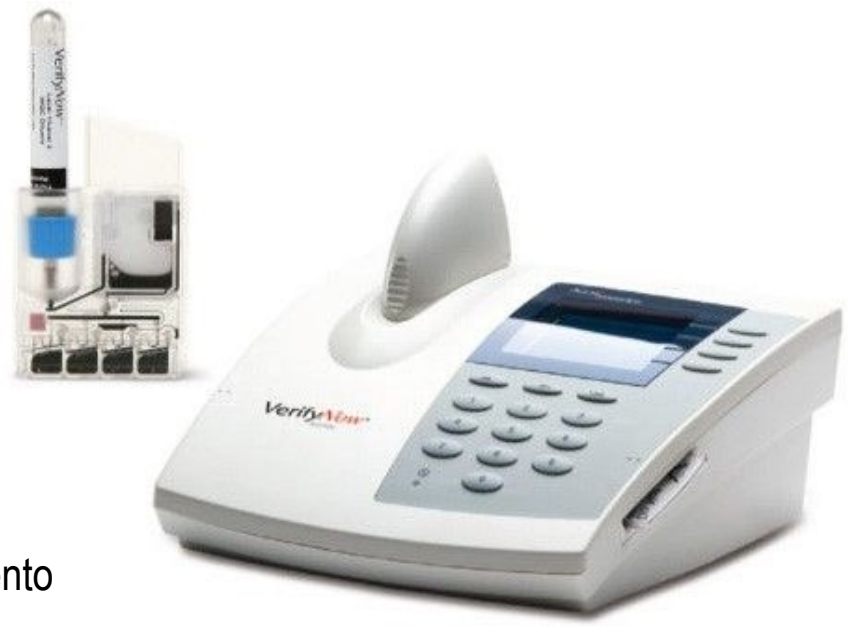
Antiaggreganti piastrinici

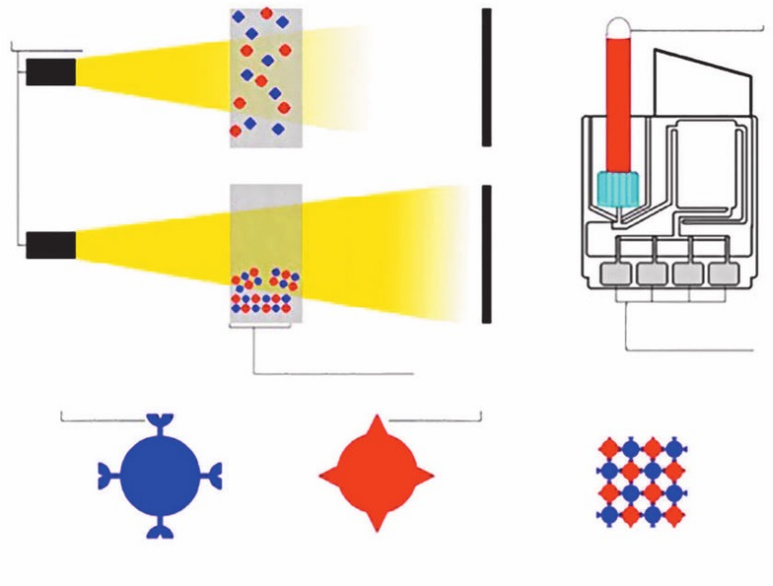


Valutazione rapida della responsività piastrinica



in corso di trattamento antiaggregante con
- acido acetilsalicilico (ASA)
- inibitori del recettore piastrinico P2Y12 (clopidogrel, ticagrelor, prasugrel, cangrelor e ticlopidina)

Può essere di aiuto:
- nella guida della terapia prima di un intervento chirurgico,
- nel sospetto di mancata aderenza alla terapia in casi di tromboembolismo sistemico recidivante in corso di trattamento antiaggregante



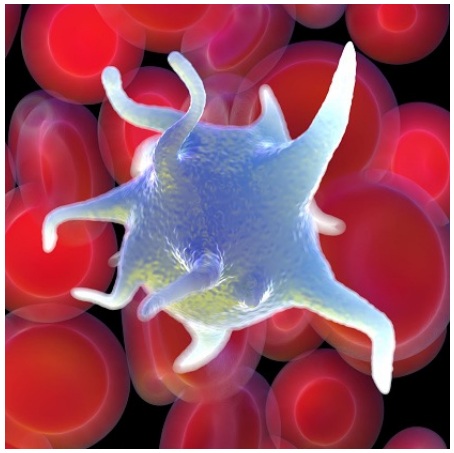
Grado dell'aggregazione piastrinica

P2Y12 Reaction Unit (PRU): <180 iporesponsività

PRI (%): <40-50% ipor

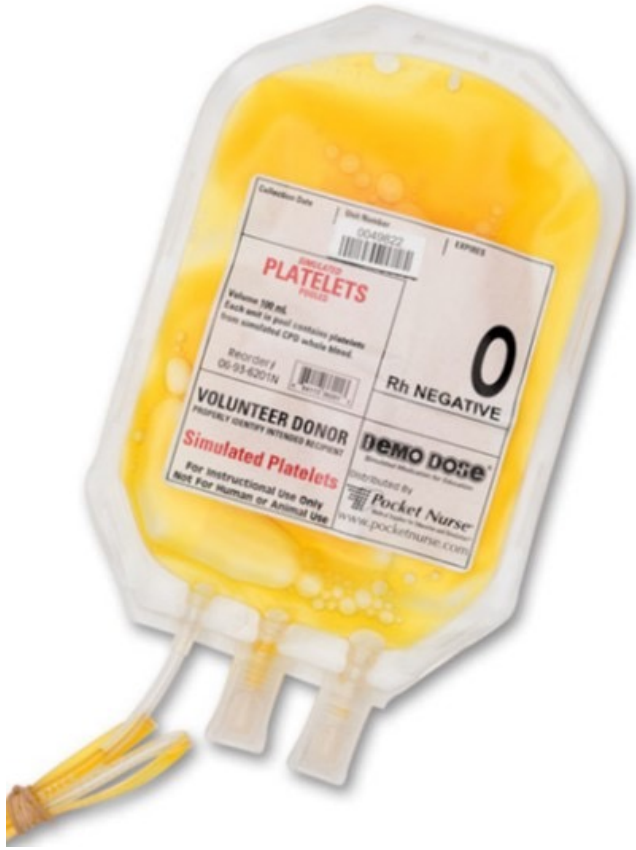
Aspirin Reaction Unit (ARU): <550 iporesponsività

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Dosaggio	60 mg/die (os)	10 mg /die (os)	180+180 mg/die (os)	**EV**
Reversibilità	NO	NO	SI'	Si'
Profarmaco	SI' (two steps)	SI' (one step)	NO	NO
Tempo alla max. inibizione piastrinica	4-6 ore	2-4 ore	1-2 ore	**immediato**
Emivita	6 ore	7 ore	7-8,5 ore	**3-5 minuti**



vita media di 5 → 10 giorni

Trasfusione di piastrine



E' ***teoricamente*** in grado di invertire adeguatamente gli effetti dell'***aspirina*** e, a dosi più elevate, anche di ***clopidogrel e prasugrel***

Non è supportata da studi clinici

- Variabilità di risposta
- ***Tempestica della somministrazione****
- Ipotizzato aumento del rischio di eventi trombotici e effetti pro-infiammatori delle trasfusioni

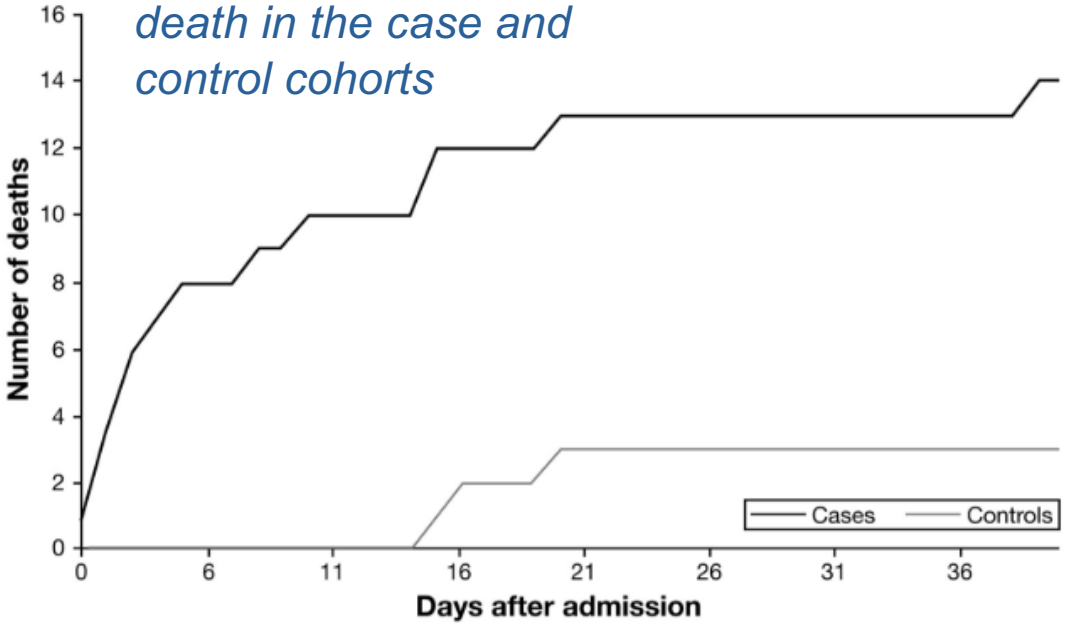
*Aspirina: almeno 2 ore dopo se dose e.v.; almeno 4-5 ore dopo se dose orale

Clopidogrel o prasugrel: 4 ore dopo la dose orale (oppiacei ritardano l'assorbimento)

No benefit from platelet transfusion for gastrointestinal bleeding in patients taking antiplatelet agents

A retrospective cohort study of patients with GIB admitted to Yale-New Haven Hospital from 2008 to 2013

Time after admission to death in the case and control cohorts



Interventions in Cases and Controls

Intervention	Cases (N = 204)	Controls (N = 204)	*P* value
Red blood cell transfusion	183 (90%)	139 (68%)	<.0001
FFP transfusion	48 (24%)	19 (9%)	.0002
First upper endoscopy	136 (67%)	134 (66%)	.92
Repeat upper endoscopy	16 (8%)	7 (3%)	.084
First colonoscopy	63 (31%)	63 (31%)	1.00
Endoscopy intervention	49 (24%)	40 (20%)	.34
Epinephrine injection alone	6 (3%)	2 (1%)	.28
Cautery alone	8 (4%)	15 (7%)	.20
Clips alone	27 (13%)	19 (9%)	.27
Epinephrine injection and second modality	8 (4%)	3 (1%)	.22
Interventional radiology treatment	36 (18%)	7 (3%)	<.0001
Surgical treatment	6 (3%)	0 (0%)	.03

