SIMPOSIO SATELLITE BOEHRINGER

Il sanguinamento maggiore tra definizioni, gestione dell'urgenza ed outcome clinico del paziente

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Emorragia Maggiore

1) Emorragia fatale

2) Sanguinamenti sintomatici in una delle seguenti sedi critiche:
- -emorragie intracraniche
- -ematoma spinale
- -ematoma intraoculare
- -ematoma retroperitoneale
- -emartro
- -emopericardio
- -emorragia intramuscolare con sindrome compartimentale

3) Emorragie con perdita acuta di ≥2 g/dl di Hb
o necessità trasfusione ≥2 Unità di GRC

4) Sanguinamento richiedente supporto inotropo
Sanguinamento richiedente trattamento chirurgico urgente

2005 Definition of major bleeding in clinical investigations. J Thromb Haemost 3(4) 692-4

Guidelines for reversal of anticoagulants

New Guidelines for Reversal Anticoagulants in Intraparenchymal Hemorrhage

-Warfarin
-Heparin
-Fondaparinux
-Bivaluridin
-DOACs

Anticoagulation Education Task Force White Paper

Managing reversal of direct oral anticoagulants in emergency situations

Anticoagulation Education Task Force White Paper

Walter Ageno[1]; Harry R. Büller[2]; Anna Falanga[3]; Werner Hacke[4]; Jeroen Hendriks[5,6]; Trudie Lobban[7]; Jose Merino[8]; Ivan S. Milojevic[9]; Francisco Moya[10]; H. Bart van der Worp[11]; Gary Randall[12]; Konstantinos Tsioufis[13]; Peter Verhamme[14]; A. John Camm[15,16]

[1]University of Insubria, Varese, Italy; [2]Academic Medical Centre, Amsterdam, The Netherlands; [3]Department of Immunohematology & Transfusion Medicine and the Hemostasis and Thrombosis Center, Hospital Papa Giovanni XXIII, Bergamo, Italy; [4]Department of Neurology, Heidelberg University, Heidelberg, Germany; [5]Centre for Heart Rhythm Disorders, University of Adelaide, Royal Adelaide Hospital, South Australian Health & Medical Research Institute, Adelaide, Australia; [6]Department of Medical and Health Sciences, Linköping University, Linköping, Sweden; [7]Arrhythmia Alliance and AF Association, Hampshire, UK; [8]Arrhythmia Research Unit, Universitario La Paz , Madrid, Spain; [9]General Hospital Cuprija, Cuprija, Serbia; [10]International Medical Services and Emergency Medicine, Vithas-Xanit International Hospital, Benalmadena, Malaga, Spain; [11]Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands; [12]Stroke Alliance For Europe (SAFE), London, UK; [13]First Cardiology Clinic, Hippokration Hospital, University of Athens, Greece; [14]University of Leuven, Leuven, Belgium; [15]Division of Cardiovascular Sciences, St George's University of London, London, UK; [16]ICMS, Imperial College, London, UK

Thrombosis and Haemostasis, 2016

Quando :

Osservare
Monitorare
Ricoagulare
Trasfondere

…PS

…Sala

Giovanni di Paolo di Grazia
(Siena, 1398-1482)
Detail of the Beheading of St. John the Baptist,
The Art Institute of Chicago.

-Endoscopia digestiva
-AngioTC per diagnosticare
-Radiologo interventista per trattare

Topic of Today

Giovanni di Paolo di Grazia
(Siena, 1398-1482)
Detail of the Beheading of St. John the Baptist,
The Art Institute of Chicago.

Approach to bleeding disorders

- **Identify and correct any specific defect of hemostasis**

  Screening tests (PT,PTT, platelet count) will often allow placement into one of the broad categories of cause of bleeding
  Specialized testing is usually necessary to establish a specific diagnosis

