Dabigatran e mondo reale: la gestione delle emergenze

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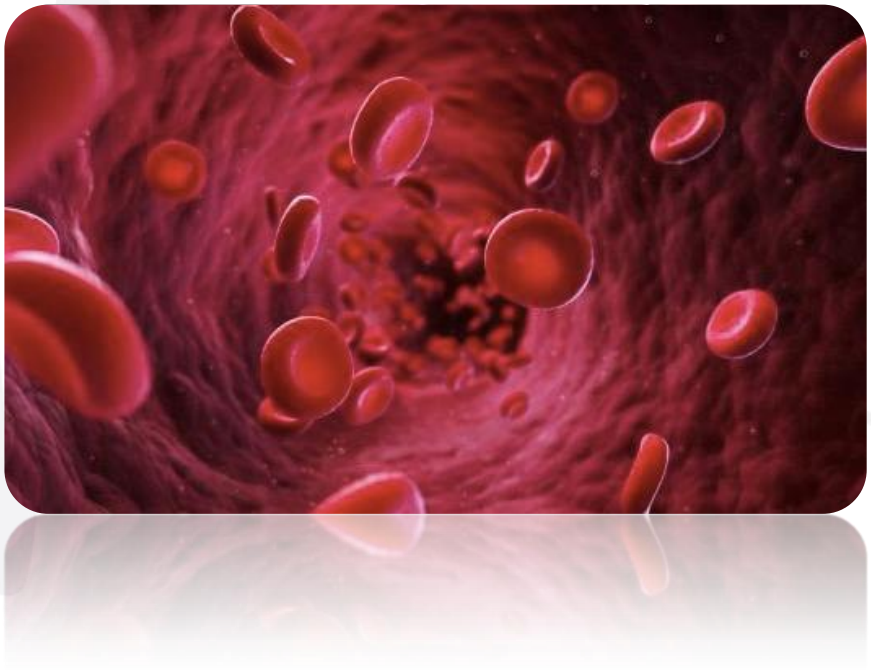
NAPOLI, 18 - 20 novembre 2016

Management delle emorragie



Management delle emorragie

- La complicanza più importante in corso di terapia anticoagulante è rappresentata dalla comparsa di eventi emorragici
- Quando il sanguinamento è grave o quando il paziente deve essere sottoposto a intervento chirurgico urgente, è necessaria la rapida **neutralizzazione** dell'attività anticoagulante.
- La ricerca ha fatto passi avanti nell'identificazione di *reversal agent* per i diversi anticoagulanti orali diretti.

Ad oggi, dabigatran è l'unico anticoagulante ad avere in commercio il proprio antidoto, idarucizumab, che antagonizza rapidamente (entro 5 min) e completamente l'effetto del farmaco.

Quali sono i pazienti più a rischio di sviluppare sanguinamenti?

Quali sono i pazienti più a rischio di sviluppare sanguinamenti?

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the **management of atrial fibrillation** of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (**EHRA**) of the ESC

Endorsed by the **European Stroke Organisation** (ESO)

HAS – BLED Score

Punteggio HAS-BLED per il rischio di sanguinamento in terapia anticoagulante orale nella fibrillazione atriale

Caratteristica	Punteggio se presente
Ipertensione (sistolica ≥ 160mmHg)	1
Alterazioni della funzione renale	1
Alterazioni della funzione epatica	1
Età ≥ 65 anni	1
Pregresso Ictus	1
Emorragia	1
Labile INR	1
Assunzione di altri farmaci	1
Assunzione di alcool	1
Score 0=1% / anno, Score 5=12.5% / anno	**Massimo 9 punti**

Da: Lip GYH, Frison L, Halperin JL, et al. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation. **J Am Coll Cardiol 2011; 57:173-80.**

ORBIT Score

– età del paziente > di 75 anni (1 punto)
– emoglobina ed ematocrito diminuiti e storia clinica di anemia (2 punti)
– emorragia (2 punti)
– insufficienza renale (eGFR < 60 mL/min/1.73 m2) (1 punto)
– assunzione antipiastrinici (1 punto)

2,4 % nel gruppo a basso rischio (score 0-2)
4,7 % nel gruppo a medio rischio (score 3)
8,1 % nel gruppo ad alto rischio (scores 4-7)

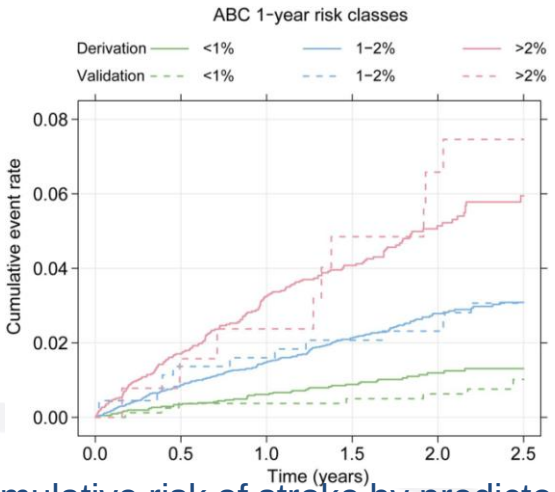
Da: The **ORBIT bleeding score**: a simple bedside score to assess bleeding risk in atrial fibrillation. O'Brien E, DaJuanicia NS et al. European Heart Journal. Sep 2015

ABC Score

A (Age)

B (Biomarker): **growth-differentiating factor-15 (GDF-15)**, a marker of oxidative stress; cardiac troponin measured with high-sensitivity assays (**cTnT-hs**), a marker of myocardial injury; **cystatin C** or estimated glomerular filtration rate (eGFR) for renal function, and **hemoglobin** or hematocrit, **NT-proBNP**, a stroke risk biomarker.

C (storia clinica)



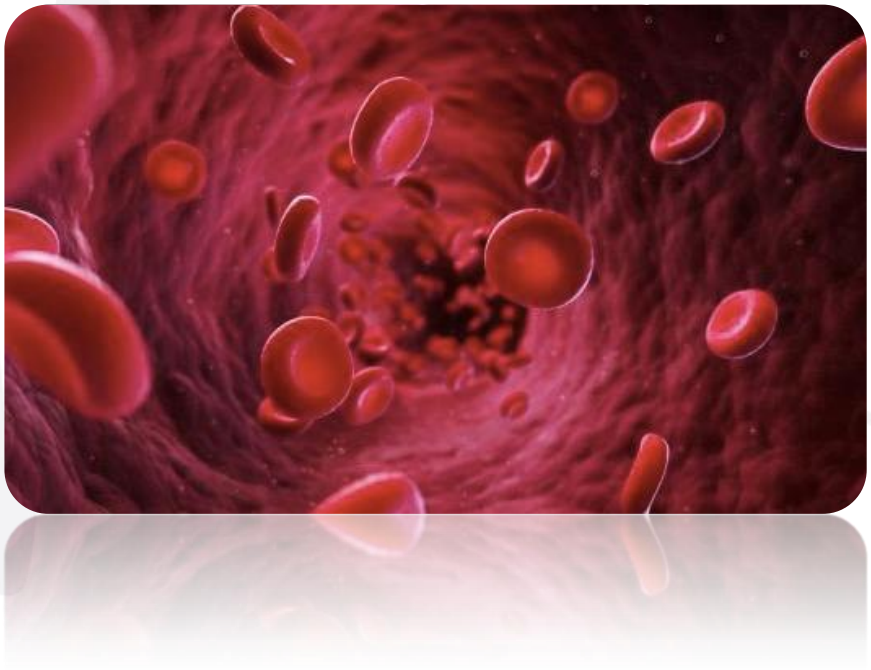
Cumulative risk of stroke by predicted 1-year ABC-stroke risk group (green <1%, blue 1–2%, and red >2%) for the derivation (solid lines, *n* = 14 701) and the external validation (dashed lines, *n* = 1400) data.