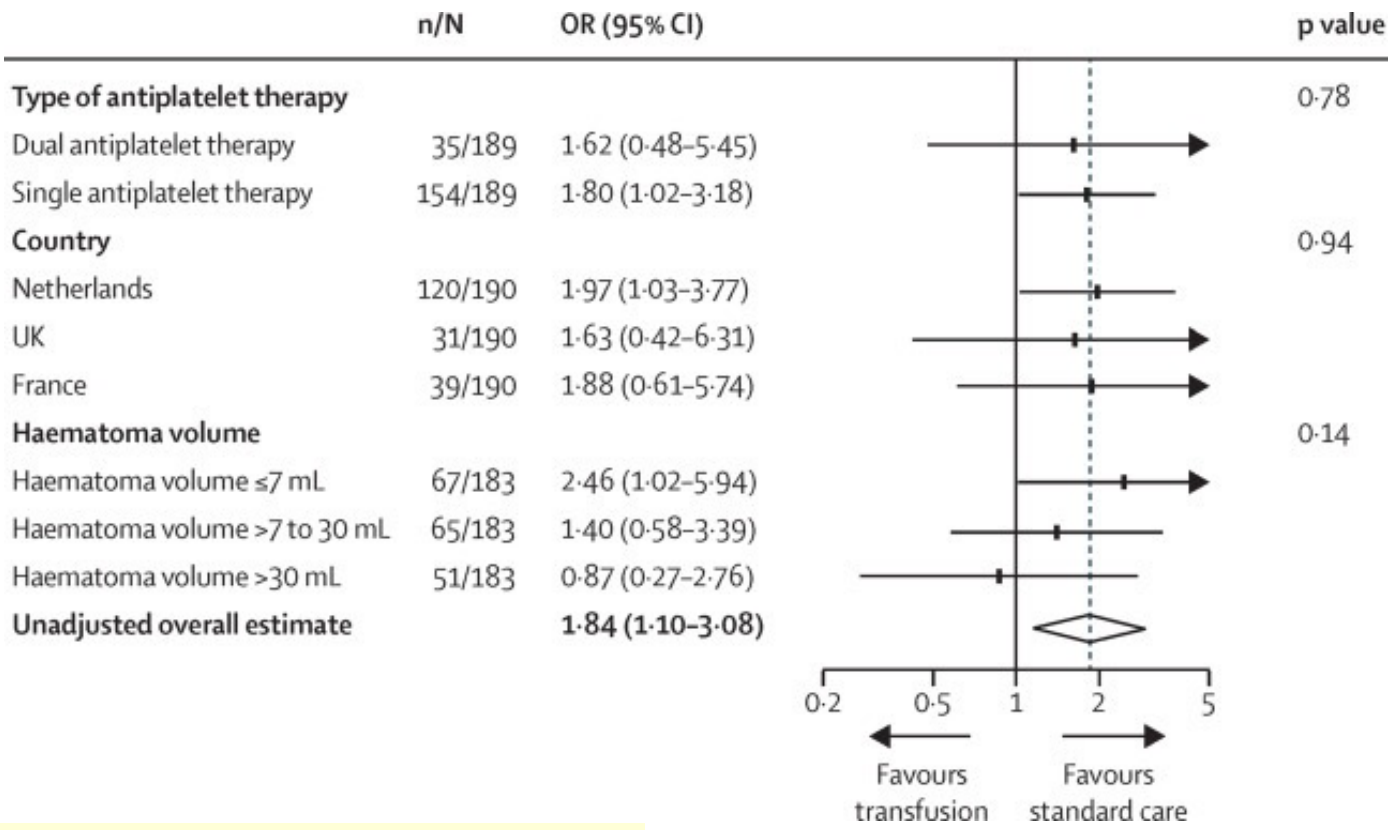
Bias of an observational study, but…….

The use of platelet transfusions in patients with GIB who are taking antiplatelet agents without thrombocytopenia did not reduce rebleeding but was associated with higher mortality

Zakko L. et al. . *Clin Gastroenterol Hepatol* 2017;**15**:46–52.

Platelet transfusion versus standard care ***after acute stroke due to spontaneous cerebral haemorrhage*** associated with antiplatelet therapy (PATCH): a randomised, open-label,phase 3 trial

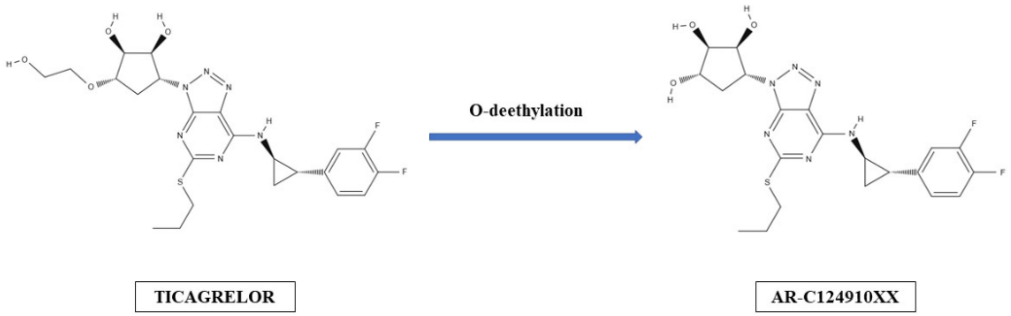
Between Feb 4, 2009, and Oct 8, 2015, 41 sites enrolled 190 participants



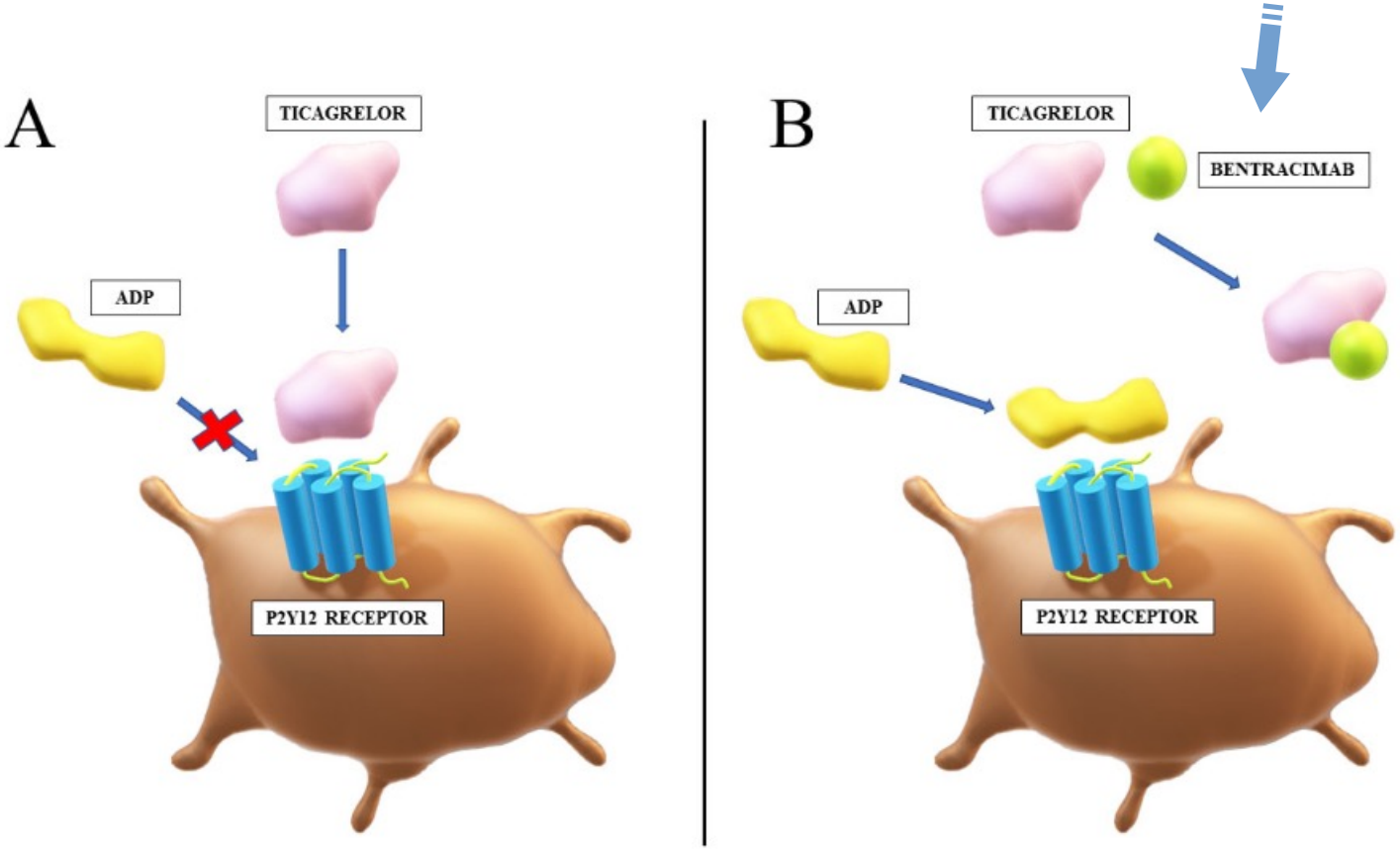
Platelet transfusion seems inferior to standard care for people taking antiplatelet therapy before intracerebral haemorrhage. Platelet transfusion ***cannot be recommended for this indication in clinical practice.***

Baharoglu MI et al. Lancet. 2016 Jun 25;387(10038):2605-2613

Hepatic formation of ticagrelor's active metabolite (AR-C124910XX)