- **Consider compression of the site of bleeding**
- **Use non-transfusional drugs whenever possible**
- **RBC pack for surgical procedures or large blood loss**
- **Search for major bleeding**

di Grazia

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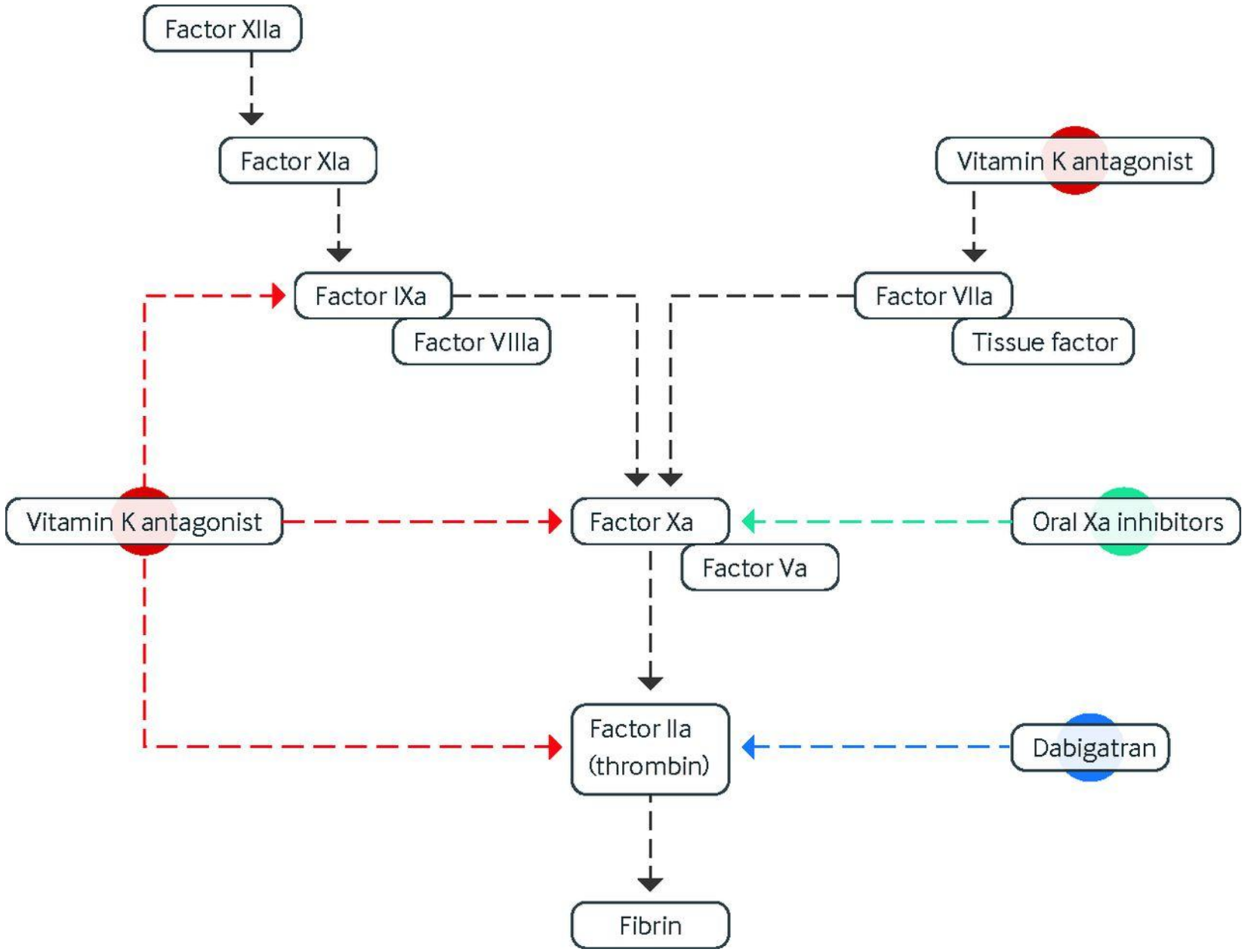
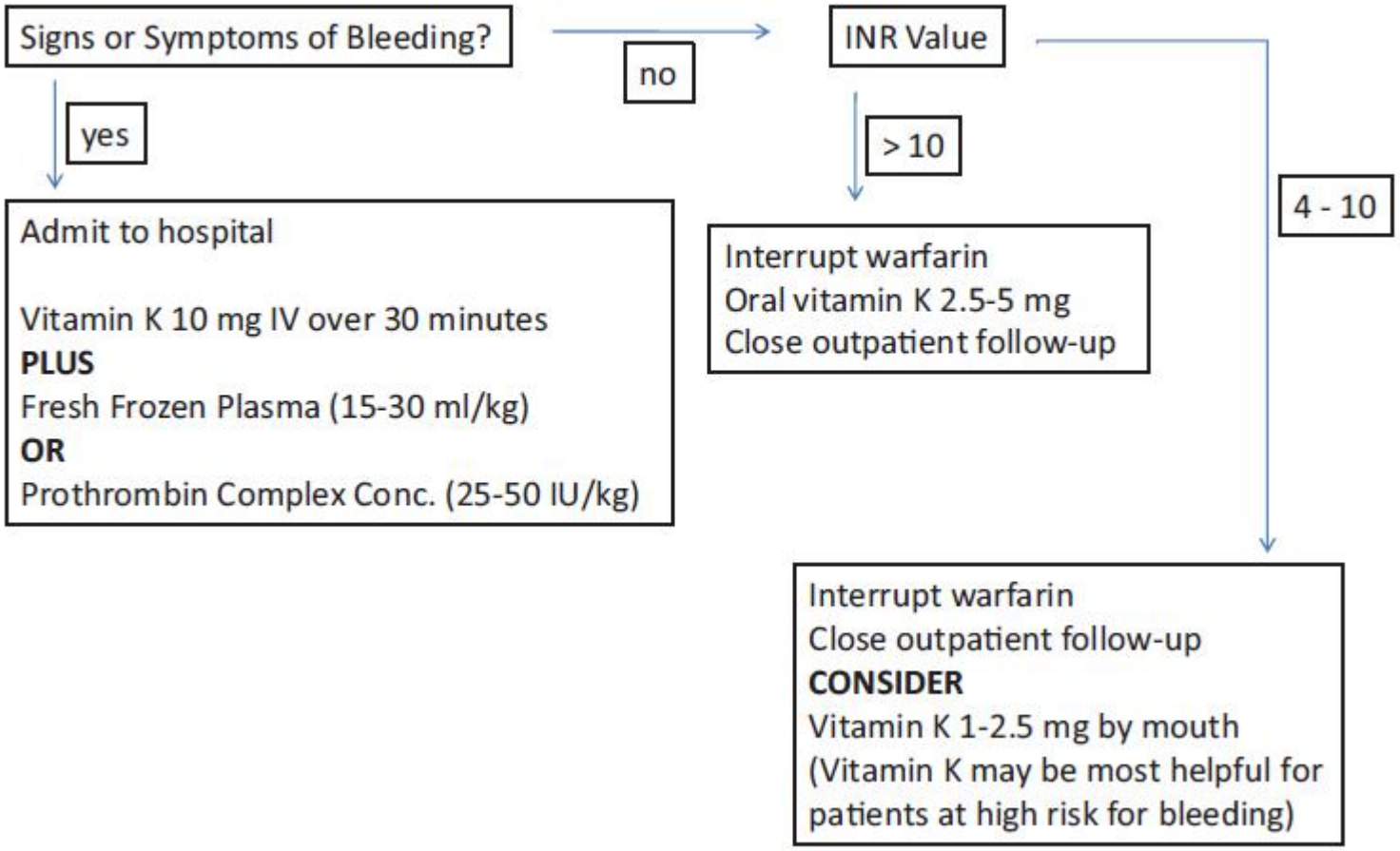
Quando il “Reversal Management”
E quando il singolo Reversal Agent?