Da: Ziad Hijazi, Johan Lindbäck, et al. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. **European Heart Journal, 2016** May 21;37(20):1582-90**.**

Table 12 **Modifiable and non-modifiable risk factors for bleeding in anticoagulated patients based on bleeding risk scores**

Modifible bleeding risk factors
Hypertension (especially when systolic blood pressure is >160 mmHg)[a,b,c]
Labile INR or time in therapeutic range <60%[a] in patients on vitamin K antagonists
Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatoy drugs[a,d]
Excess alcohol (≥8 drinks/week)[a,b]
Potentially modifible bleeding risk factors
Anaemia[b,c,d]
Impaired renal function[a,b,c,d]
Impaired liver function[a,b]
Reduced platelet count or function[b]
Non-modifible bleeding risk factors
Age[e] (>65 years)[a] (≥75 years)[b,c,d]
History of major bleeding[a,b,c,d]
Previous stroke[a,b]
Dialysis-dependent kidney disease or renal transplant[a,c]
Cirrhotic liver disease[a]
Malignancy[b]
Genetic factors[b]
Biomarker-based bleeding risk factors
High-sensitivity troponin[e]
Growth differentiation factor-15[e]
Serum creatinine/estimated CrCl[e]

Quali sono gli esami di laboratorio che devono essere disponibili in urgenza per la gestione del paziente emorragico?



Esami di laboratorio

Nel setting di un sanguinamento massivo, si sente spesso la necessità di conoscere l'attività anticoagulante residua.

Indicazioni:

in caso di sovradosaggio, di sanguinamento acuto o in caso di complicanze trombotiche, oppure per la valutazione preliminare a interventi chirurgici in urgenza o per la valutazione a manovre invasive (diagnostiche o terapeutiche in urgenza)

Limiti:

richiedono una convalida, non sono universalmente disponibili e spesso hanno dei tempi di risposta che riduce la loro utilità in situazioni di emergenza

Esami di laboratorio

Tempo di trombina (TT): misura con accuratezza l'effetto anticoagulante di dabigatran, stimando direttamente l'attività della trombina (Van Ryn).

Tempo di trombina diluito (dTT): test quantitativo che ha una buona correlazione con una vasta gamma di concentrazioni del farmaco.

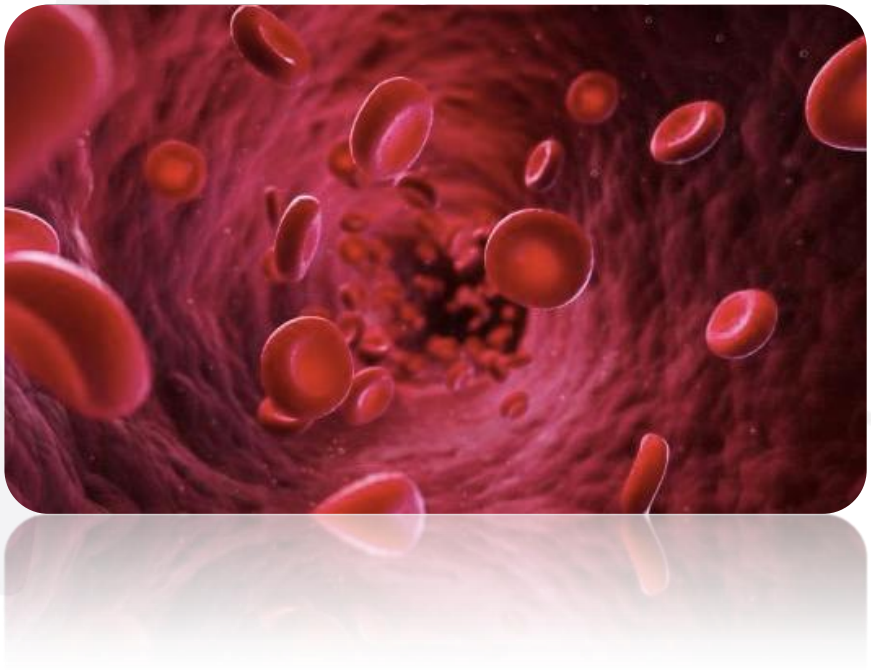
Ecarin Clotting Time (ECT): misura direttamente l'inibizione della trombina ma è un test meno specifico.

Tempo di tromboplastina parziale attivata (aPTT): valutazione qualitativa dell'attività anticoagulante di dabigatran, ma la correlazione non è lineare, specialmente in caso di sovradosaggio (van Ryn, Stangier).

Esami di laboratorio

chiedere al paziente quando ha assunto l’ultima compressa di dabigatran è spesso il metodo più pratico per valutare rapidamente l'attività anticoagulante residua (Ruff, Circulation)

Quando un’emorragia deve essere considerata un’emergenza ?



Subcommittee of Control of Anticoagulation

International Society on Thrombosis and Haemostasis, 2005

Emorragia maggiore	Emorragia life-threatening
Riduzione dell'Hb≥2 gr/dl	Emorragia fatale
Necessità di trasfusione di oltre 2 unità di emazie	Emorragia intracranica sintomatica
Sanguinamento in un sito critico (intracranico, oculare, spinale, pericardico, intra-articolare, intra-muscolare con sindrome compartimentale, retroperitoneale)	Riduzione dell'Hb≥5 gr/dl
	Necessità di trasfusione di oltre 4 unità di emazie
	Sanguinamento che richieda supporto inotropo
	Sanguinamento che richieda trattamento chirurgico urgente

Gestione dei sanguinamenti

Emivita degli anticoagulanti

Ageno W et al. Thrombosis and Haemostasis, 2016

Agent	Half – Life, hours
Warfarin	mean 40
Dabigatran	12-17
Rivaroxaban	5-13
Apixaban	12
Edoxaban	10-14

Gestione dei sanguinamenti in epoca pre-reversal agent

Management and Outcomes of Major Bleeding during Treatment with Dabigatran or Warfarin

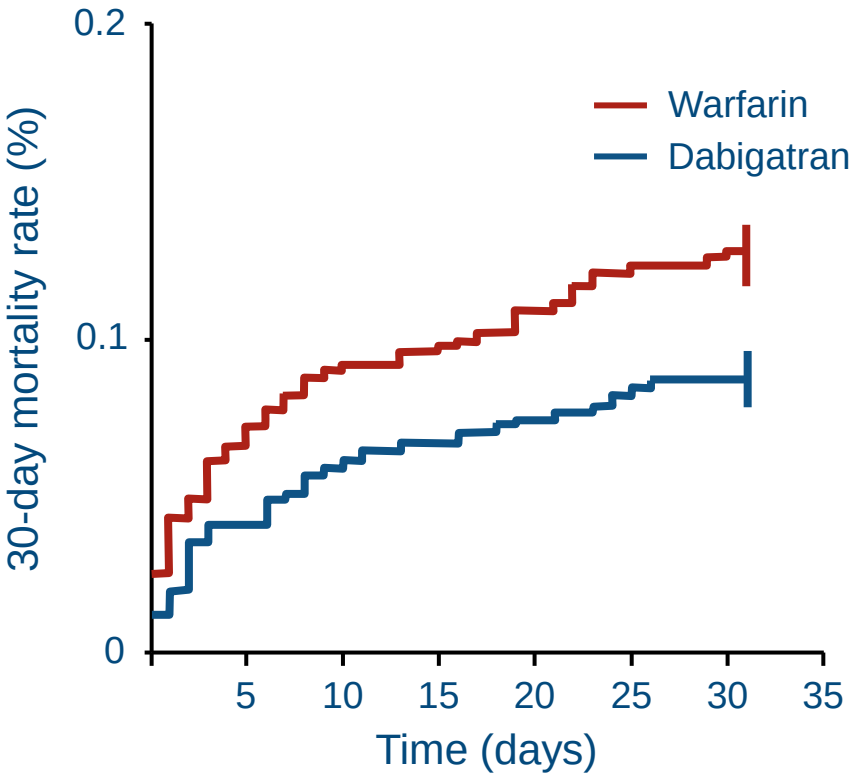
Ammar Majeed, Hun-Gyu Hwang, Stuart J. Connolly, John W. Eikelboom, Michael D. Ezekowitz, Lars Wallentin, Martina Brueckmann, Mandy Fraessdorf, Salim Yusuf and Sam Schulman. **Circulation**. 2013; september 30 2013