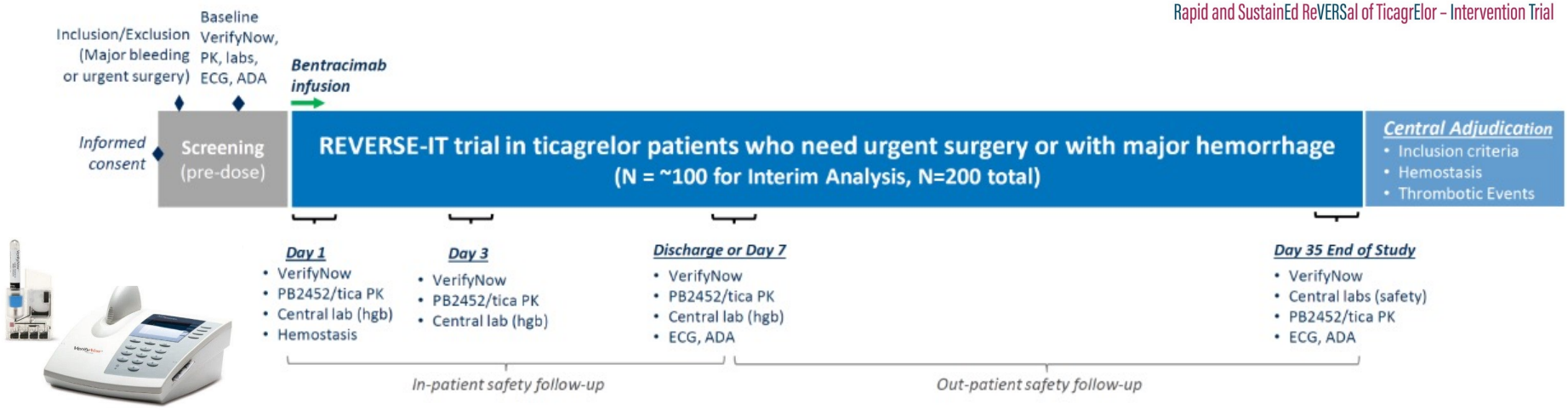
Bentracimab
the first specific antidote for ticagrelor



*an antigen-binding fragment (Fab) that displays **100-fold greater affinity** for ticagrelor and its active metabolite (AR-C124910XX) than for their target, platelet P2Y12 receptor*

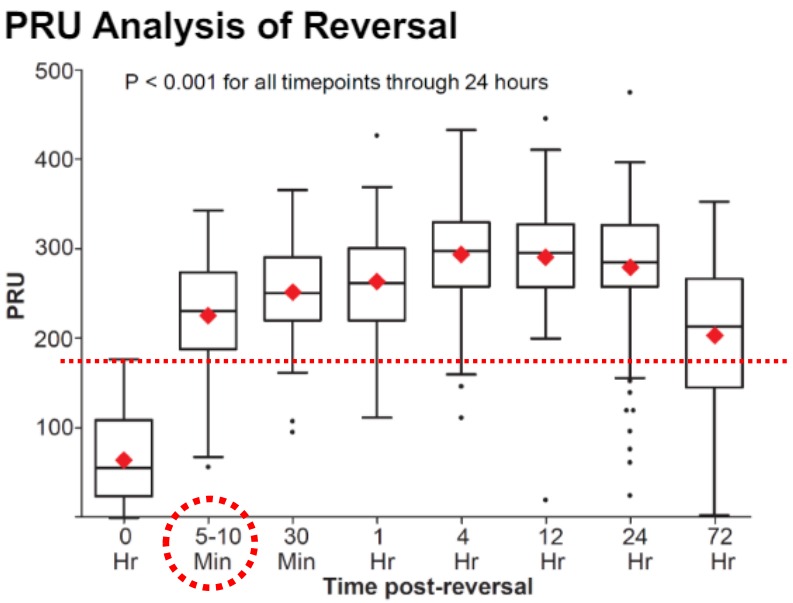
REVERSE-IT

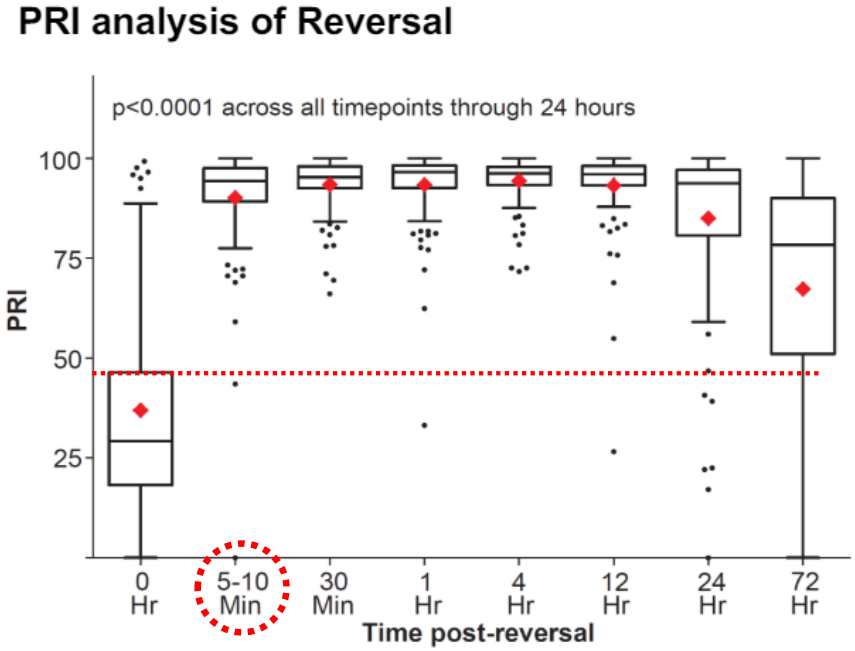
Rapid and SustainEd ReVERSal of TicagrElor – Intervention Trial



REVERSE-IT: Platelet Function Tests

>90%





NEJM Evidence 2021; 1 (3)

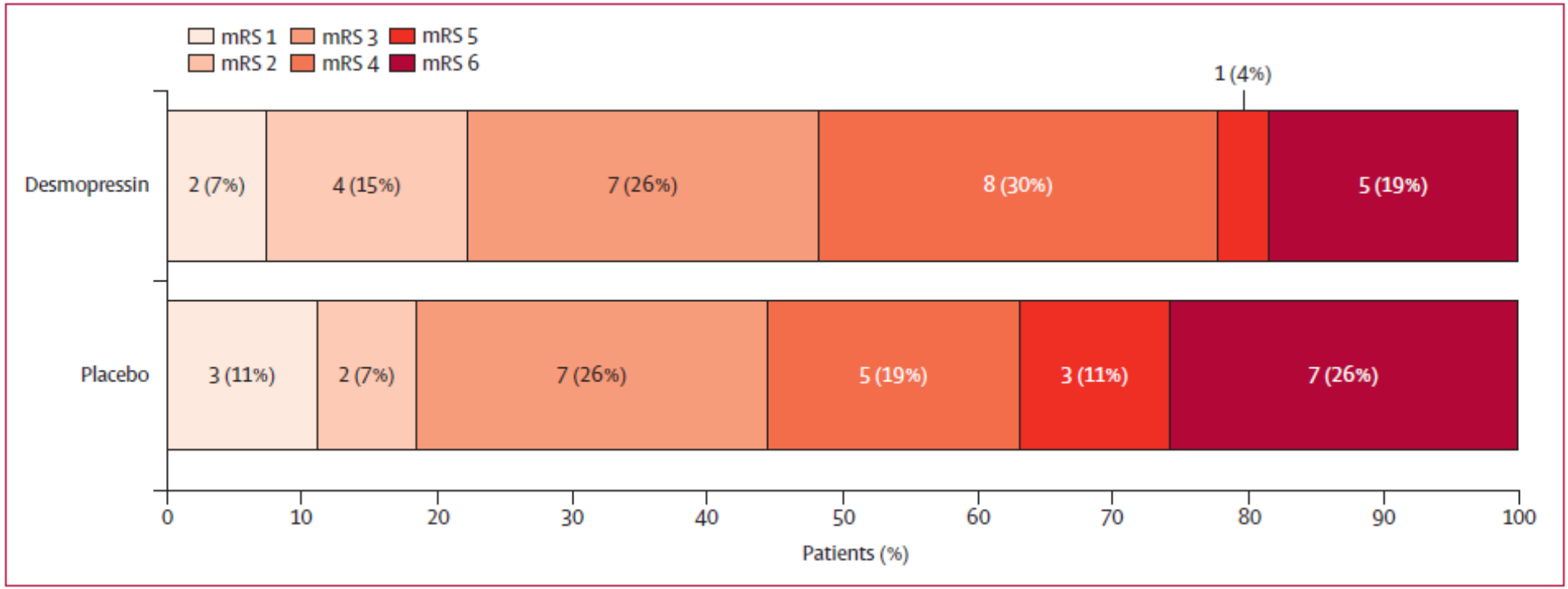
Desmopressin for patients with ***spontaneous intracerebral haemorrhage taking antiplatelet drugs*** (DASH): a UK-based, phase 2, randomised, placebo-controlled, multicentre ***feasibility trial***

a single dose of intravenous desmopressin 20 µg or matching placebo

within a 24 h window

Shift analysis of the *modified Rankin Scale score* in participants at day 90

mRS= modified Rankin Scale

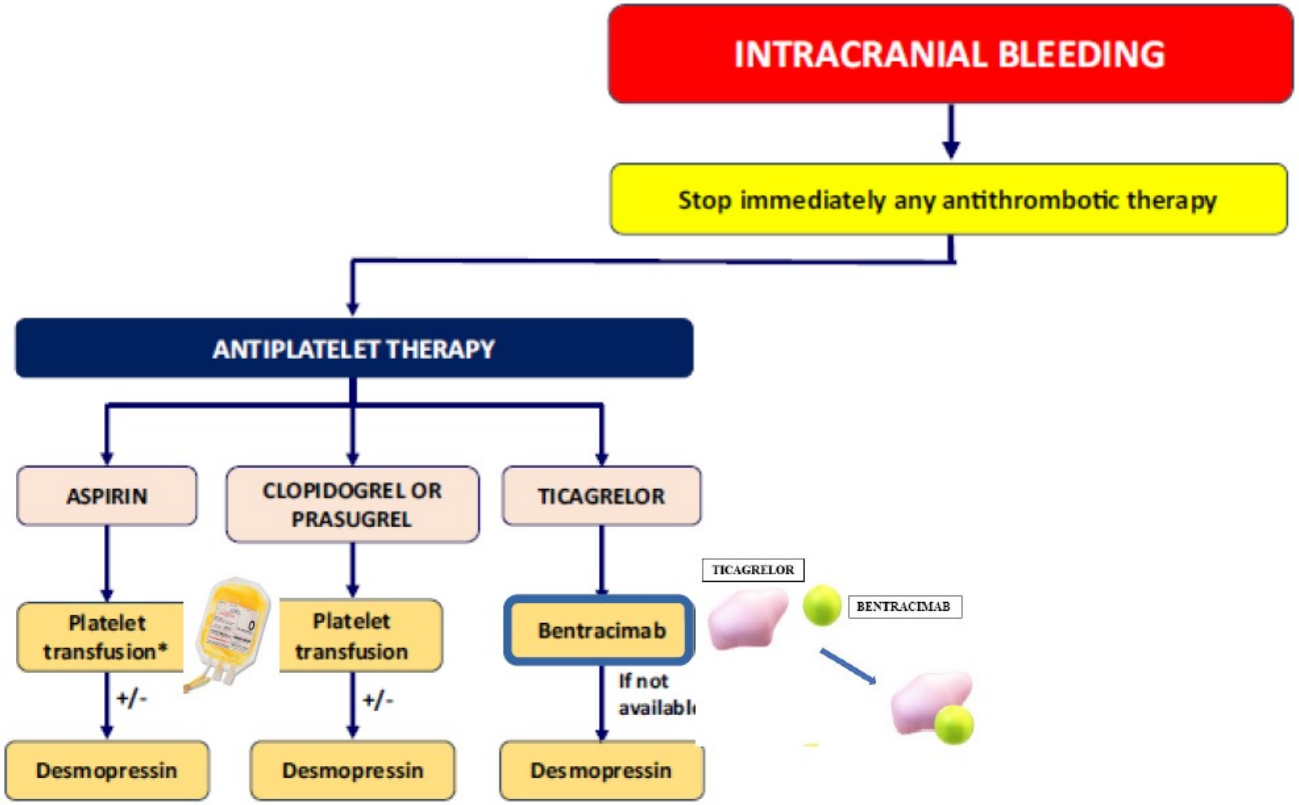


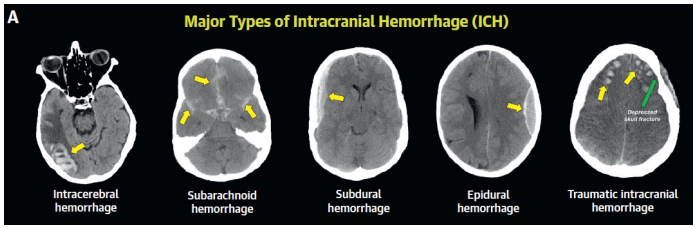
…….it should be feasible to conduct a definitive trial

Unfortunately, the results of DASH have not adequately resolved the optimal timing of administration of desmopressin for a future trial.

Desborough MJR et al. Lancet Neurol. 2023 Jul;22(7):557-567

Flowchart for the use and dosage of reversal agents in the case of intracranial haemorrhage





European Heart Journal Supplements (2024) **26** (Supplement 2), ii211-ii220
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suae033

ESC
European Society of Cardiology

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Interval since last dose

*We consider anticoagulation to have resolved **fully** after five half-lives have elapsed since the last dose*

	Half-lives	***Five half-lives after the last dose (day)***	Renal Excretion (%)
	normal renal function		
Dabigatran	12 to 17 hours	2.5 to 3.5	**80-85**
Rivaroxaban	5 to 9 hours	1 to 2	35
Apixaban	8 to 15 hours	1.5 to 3	25
Edoxaban	6 to 11 hours	1.3 to 2	35

Severe hepatic impairment could result in bioaccumulation

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Scaglione F. Clin Pharmacokinet 2013; 52:69.

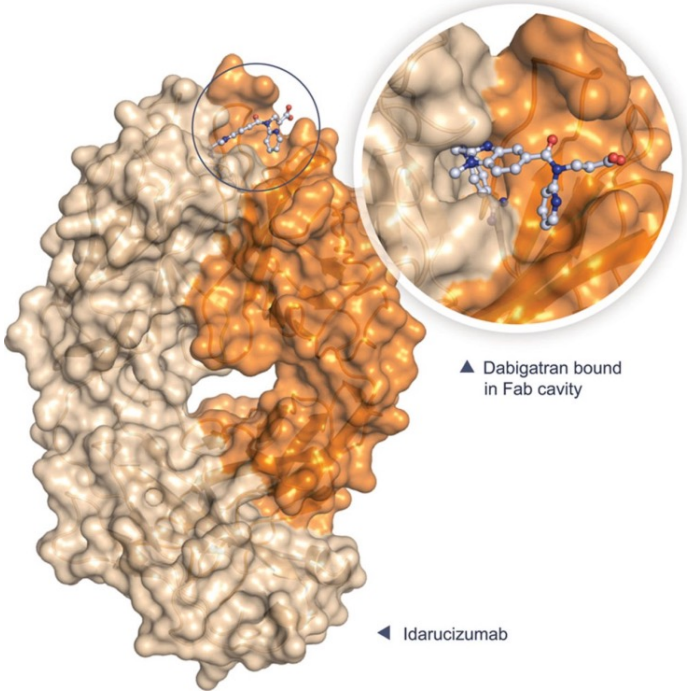
*Test coagulativi specifici possono essere utili solo se rapidamente disponibili (**sopra i 50 ng/ml di att. anti X** esiste un sicuro effetto anticoagulante da trattare)*

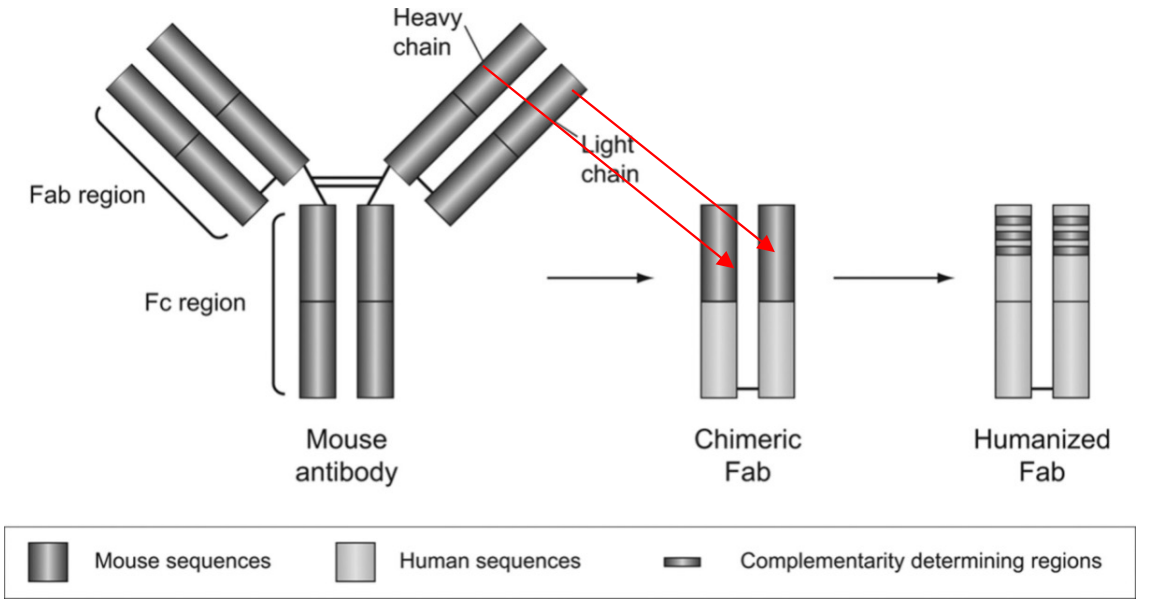
Non vengono perlopiù considerati dalle LG

*Le maggiori istruzioni operative consigliano **sempre** di chiedere il dosaggio dell'attività del DOAC (dTT per dabigatran e attività anti fatt.X per gli altri)*

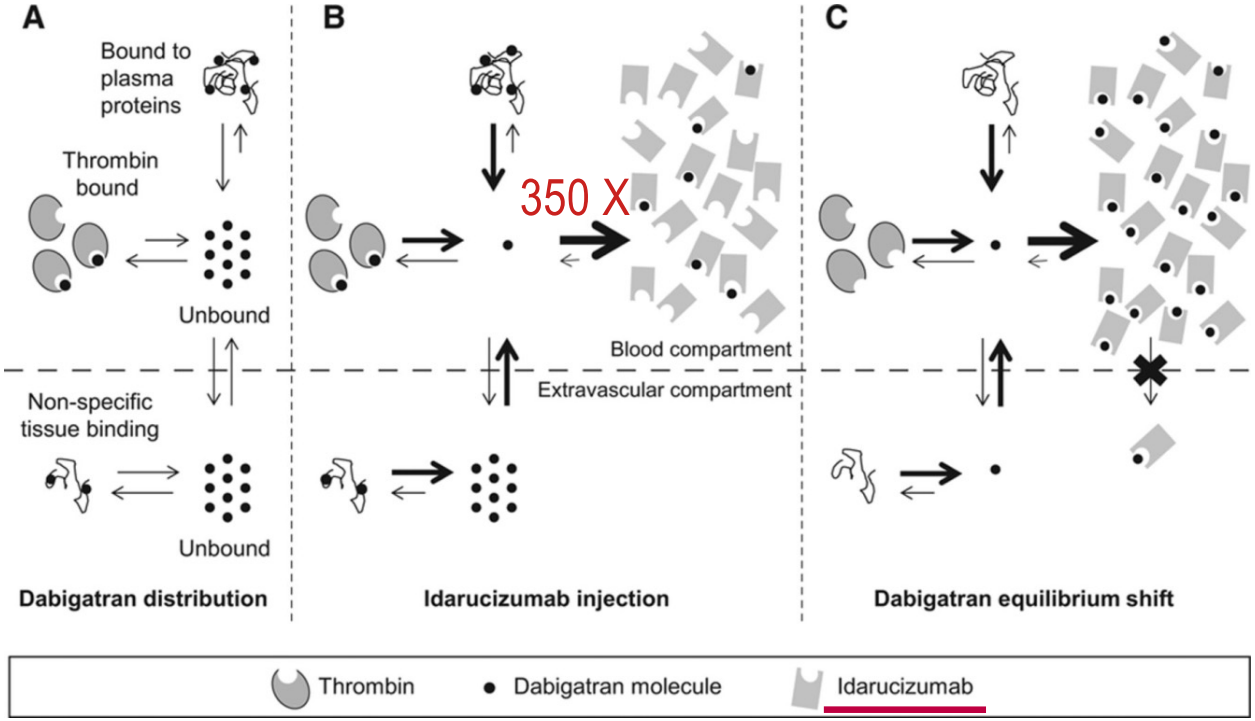
Idarucizumab

Frammento di anticorpo monoclonale umanizzato (Fab)





Circulation. 2015;132:2412-2422.