Table 3. Hemostatic treatment for all major bleeding events in the RE-LY trial, GEE method*

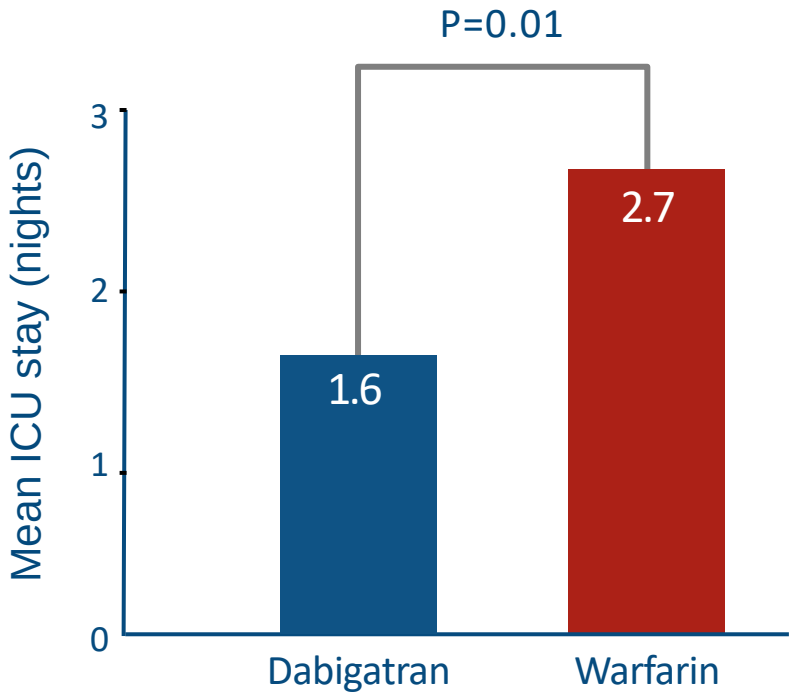
	D 110 mg	D 150 mg	Dabigatran	Warfarin	P-value D 110 vs D 150	P-value D vs Warfarin	P-value D110 vs Warfarin	P-value D 150 vs Warfarin
Fresh frozen plasma, %	18	22	20	30	0.12	<0.001	<0.001	0.01
Cryoprecipitate, %	0.7	1.0	0.9	1.4	0.65	0.36	0.30	0.55
Platelets, %	3.2	3.7	3.5	5.0	0.69	0.17	0.17	0.31
Vitamin K, %	9.1	11	10.2	26	0.34	<0.001	<0.001	<0.001
Prothrombin complex concentrate, %	0.7	0.4	0.6	1.0	0.52	0.36	0.64	0.25
Recombinant factor VIIa, %	0.2	1.4	0.9	0.6	0.05	0.96	0.39	0.21
Coagulation factor replacement, %	0.2	0.6	0.4	1.0	0.39	0.21	0.13	0.47

*The generalized estimating equation for estimation of the parameters of a generalized linear model with a possible unknown correlation between outcomes. Includes events on treatment and up to 3 days after last dose.

Trend for reduced risk for death with dabigatran vs warfarin during 30 days after a major bleeding event (P=0.052)*



Shorter ICU stay after a major bleed with dabigatran vs warfarin in RE-LY®



For RE-LY® population alone, significant RRR of 44% in mortality rate was evident at 30 days

*Only first major bleed included; analysis not adjusted for covariates. Combined data for dabigatran 150 mg and 110 mg BID treatment groups from five Phase III trial populations with SPAF and DVT/PE; ICU, intensive care unit

Majeed A et al. Circulation 2013;128:2325–32

Gestione dei sanguinamenti in epoca pre-reversal agent

Periprocedural Bleeding and Thromboembolic Events With Dabigatran Compared With Warfarin

Results From the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Randomized Trial

Jeff S. Healey, John Eikelboom et al.

Circulation. 2012;126:343-348

RE-LY® demonstrated no significant difference in major bleeding with dabigatran vs warfarin for urgent and elective procedures

	% patients (n/N)			D150 vs warfarin		D110 vs warfarin	
	D150	**D110**	**Warfarin**	**RR (95% CI)**	**P value**	**RR (95% CI)**	**P value**
Urgent surgery	**17.7** (25/141)	**17.8** (19/107)	**21.6** (24/111)	0.82 (0.50–1.35)	0.43	0.82 (0.48–1.41)	0.47
% of total surgeries	9.2	7.2	7.1				
Elective surgery	**3.8** (53/1405)	**2.8** (38/1380)	**3.3** (48/1447)	1.14 (0.77–1.67)	0.51	0.83 (0.55–1.26)	0.38
% of total surgeries	90.1	92.8	92.9				
P (interaction)					0.31		0.90

In RE-LY®, major bleeding was 5–6 times more common after urgent vs elective surgery (P<0.001) regardless of the OAC used

In RE-LY®, 4591/12 091 patients underwent at least one invasive procedure. Surgeries were classified as urgent according to the judgment of the local investigator

Healey JS et al. Circulation 2012;126:343–48

What to do if there is a (suspected) overdose *without* bleeding, or a clotting test is indicating a risk of bleeding?

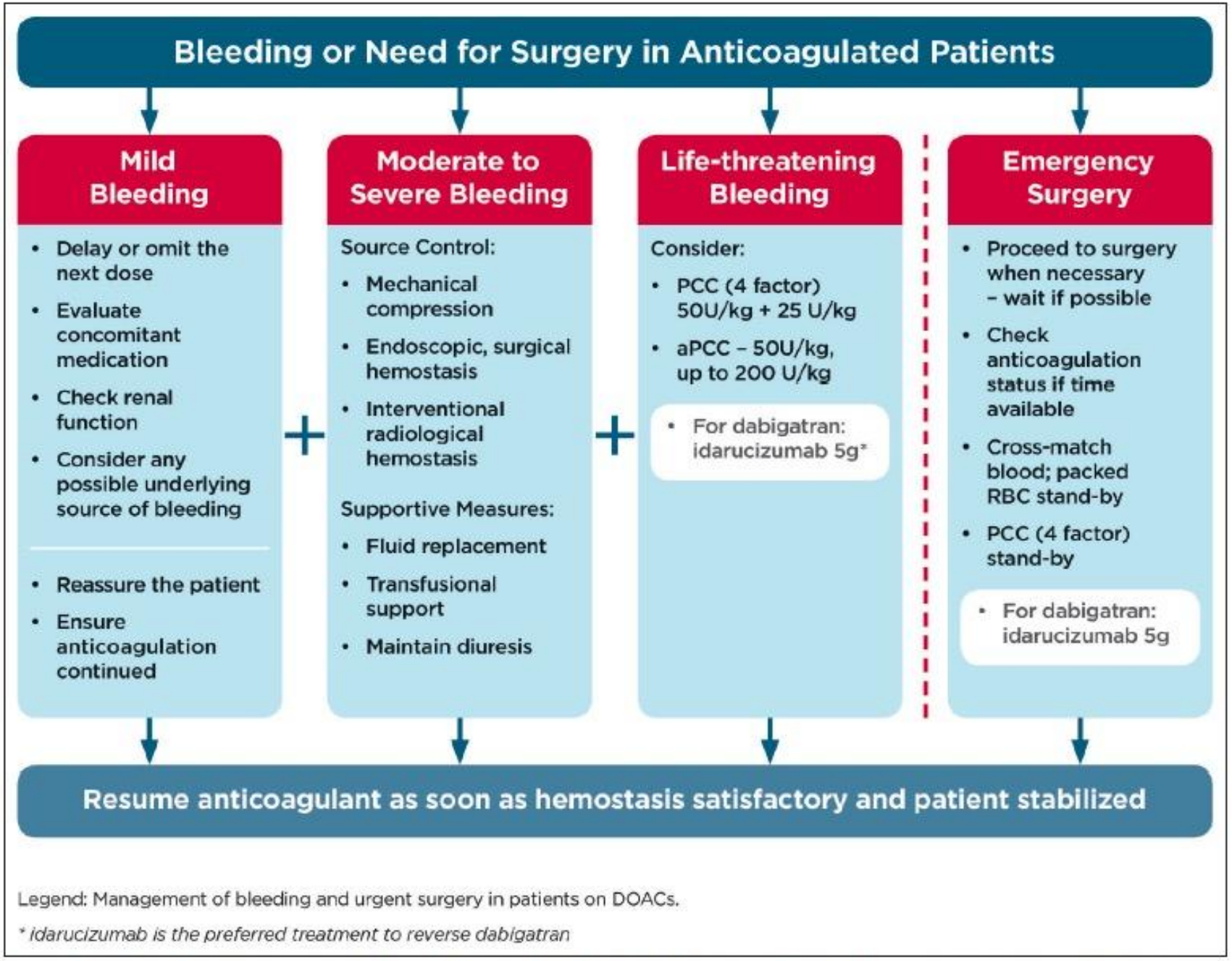
1. Quando un paziente assume volontariamente una dose maggiore

1. Quando intercorrono altri eventi (interazioni DRUG-DRUG o insufficienza renale)

Se NON c'è EMORRAGIA:

carbone attivato 30-50 gr in totale se l'ingestione è recente

WAIT and SEE!