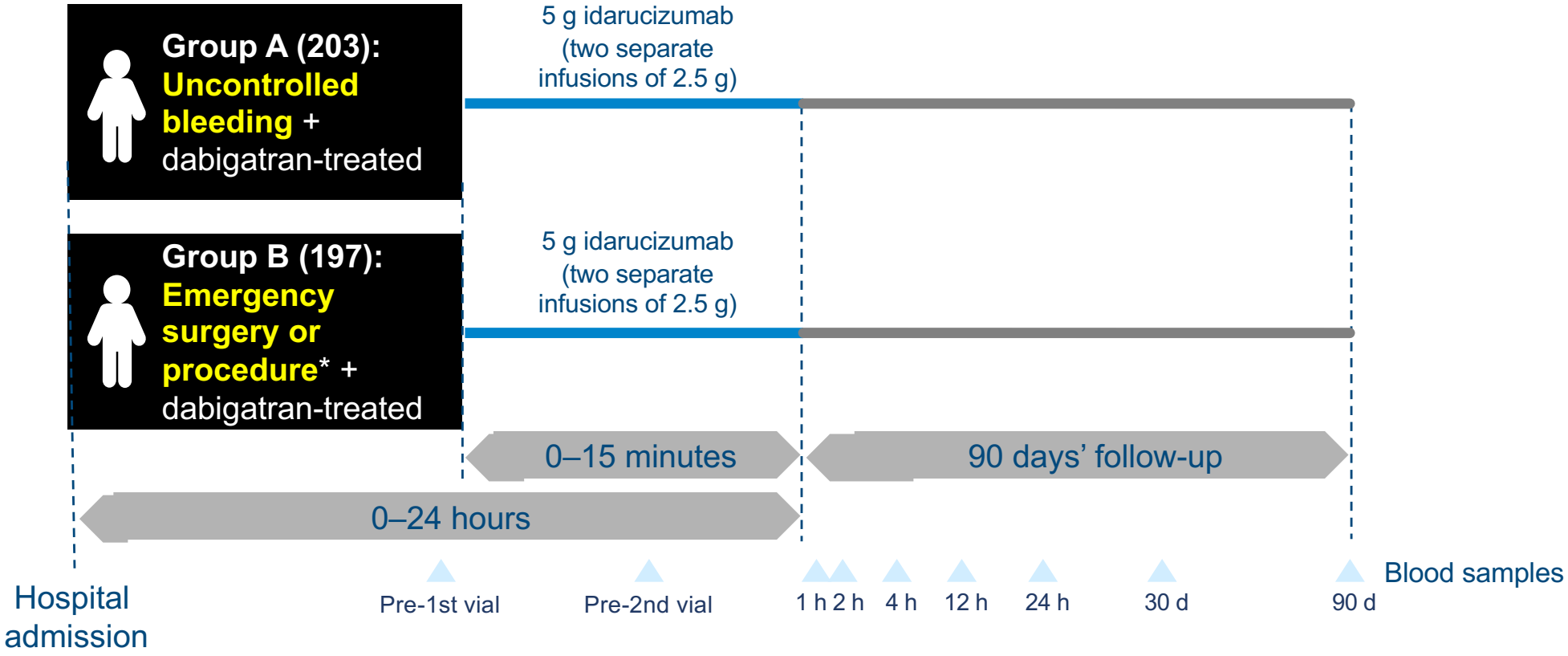


RE-VERSE AD™

Study of reversal effects of idarucizumab in patients on active dabigatran

Idarucizumab in RE-VERSE AD™

The first patient study of a NOAC-specific reversal agent



*Other than bleeding

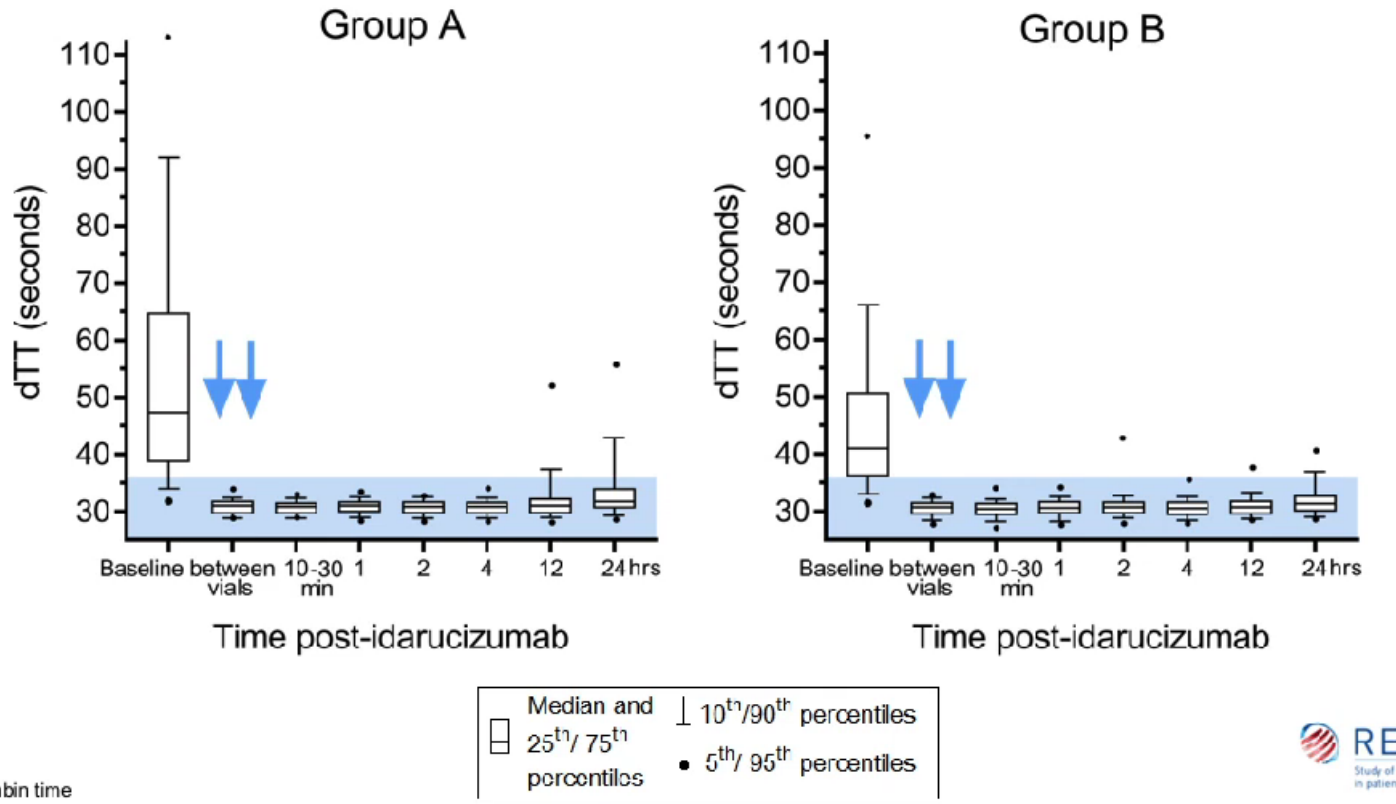
Pollack et al. Thromb Haemost 2015

RE-VERSE AD™

Study of reversal effects of idarucizumab in patients on active dabigatran

Primary EP
Haemostatic efficacy

Diluted Thrombin Time Assessment of Dabigatran Reversal



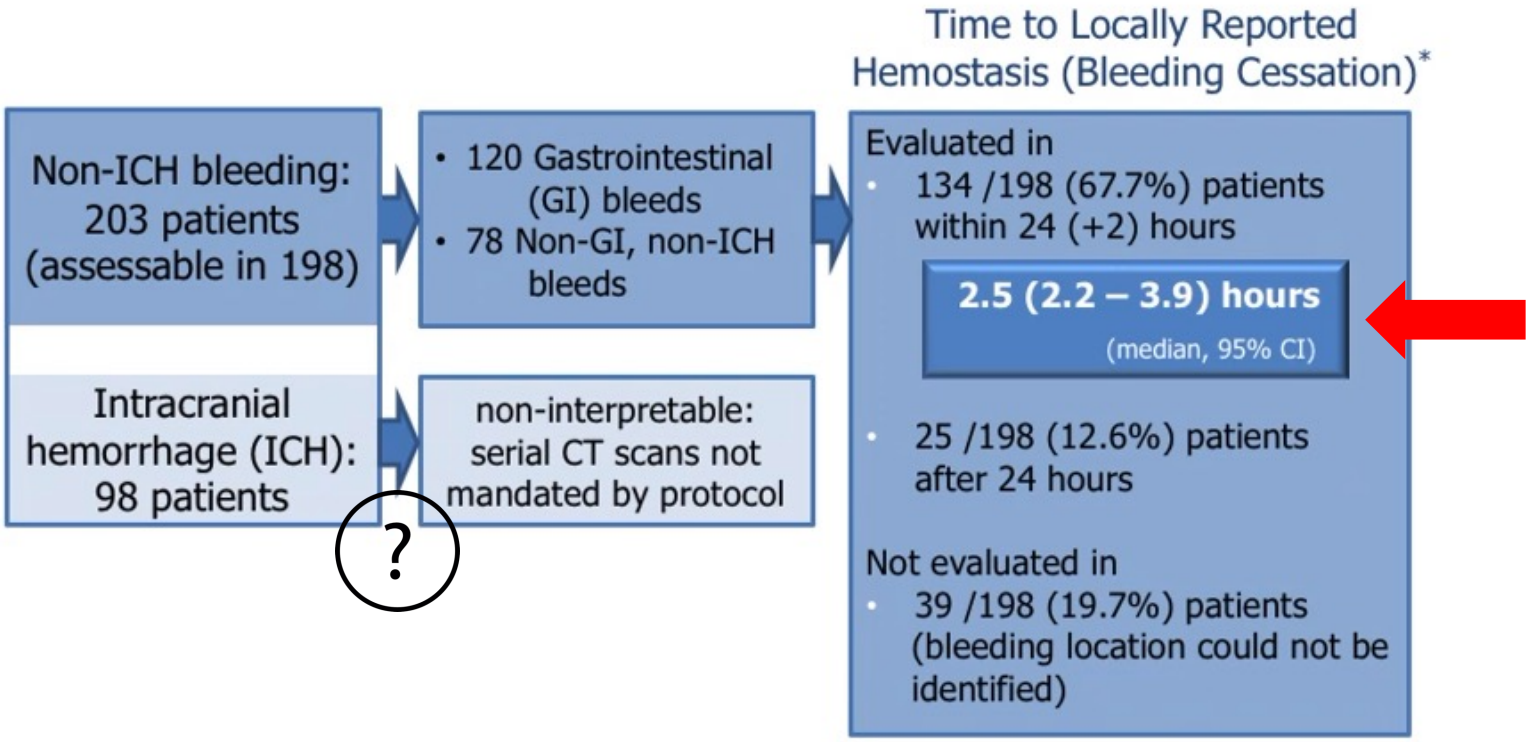
dTT diluted thrombin time

RE-VERSE AD™
Study of reversal effects of idarucizumab in patients on active dabigatran

RE-VERSE AD™
Study of reversal effects of idarucizumab in patients on active dabigatran

Group A
Secondary EP (bleeding cessation)

Group A (n=301): Hemostasis (bleeding cessation) in 24 hours



*Based on visualization where possible, or changes in hemoglobin / hematocrit within 24 hrs of idarucizumab administration by the local investigator

RE-VERSE AD™
Study of reversal effects of idarucizumab in patients on active dabigatran

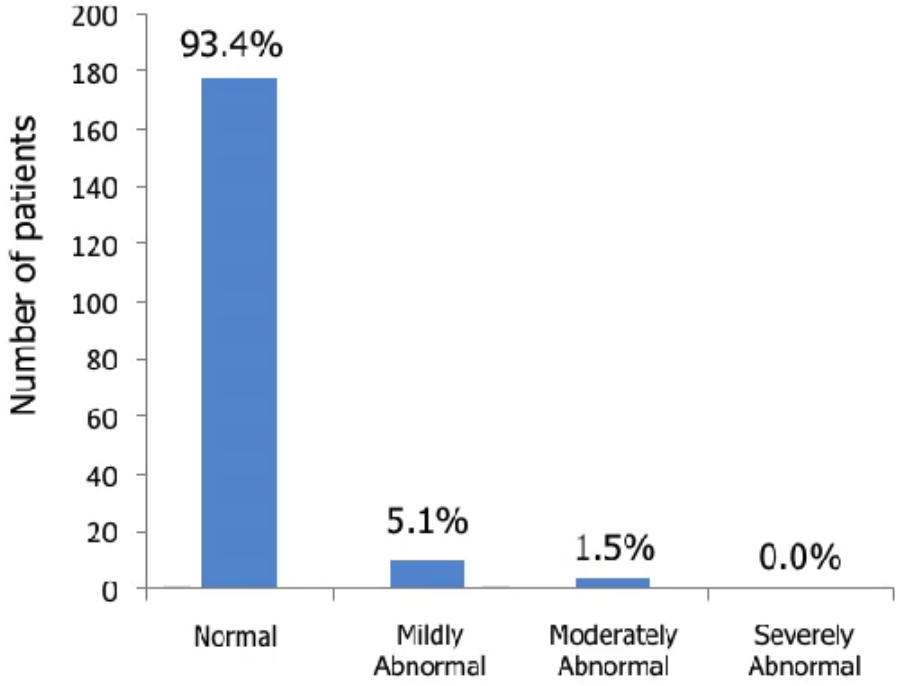
RE-VERSE AD™

Study of reversal effects of idarucizumab in patients on active dabigatran

Group B
Secondary EP

Group B: Peri-procedural Hemostasis

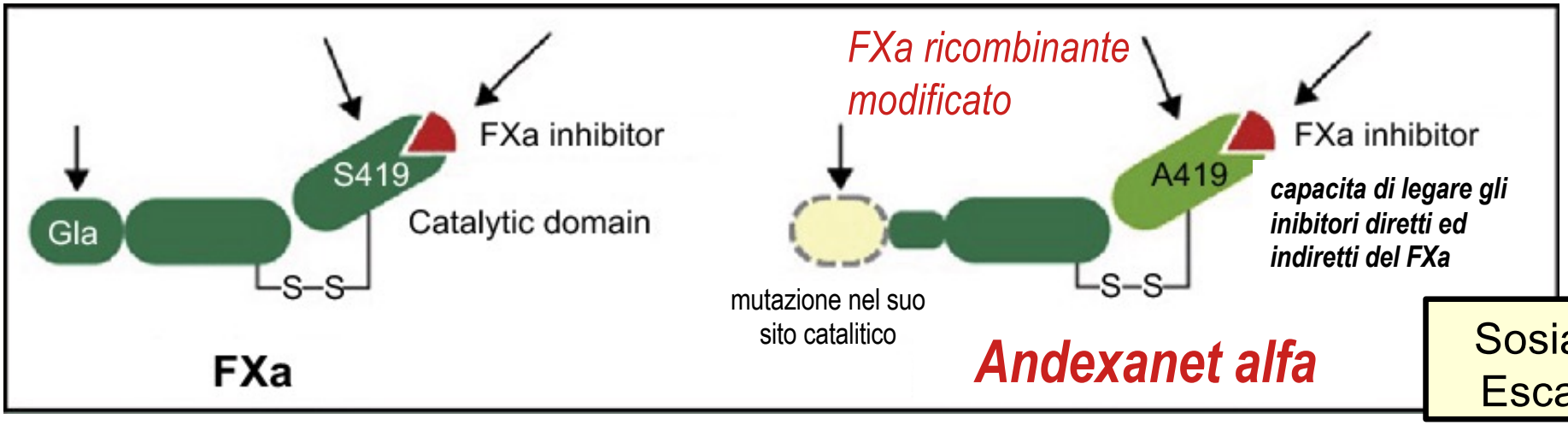
- 197 of 202 (97.5%) patients underwent anticipated surgery/procedures
- Median time from administration of first vial to procedure was 1.6 hours
- Adequacy of hemostasis during surgery determined locally



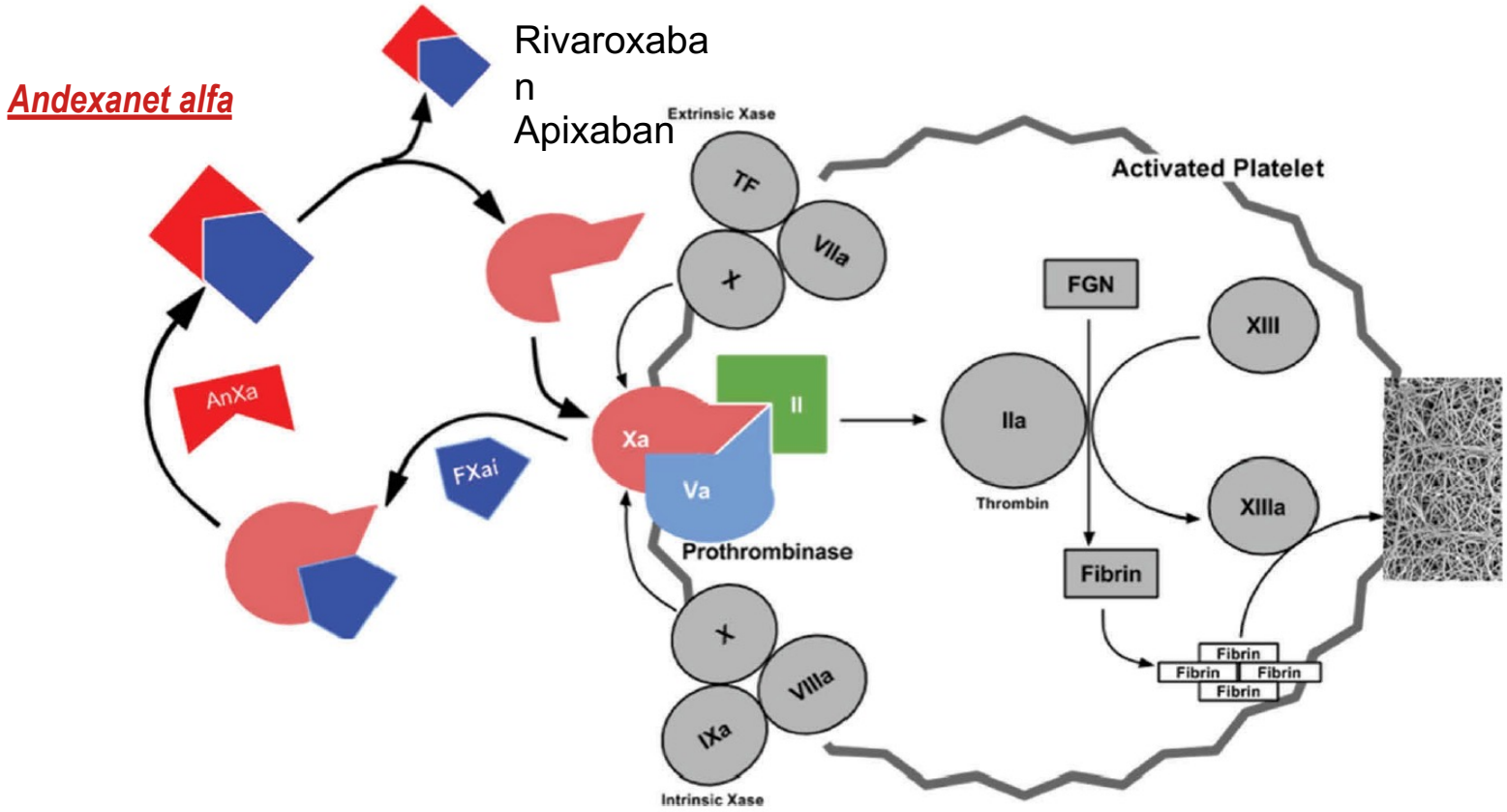
Normal:
as if anticoagulation were absent

Abnormal:
Mild – oozing, not requiring intervention
Moderate – controlled with local intervention
Severe – refractory hemorrhage

RE-VERSE AD™
Study of reversal effects of idarucizumab in patients on active dabigatran


FXa ricombinante modificato
FXa inhibitor
S419
Gla
Catalytic domain
S–S
FXa
mutazione nel suo sito catalitico
A419
FXa inhibitor
capacita di legare gli inibitori diretti ed indiretti del FXa
S–S
Andexanet alfa

Sosia Esca


Andexanet alfa
Rivaroxaban
Apixaban
Extrinsic Xase
TF
VIIa
X
Activated Platelet
FGN
XIII
AnXa
FXai
Xa
II
Va
IIa
Thrombin
XIIIa
Prothrombinase
Fibrin
X
VIIIa
IXa
Fibrin
Fibrin
Fibrin
Fibrin
Intrinsic Xase