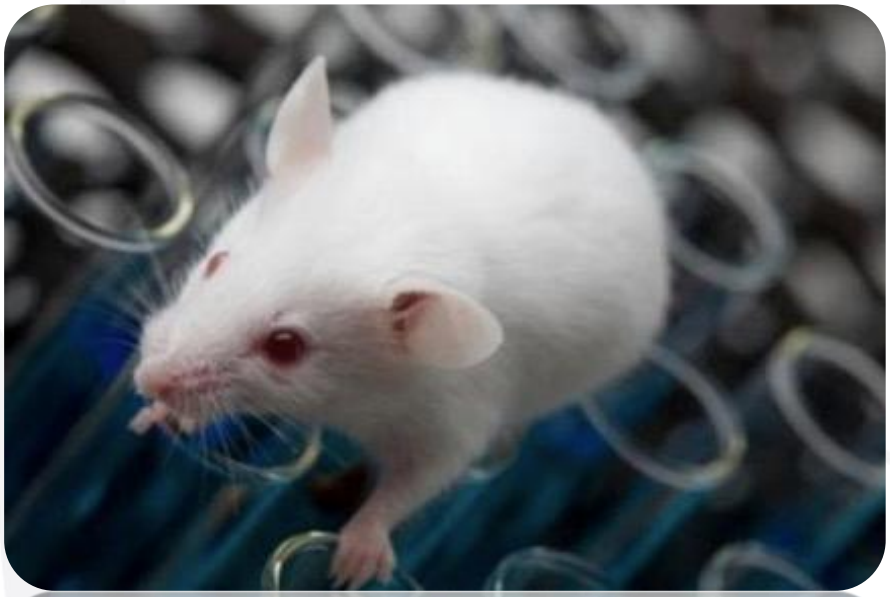


Legend: Management of bleeding and urgent surgery in patients on DOACs.

** idarucizumab is the preferred treatment to reverse dabigatran*

Figure 1: An algorithm for management of patients treated with a DOAC who present with mild, moderate to severe, or life-threatening bleeding or who require emergency surgery. DOAC, direct oral anticoagulant.

Reverse di Dabigatran : Idarucizumab



Idarucizumab (Humanized Fab fragment)

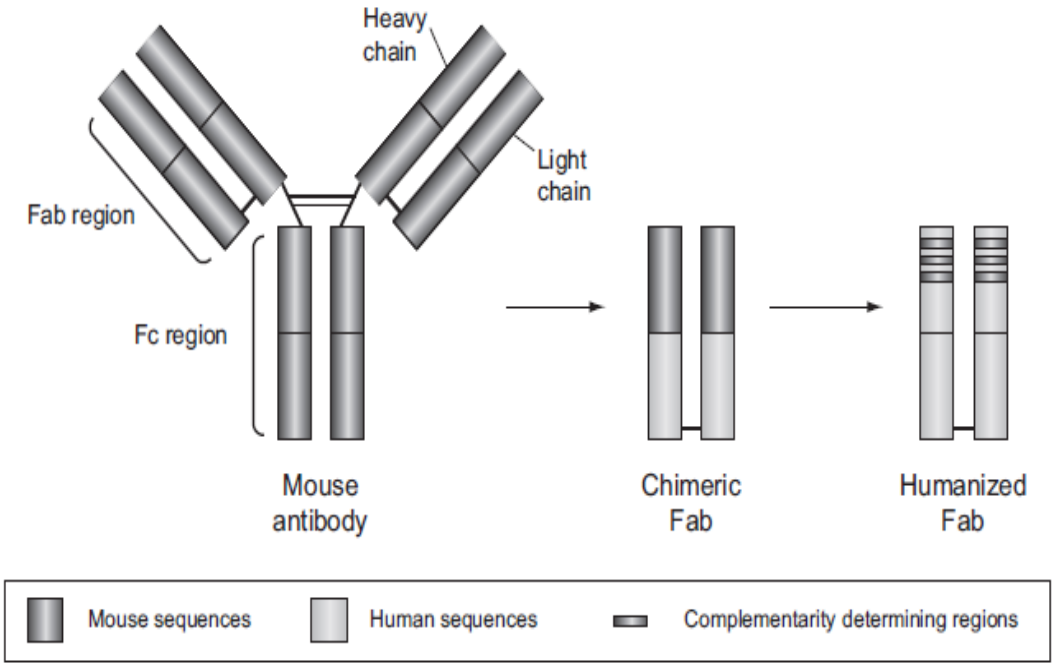


Figure 1. Development of idarucizumab. The fragment antigen-binding (Fab) region is composed of a light and heavy chain and contains the part of the antibody that binds to dabigatran. It also contains a constant region, which, when murine sequences are replaced with human ones, is called a chimeric Fab. The fragment constant (Fc) region interacts directly with the immune system; however, such non-specific binding is avoided by removal of the Fc region.

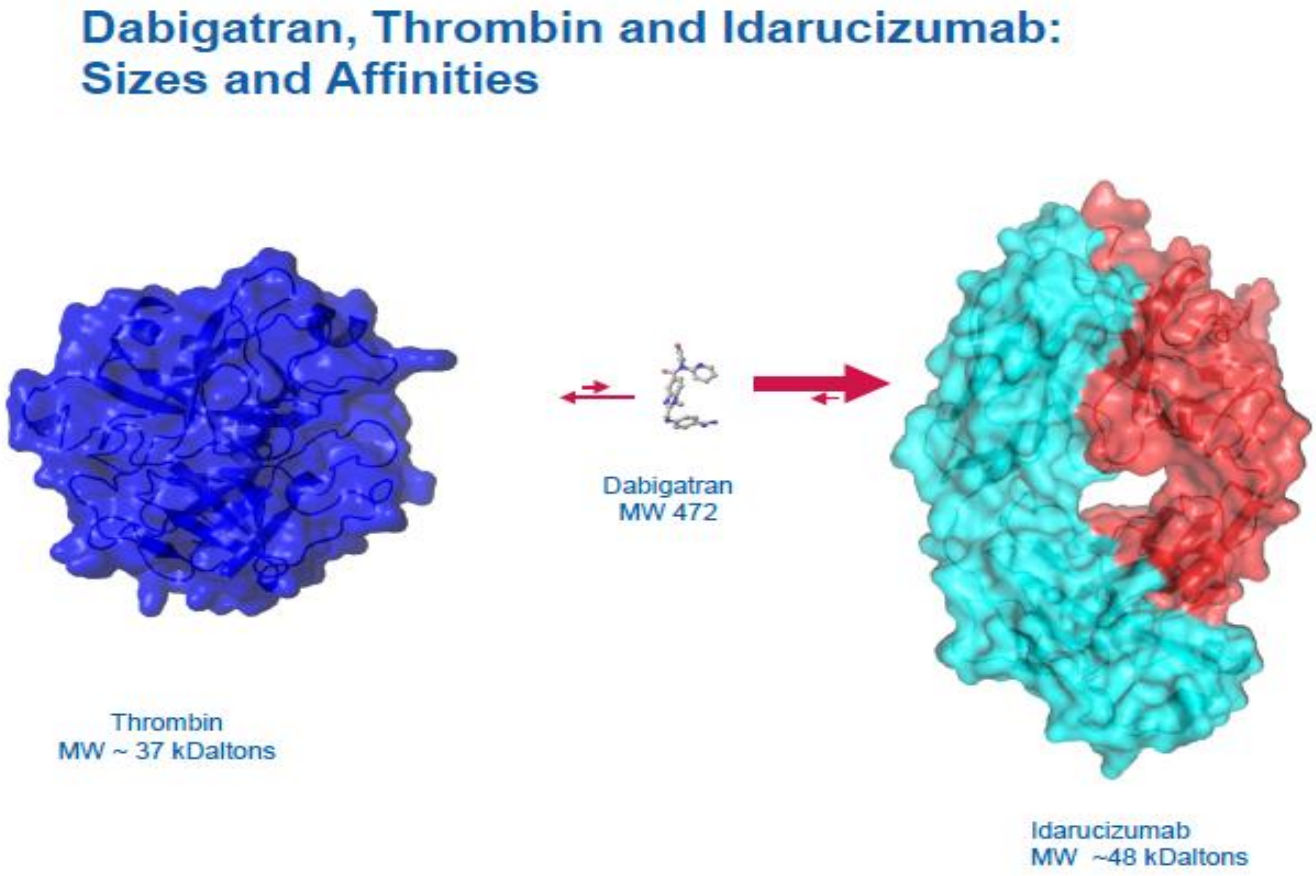
Immunization of mice with dabigatran derived aptens coupled to carrier proteins