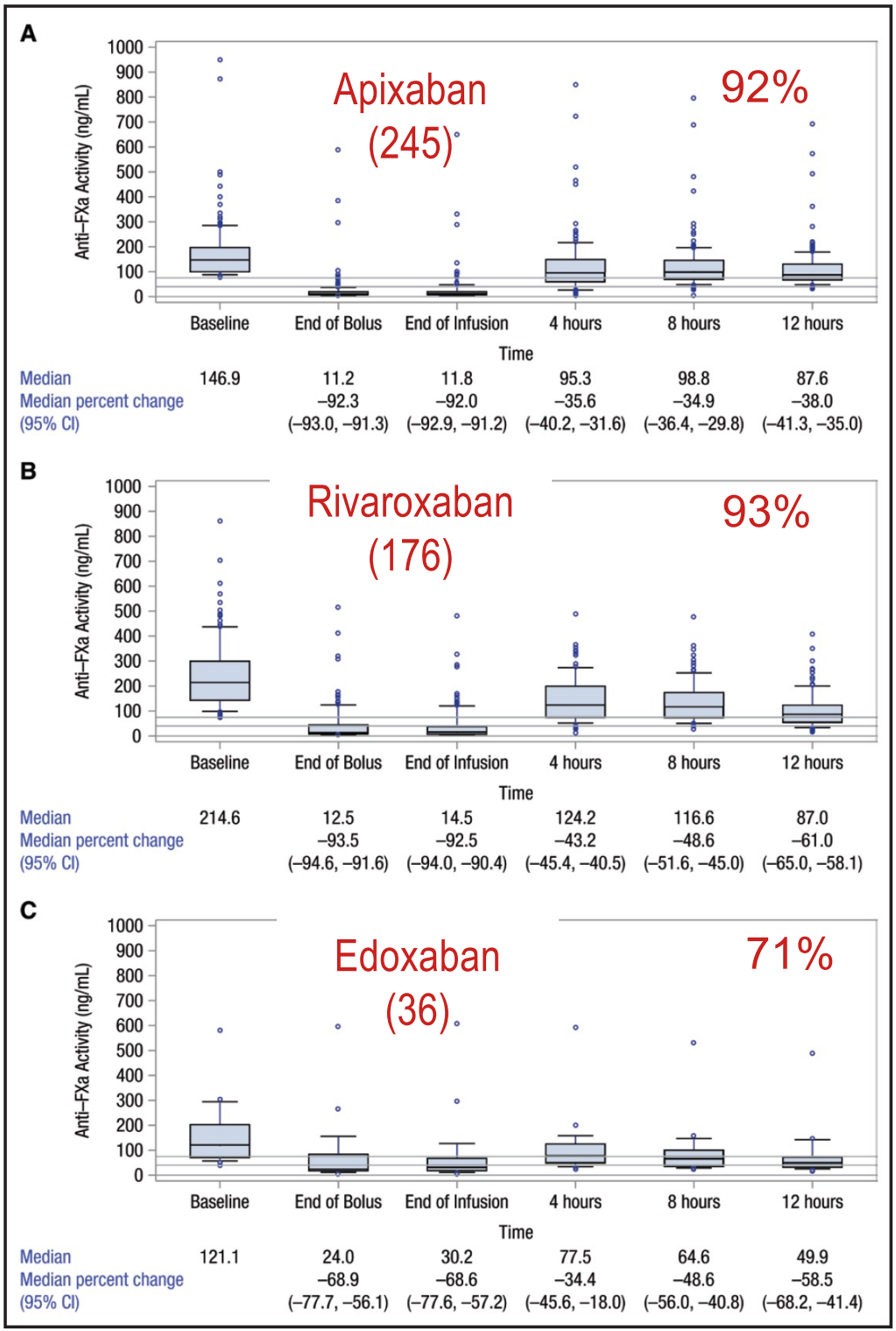
studio multicentrico di fase IIIb/IV a braccio singolo, in aperto

Adattata da Connolly SJ et al. N Engl J Med. 2019;380(14):1326-1335

ANNEXa 4

Haemostatic efficacy:
Anti–Factor Xa Activity

Final Report
March 23
479 patients
with major
bleeding

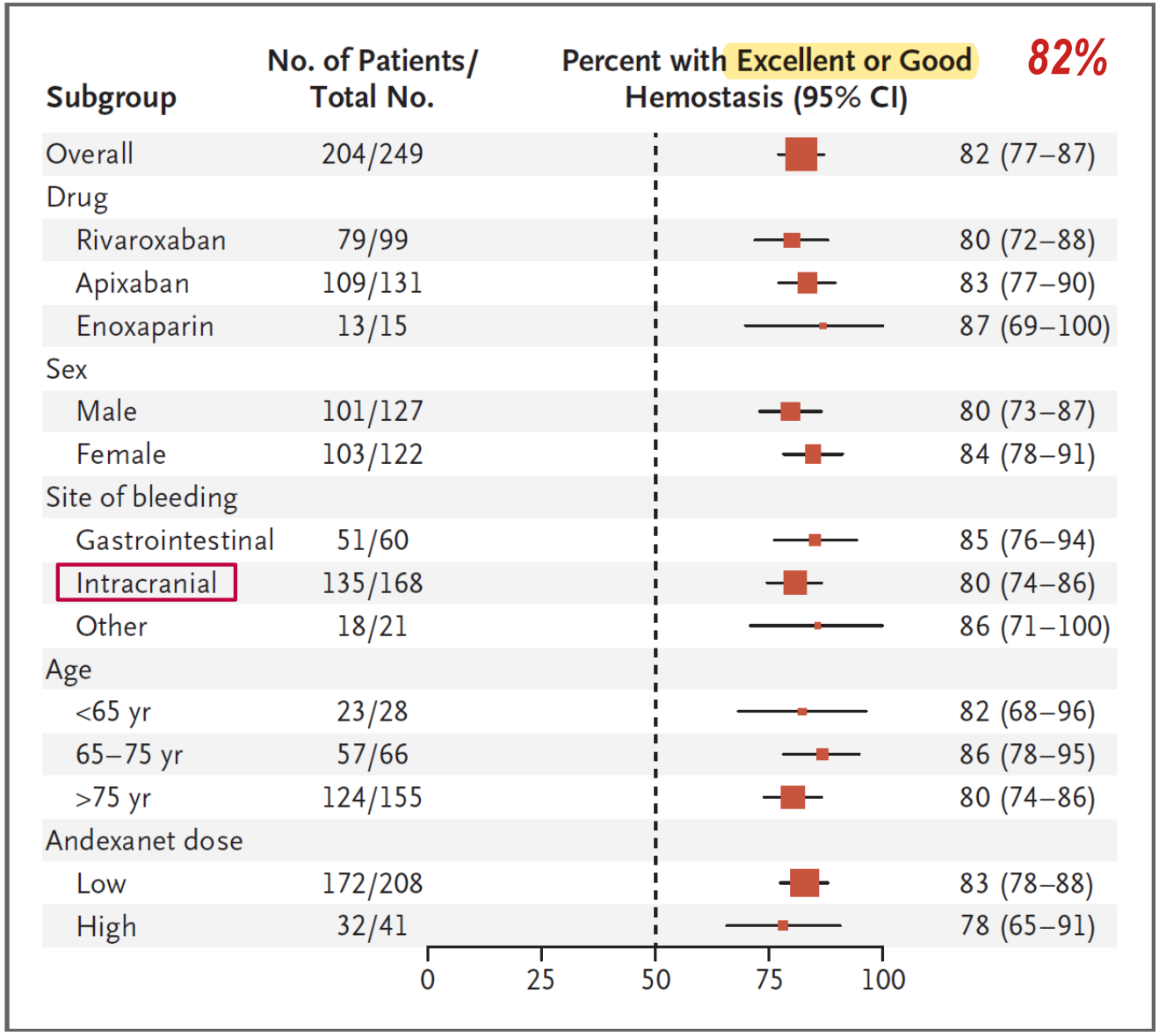


T.J. Milling Jr et al. *Circulation*. 2023;147:1026–1038.

12 hr Hemostatic Efficacy (clinical: positive correlation with mortality)

The ***definition of excellent or good hemostatic efficacy 12 hours after infusion*** was determined as follows:

1) ***Intracranial hemorrhage*** was measured by CT/MRI scan. For intracerebral hemorrhage, an increase in hematoma volume of ≤20% at both 1 hour and 12 hours compared to baseline constituted an excellent rate, while an increase of >20% but ≤35% at 12 hours constituted a good rate.
2) For ***GI, urinary, or other nonvisible bleeding***, a decrease in both hemoglobin/hematocrit of ≤10% compared to baseline constituted an excellent rate, while a decrease of >10% but ≤20% constituted a good rate



Connolly SJ et al. N Engl J Med. 2019;380(14):1326-1335

Andexanet for Factor Xa Inhibitor-Associated *Acute Intracerebral Hemorrhage*

530 adults

Mean age, 78.9 years

Men: 54%; Women: 46%

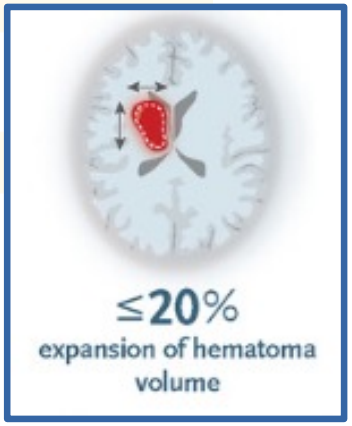
Acute ICH with hematoma volume of 0.5 to 60 ml

FXa inhibitor use in previous 15 hours

87% PCC

better control of hematoma expansion than usual care

End Point	Andexanet (N=224)	Usual Care (N=228)	Adjusted Difference per 100 Patients (95% CI)*	P Value*
	no./total no. (%)		*percentage points*	
Hemostatic efficacy	150/224 (67.0)	121/228 (53.1)	13.4 (4.6 to 22.2)	0.003
Hematoma volume change ≤35%†	165/215 (76.7)	137/212 (64.6)	12.1 (3.6 to 20.5)	
NIHSS score change <7 points	188/214 (87.9)	181/218 (83.0)	4.6 (−2.0 to 11.2)	
No receipt of rescue therapy between 3 hr and 12 hr	218/224 (97.3)	213/228 (93.4)	3.8 (0.0 to 7.6)	
Hematoma volume increase ≥12.5 ml‡	24/216 (11.1)	36/214 (16.8)	−5.6 (−12.0 to 0.8)	
Hemostatic efficacy, excluding patients nonevaluable for administrative reasons	150/218 (68.8)	121/225 (53.8)	14.5 (5.7 to 23.4)	



* The between-group difference, P value, and 95% CI were calculated with the use of a Cochran–Mantel–Haenszel test stratified according to the time from symptom onset to the performance of the baseline imaging scan (<180 or ≥180 minutes).

† Patients whose hematoma volume change was nonevaluable are excluded.

‡ Patients who died within 12 hours without follow-up brain imaging are included.

Connolly SJ et al: ANNEXa-I Investigators. N Engl J Med. 2024 May 16;390(19):1745-1755.