Isolation of Antigen Binding Fragment (FAB) from Monoclonal Antibodies exhibiting the highest affinity for dabigatran

Murine protein sequences were replaced with human sequences

The use of humanized Fab instead of an intact antibody results in a shorter half-life and a reduced potential for immunologic reactions

Idarucizumab is a FAB fragment antibody that binds dabigatran with a 300 – fold higher affinity than dabigatran binds to thrombin



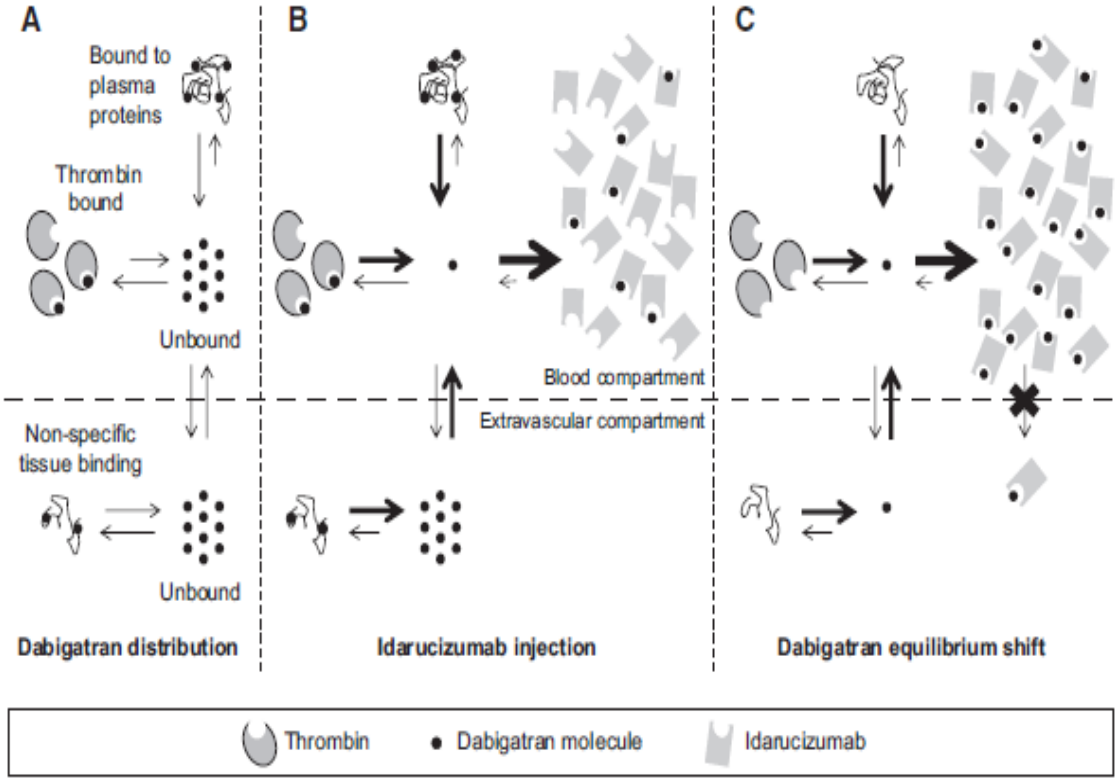
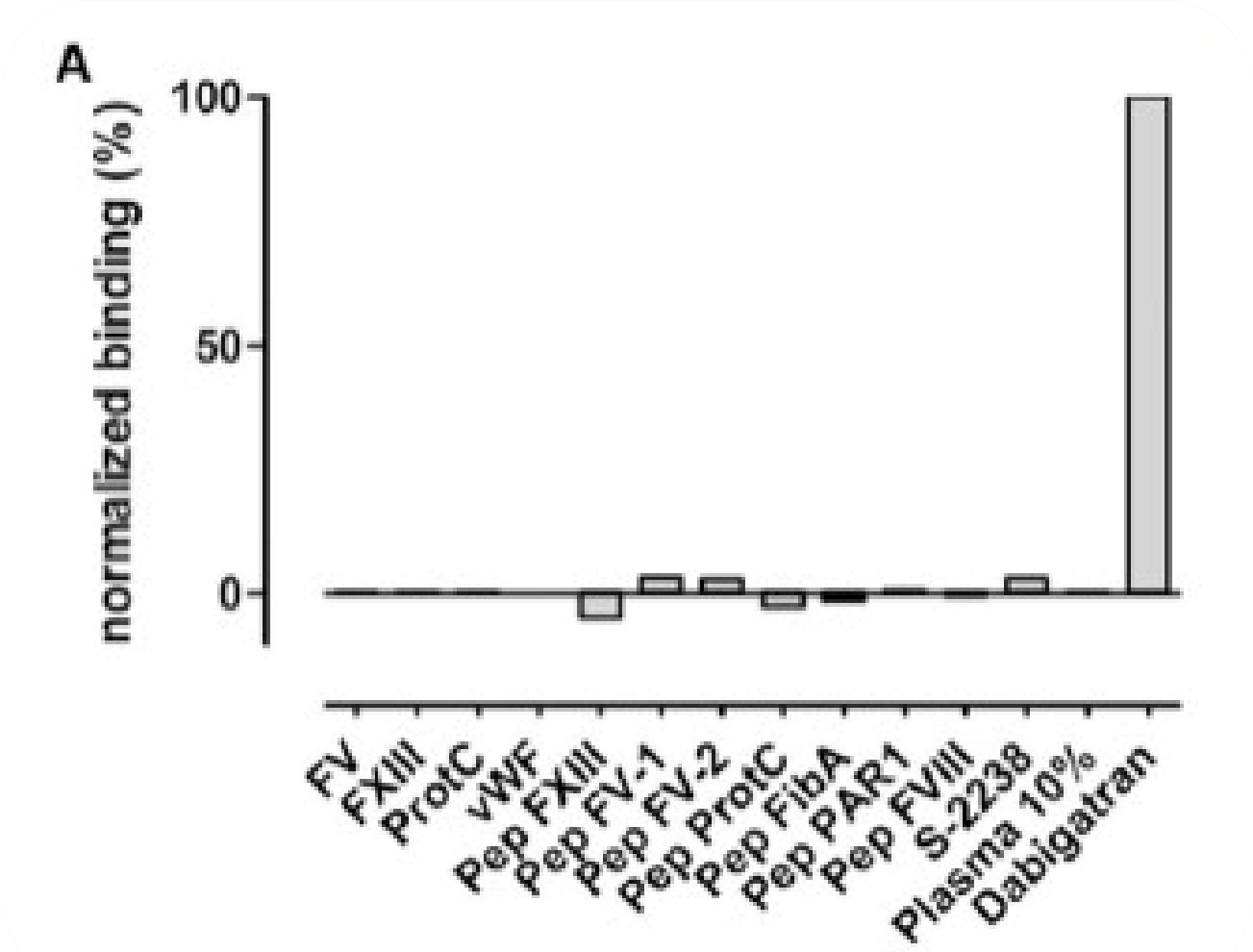


Figure 3. Changes in the distribution of dabigatran after idarucizumab administration. **A**, Circulating dabigatran exists in a state of equilibrium between the plasma and the extravascular compartments. Only unbound dabigatran in the plasma is able to bind thrombin and to inhibit coagulation. **B**, Idarucizumab rapidly binds dabigatran in the plasma. This alters the equilibrium, causing dabigatran in the extravascular compartment to move into the plasma and to potentially dissociate from thrombin (larger arrows). **C**, Because of the high affinity of idarucizumab for dabigatran, thrombin is no longer inhibited, and it regains its capacity to trigger clotting.

Schiele F, Blood 2013



Idarucizumab (Humanized Fab fragment)

- Idarucizumab is eliminated mainly renally
- Idarucizumab clearance is attenuated in patients with renal impairment, resulting in increased plasma concentrations of idarucizumab
- However, because patients with renal impairment often have elevated dabigatran plasma concentrations, the higher idarucizumab exposure may be advantageous

Idarucizumab sviluppo clinico

Idarucizumab for Dabigatran Reversal

Pollack CV, Reilly PA et al. **N Eng J Med**. August 6, 2015. 511-520.

American Heart Association. life is why™

SCIENTIFIC SESSIONS 2016

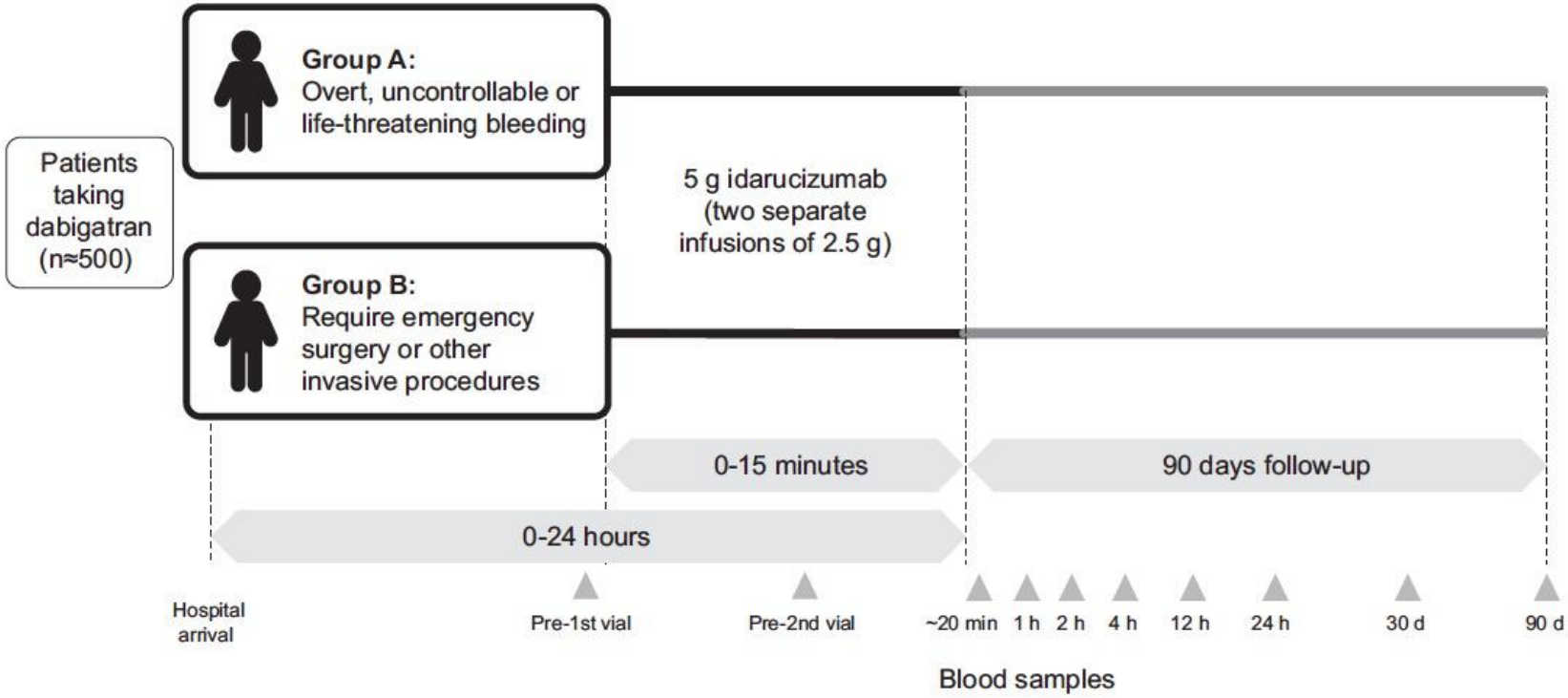
New Orleans, Louisiana | Nov 12–16

Idarucizumab For Dabigatran Reversal: Updated Results Of The Re-verse Ad Study

Charles V Pollack, Thomas Jefferson et al. AHA Congress, New Orleans, Louisiana **Nov 12-16 2016**

494 patients enrolled; 60% in Group A and 40% in Group B.
Efficacy and safety were reported in patients with intracranial bleeding, with gastrointestinal bleeding, with traumatic injuries, and those requiring urgent procedures.

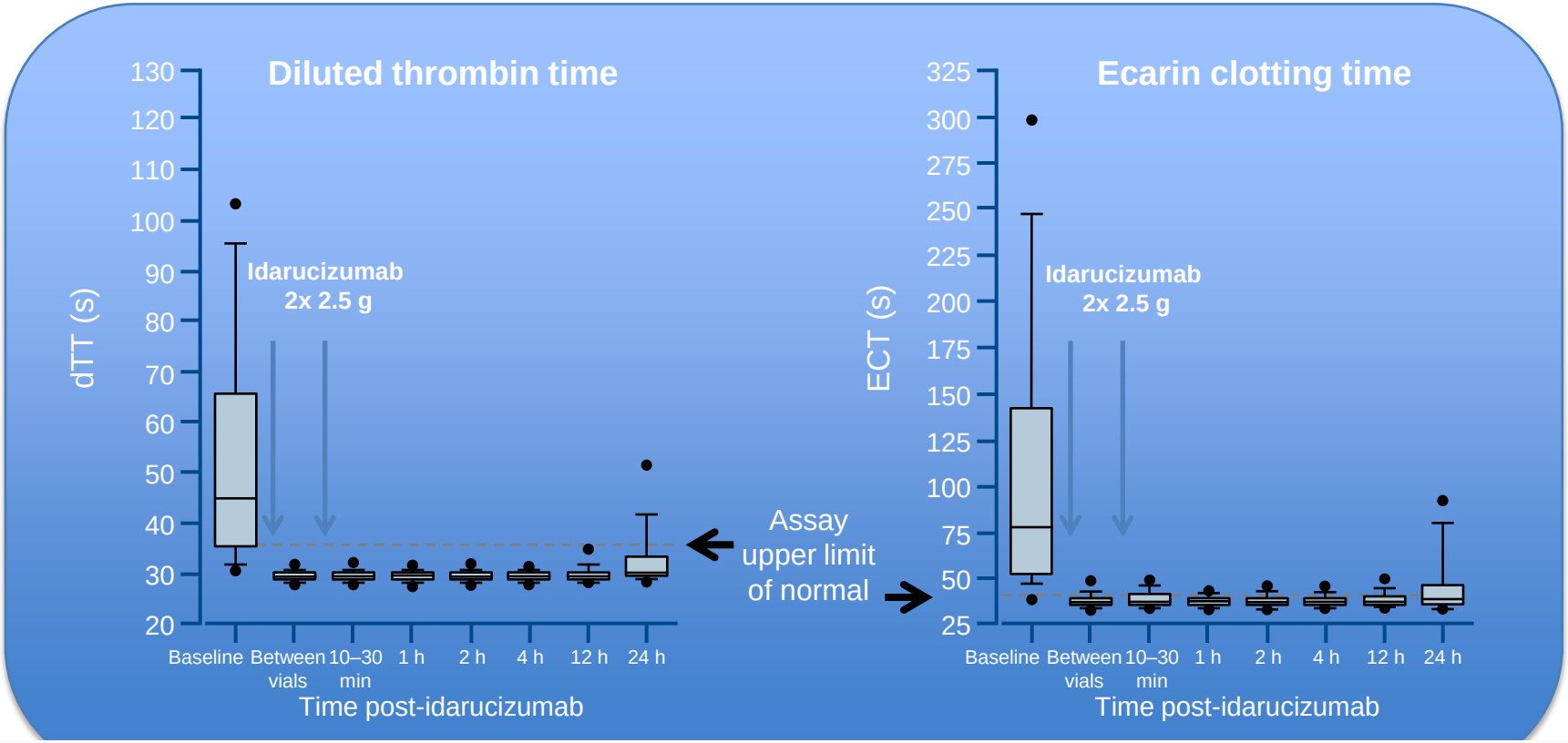
Consistent with initial results, **idarucizumab rapidly normalized the dTT and ECT** with sustained reversal in the majority of patients.
Cases of recurrent bleeding, repeat doses of idarucizumab, post-reversal thrombotic events, other safety outcomes, and 3 month follow-up will be reported.