Andexanet for Factor Xa Inhibitor-Associated *Acute Intracerebral Hemorrhage*

…..but was associated with thrombotic events, including ischemic stroke

Thrombotic Events and Deaths at 30 Days.*

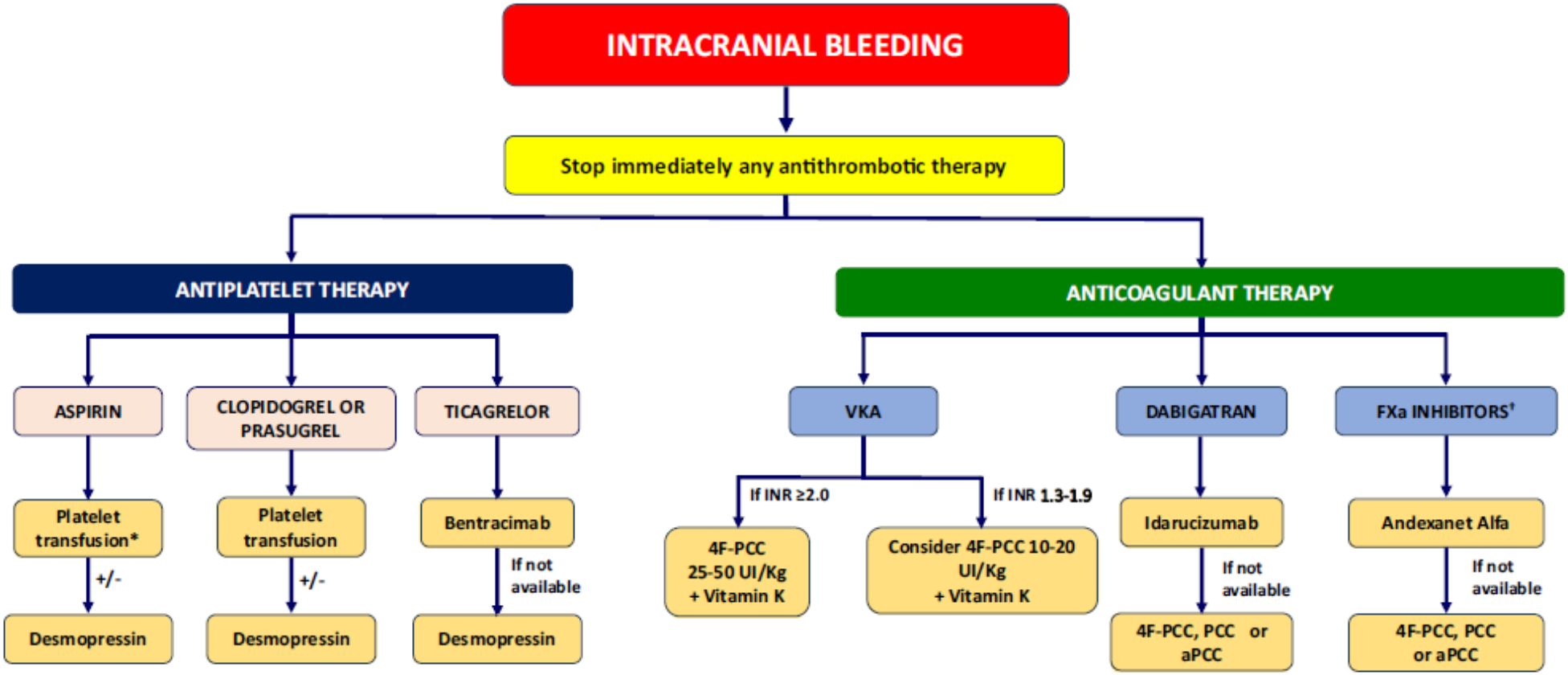
Event	Andexanet (N=263)	Usual Care (N=267)	Increase per 100 Patients (95% CI)†	P Value†
	no. of patients (%)		*percentage points*	
≥1 Thrombotic event	27 (10.3)	15 (5.6)	4.6 (0.1 to 9.2)	0.048
Transient ischemic attack	0	0	—	
Ischemic stroke	17 (6.5)	4 (1.5)	5.0 (1.5 to 8.8)	
Myocardial infarction	11 (4.2)	4 (1.5)	2.7 (–0.2 to 6.1)	
Deep-vein thrombosis	1 (0.4)	2 (0.7)	–0.4 (–2.4 to 1.5)	
Pulmonary embolism	1 (0.4)	6 (2.2)	–1.9 (–4.5 to 0.2)	
Arterial systemic embolism	3 (1.1)	2 (0.7)	0.4 (–1.7 to 2.7)	
Death	73 (27.8)	68 (25.5)	2.5 (–5.0 to 10.0)	0.51

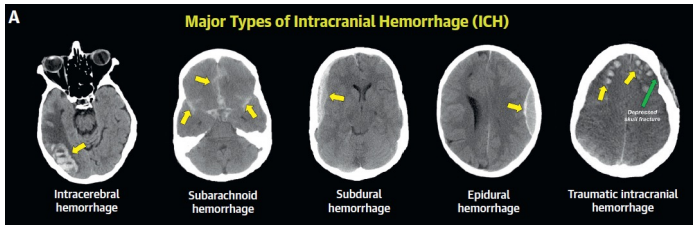
Connolly SJ et al: ANNEXA-I Investigators.
N Engl J Med. 2024 May 16;390(19):1745-1755.

Indicazioni e approvazione

	IDARUCIZUMAB	ANDEXANET alfa
Indicazioni Approvazione AIFA	In caso di episodi emorragici incontrollati o pericolosi per la vita in corso di Dabigatran	In caso di sanguinamento maggiore in corso di **Apixaban e Rivaroxaban** (Edoxaban off label)
	In caso di interventi chirurgici di emergenza in corso di Dabigatran	***Prima di un intervento chirurgico urgente non è stato valutato***
Approvazione AIFA	2015	2019
Rimborso	SI	***In corso richiesta*** ***Conf. 4 flaconi: 23.407,34 €***

Flowchart for the use and dosage of reversal agents in the case of intracranial haemorrhage

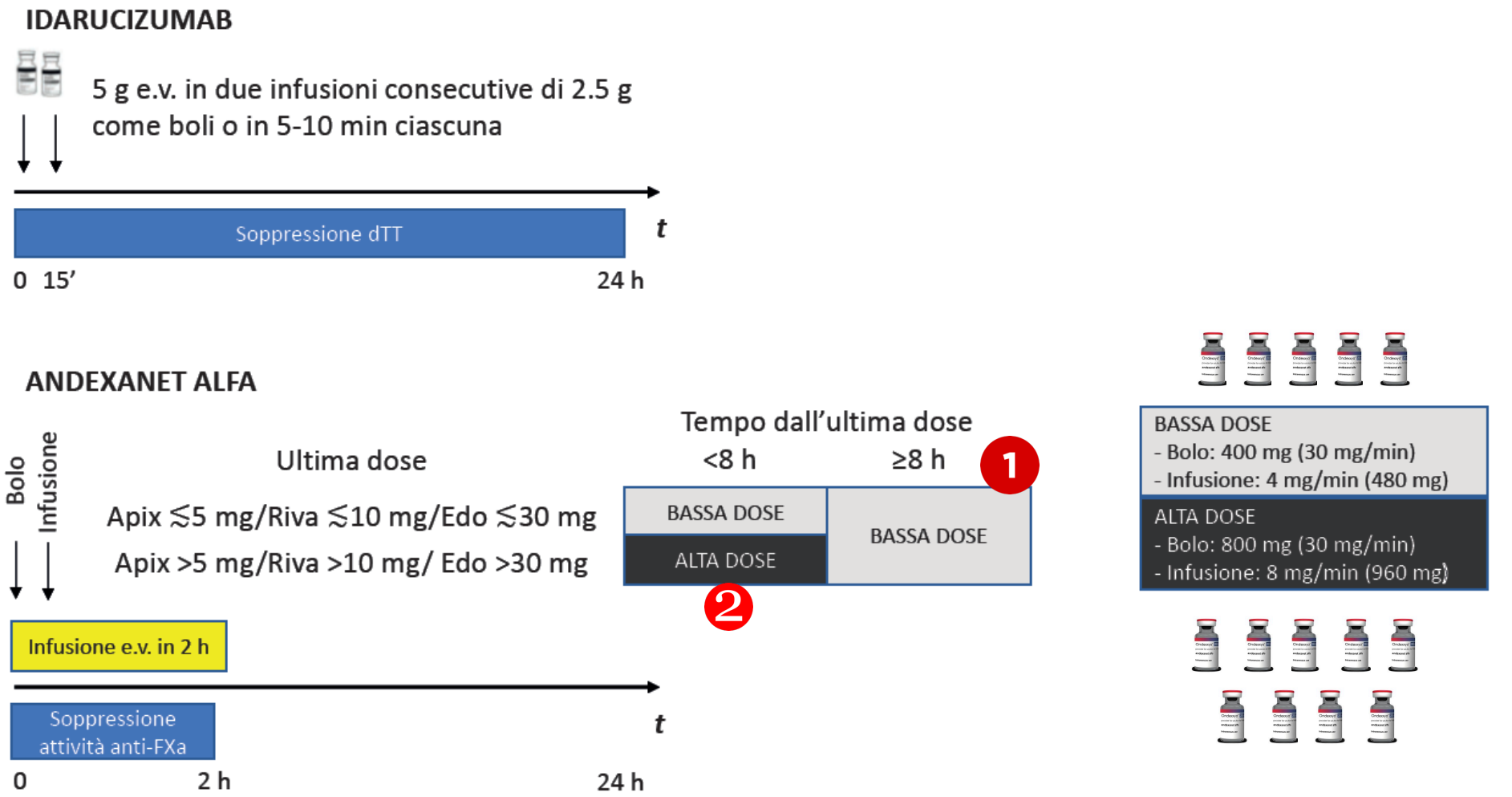




European Heart Journal Supplements (2024) **26** (Supplement 2), ii211-ii220
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suae033

ESC
European Society of Cardiology

Modalita di somministrazione di idarucizumab ed andexanet alfa



Modificata da Steffel J et al. 2021 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Europace 2021;23:1612-76

AGENDA

1. Introduzione e scenari clinici
2. Misure emostatiche aspecifiche
3. Reversione
4. Conclusioni

Conclusioni

La gestione del paziente in terapia antiaggregante o anticoagulante che sanguina è una sfida terapeutica

1)Pur in assenza di grandi trial randomizzati che supportino la pratica, ***il ripristino della coagulazione è considerato desiderabile dalle LG* in caso di sanguinamenti severi e pericolosi per la vita *in pazienti che rimangano attivamente anticoagulati e antiaggregati.***

2)Le valutazioni devono essere **rapide** ma sono spesso soggettive e dipendenti dall'**esperienza clinica**

3)La maggior parte delle LG internazionali raccomandano *in primis* l'utilizzo di ***antidoti specifici* se disponibili**