Primary Endpoint: Maximum % reversal of the anticoagulant effect of dabigatran within 4 hours, based on central laboratory determination of the dTT or ECT

% reversal = [pre-dose test result (seconds) - minimum post-dose test results (seconds)] / [pre-dose test result (seconds) - upper limit of normal] x 100

Patients with uncontrolled bleeding (Group A)



(51 patients) Median maximum reversal within 4 hours was 100% (95% CI: 100–100)

dTT normalized in 98% and ECT in 89% of patients with elevated values at baseline*

Pazienti che necessitano di intervento chirurgico urgente

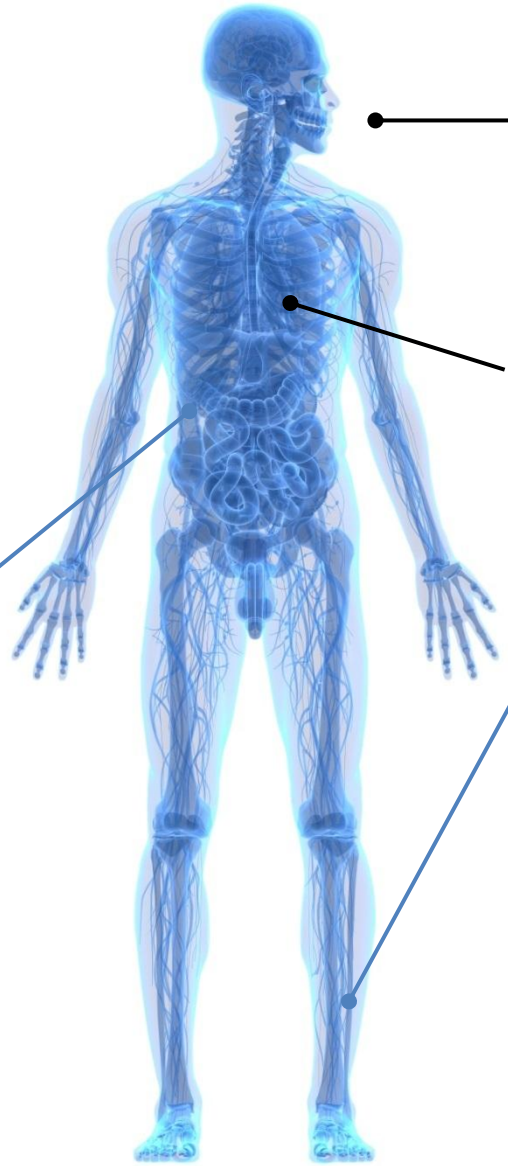
24 agosto 2016, incidente stradale su via Appia, Roma.

Motivo dell'accesso in Pronto Soccorso

Uomo di 54 anni, Signor GC, accede in PS con **codice ROSSO, politrauma della strada, alle ore 10.28**

Anamnesi:
Ipertensione
Precedente attacco ischemico transitorio
Fibrillazione atriale
Iperplasia prostatica benigna

Patient presentation



BP: 193/101 mmHg
Pulse: 105 bpm
Cute pallida.
Tachipnoico

EO del torace: dolore durante l'inspirazione profonda, rumori respiratori normali su tutto l'ambito polmonare.

EO dell'addome: trattabile, non dolorabile

Frattura esposta della tibia sinistra

Terapia

assume DABIGATRAN 150 mg *bis in die* per la FIBRILLAZIONE ATRIALE
e VALSARTAN per l'ipertensione + STATINE

Il paziente aveva assunto tutta la terapia 2 ore e 30 min prima dell'incidente

Esami ematochimici

	Ingresso in PS
Emoglobina (gr/dl)	14,8
WGC uL	6.002
PLTuL	231000
Crea mg/dl	1,02
azotemia mg/dl	27
sodio mEq/l	146
potassio mEq/l	5,1
cloro mEq/l	105
GOTU/L	48
GPTU/L	35
G-G U/LT	65
Bilir C mg/dL	0,6
uric mg/dl	15
LDH U/L	611
CPK U/L	650
Mio U/L	750
Troponina ug/L	0,00
D-dimero ug/L	0,7
aPTT(sec)	56

esami strumentali

TC TORACE – ADDOME: fratture costali multiple a sinistra, non versamento pleurico, non versamento addominale

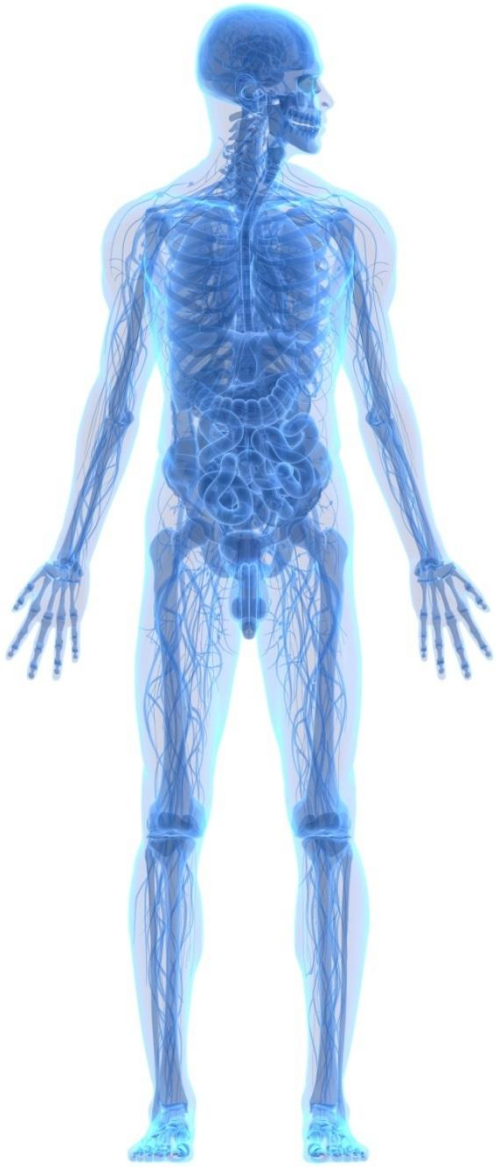
RX ARTI INFERIORI: frattura scomposta della tibia di sinistra

Consulenza ortopedica

“Frattura scomposta ed esposta della tibia che necessita di intervento chirurgico di stabilizzazione”

Rivalutazione clinica, ore 11.30

BP: 80/50 mmHg
Pulse: 130 bpm
Cute pallida.
Tachipnoico,
lievemente confuso



Somministrazione di IDARUCIZUMAB

Inizio intervento di Osteosintesi: l'ortopedico nota una emostasi normale

Idarucizumab given

Normal HAEMOSTASIS

Admission

1h 10m

1h 17m

11:38

12:55

10:28

12:06 (immediately after infusion)

23:36 (12h after infusion)

11:13 (24h after infusion)

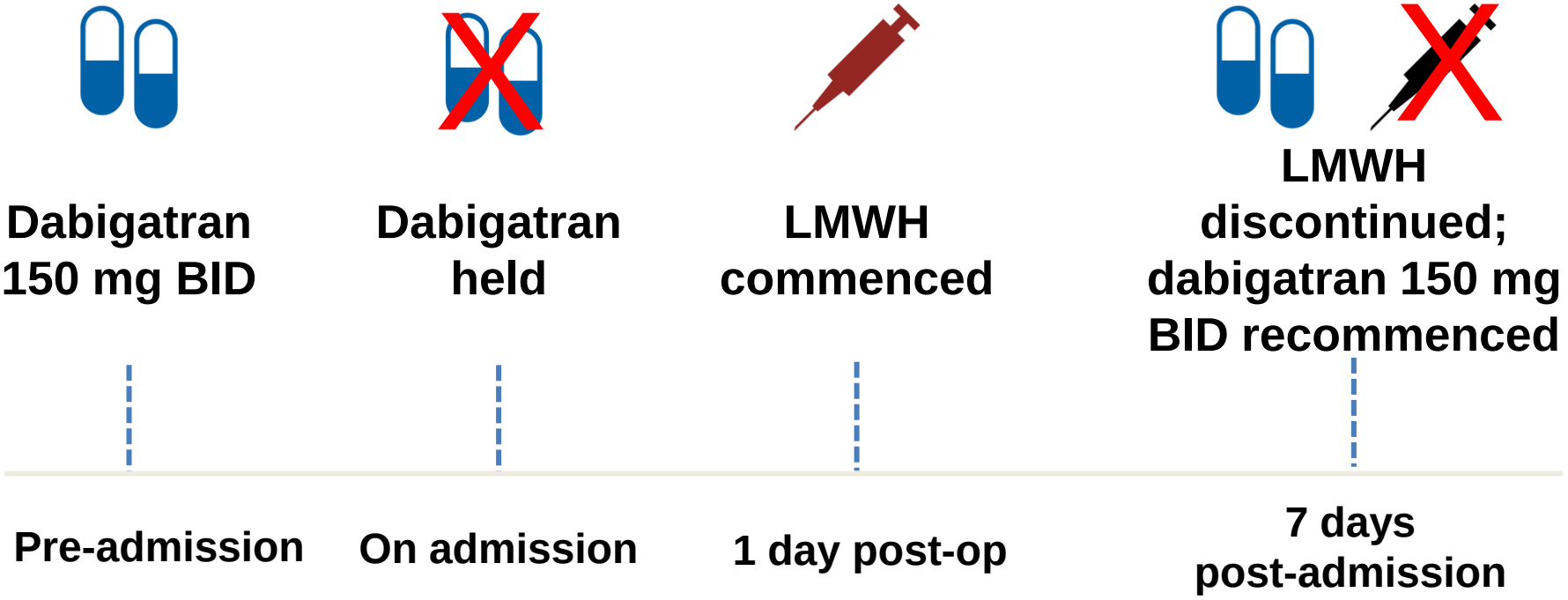
Test	Result
Hb (g/dL)	14,8
aPTT (s)	51.3
CrCl (mL/min)	85

Result
–
29.4
–

Result
–
29.7
–

Result
11,5
–
–

Scelta per il paziente GC



- LMWH, low-molecular-weight heparin

Chi dovrebbe ricevere un reversal agent?

Emergency event

Confirm dabigatran presence: i.e. patient records, relatives, prescriptions
If possible, determine degree of anticoagulation i.e. verify time of last dose, measure aPTT and/or TT [dTT]

Mild to moderate bleeding

Uncontrolled or life-threatening bleeding

Requirement for urgent surgery or invasive procedure in next 8 hours

Administer idarucizumab* 5 g

Institute local bleeding management protocol

Proceed immediately to surgery or invasive procedure

If time permits, measure aPTT and/or TT [dTT]

Reintroduce anticoagulation appropriately after event, depending on patients thrombotic/bleeding risk

International Journal of Stroke WSO

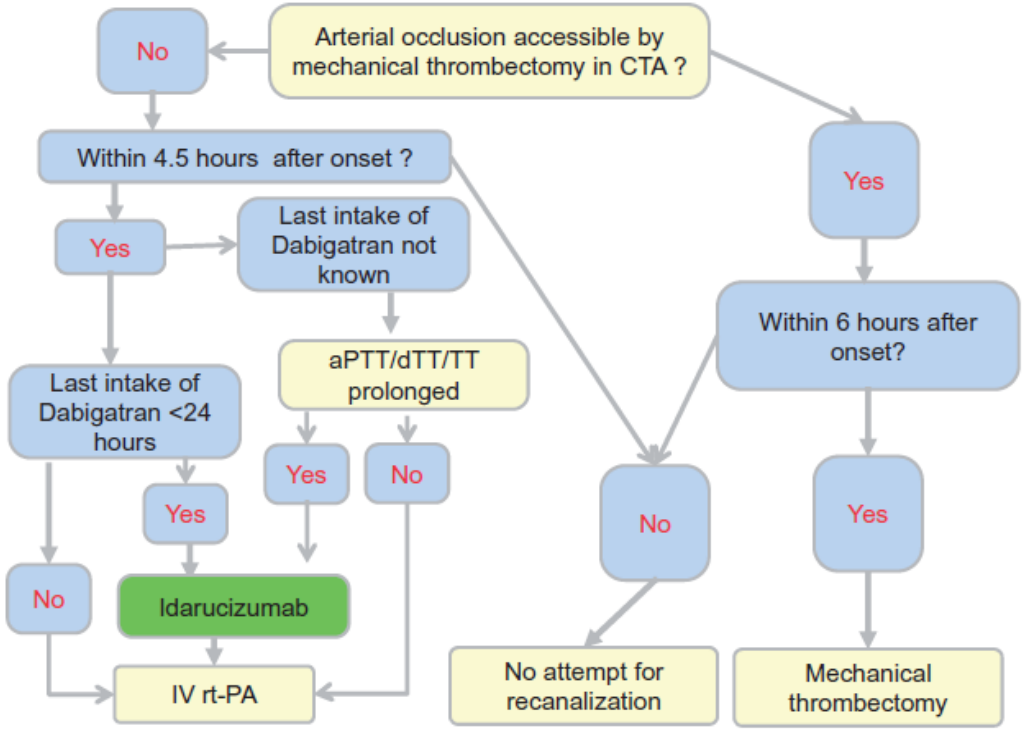
Thrombolysis and thrombectomy in patients treated with dabigatran with acute ischemic stroke: Expert opinion

International Journal of Stroke
0(0) 1–4

DOI: 10.1177/1747493016669849
wso.sagepub.com
SAGE

HC Diener[1], R Bernstein[2,3], K Butcher[4], B Campbell[5], G Cloud[6], A Davalos[7], S Davis[8], JM Ferro[9], M Grond[10], D Krieger[11,12], G Ntaios[13], A Slowik[14] and E Touzé[15]

Figure 1. Flow diagram for thrombolysis or thrombectomy inpatients treated with Dabigatran



aPPT, activated partial thromboplastin time; CTA, computerized tomography angiography; dTT, diluted thrombin time; IV, intravenous; rt-PA, recombinant tissue plasminogen activator

Take Home Message

- La sicurezza del paziente deve essere la priorità quando si introduce un nuovo anticoagulante.
- L’arrivo dei reverse dei NAO può aumentare la confidenza, facilitando la gestione delle emorragie pericolose per la vita.
- L'uso dei reverse non potrà mai prescindere dalle altre misure di supporto.

Grazie
per l’attenzione