Topic

Coaugulation cascade



Management of a warfarin-treated patient whose INR exceeds 4. A suggested algorithm



Garcia DA, Crowther MA. Circulation 2012; 125:2944-2947.

Product for bleeding management of a warfarin-treated patient

Product	Time to Effect (After Administration)	Duration of Effect	Evidence of Efficacy for Warfarin Revesal	Risk of Thrombosis
Oral vitamin K	24 h	Days	++++	NS
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Fresh frozen plasma	Immediate	12–24 h	++	NS
PCC	Immediate	12–24 h	+++	+ (Higher with activated PCC)
Recombinant factor VIIa	Immediate	2–6 h	+	++

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Guidelines for reversal of anticoagulants

NAMES		STRATEGIES TO REVERSE OR MINIMIZE DRUG EFFECT
Warfarin *(Coumadin)*		

INR	CLINICAL SCENARIO	MANAGEMENT
< 4.5	No bleeding	• Hold warfarin until INR in therapeutic range
	Rapid reversal required	• Hold warfarin • Consider vitamin K 2.5mg oral
4.5-10	No bleeding	• Hold warfarin until INR in therapeutic range • Consider vitamin K 2.5mg oral
	Rapid reversal required	• Hold warfarin • Give vitamin K 2.5mg oral or 1mg IV infusion *(IV administration of vitamin K has faster onset of action)*
>10	No bleeding	• Hold warfarin until INR in therapeutic range • Give vitamin K 2.5mg oral or 1-2mg IV infusion over 30 minutes, and repeat q24h as needed *(IV administration of vitamin K has faster onset of action)*
	Rapid reversal required	• Hold warfarin • Give vitamin K 1-2mg IV infusion over 30 minutes, and repeat q6-24h as needed
Any INR	Serious or life-threatening bleeding	• Hold warfarin • Give vitamin K 10mg IV infusion over 30 minutes • Give 4 units FFP/plasma • *OR consider 4-factor PCC (Kcentra)* *(preferred for life-threatening bleeding)* *INR 1.5 – 3.9: 25 units/kg (maximum 2500 units)* *INR 4.0 – 6.0: 35 units/kg (maximum 3500 units)* *INR > 6.0: 50 units/kg (maximum 5000 units)*

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Reverse dell'anticoagulazione da VKA

Trattamenti SPECIFICI da adottare in caso di emorragia maggiore a rischio di vita o perdita di organo/funzione in corso di Warfarin

- Sospendere la TAO in corso
- Determinare INR
- Somministrare Vit.K (10mg/100 SF lentamente) efficacia max in 24h
- Concentrati di complesso protrombinico

se INR <2	20 U/Kg
se INR 2-4	30 U/Kg
se INR >4	40 U/Kg
se **INR >6**	**50 U/Kg**

Controllare INR dopo 15' dall'infusione e se >1,5 ripetere lo schema di terapia partendo dal valore di INR per ripetere lo schema

- Infondere Plasma (15 mL/Kg)
- Trasfusione di piastrine se < 60000

LG

FCSA 2014

Caso clinico 5

Caso clinico 5

Il TIRRENO

Cade dal palco durante lo spettacolo, muore attrice

Stava recitando quando ha fatto un volo di tre metri: la commedia è stata sospesa e la donna trasportata in ospedale, dove è deceduta

SPETTACOLI INCIDENTI

23 luglio 2017

Caso clinico 5

ore 22.30 sabato:
Femmina di 57 anni
Codice di accesso in PS: ROSSO

Motivo: trauma cranico grave GCS 7

Parametri d'ingresso:
PA 100/60 mmHg, FC 105 bpm, ritmico, Sat.O2 99% in FiO2 21%

Paziente caduta dal palco teatrale (meno di 2 metri)
con trauma cranico e toraco addominale

APR: ipertensione arteriosa, pregressa embolia polmonare
TD: Bisoprololo 2,5 mg cpx2, Coumadin

MONTIGNOSO. Un malore, oppure un capogiro, le ha fatto perdere l'equilibri e l'ha fatta precipitare giù dal balconcino del palco dove stava recitando insieme ai suoi amici del Gruppo folcloristico Montignoso. Lorena Baldi, 56 anni, ha fatto un volo di circa tre metri, terminato rovinosamente sull'asfalto. Lasciando una macchia di sangue che non faceva presagire nulla di buono. L donna è stata portata d'urgenza al Noa in ambulanza, poi è stato deciso di trasferirla a Cisanello in elicottero. Una viaggio disperato, di notte, che non è servito a salvarle la vita, dato che l'attrice amatoriale è deceduta nel primo pomeriggio di domenica a Pisa. A causa di un'emorragia irreversibile che non le ha lasciato scampo. Prendeva un farmaco, per curare una patologia che la tormentava da un paio di anni, che ha impedito al sangue di coagularsi. Una beffa del destino.

Il punto, dietro al palco, dov'è caduta l'attrice

Esami ed Obiettività

Paziente su tavola spinale, collare cervicale.
Paziente ventilata con ambu, GCS 7, cannula di Guedel in sede
Grossolana ferita LC occipitale (apposti punti di accostamento)
Non evidenti ematomi toraco addominali
Deformazione caviglia SX con deformità del malleolo peroneale
Midriasi fissa

Trattamento:
Inizia colloidi 1000 ml
Linea arteriosa per monitoraggio continuo
Richieste 3 Unità GRC

Si esegue ECO FAST che risulta negativa

Si contatta Anestesista che procede immediatamente con IOT e successiva esecuzione TC total body

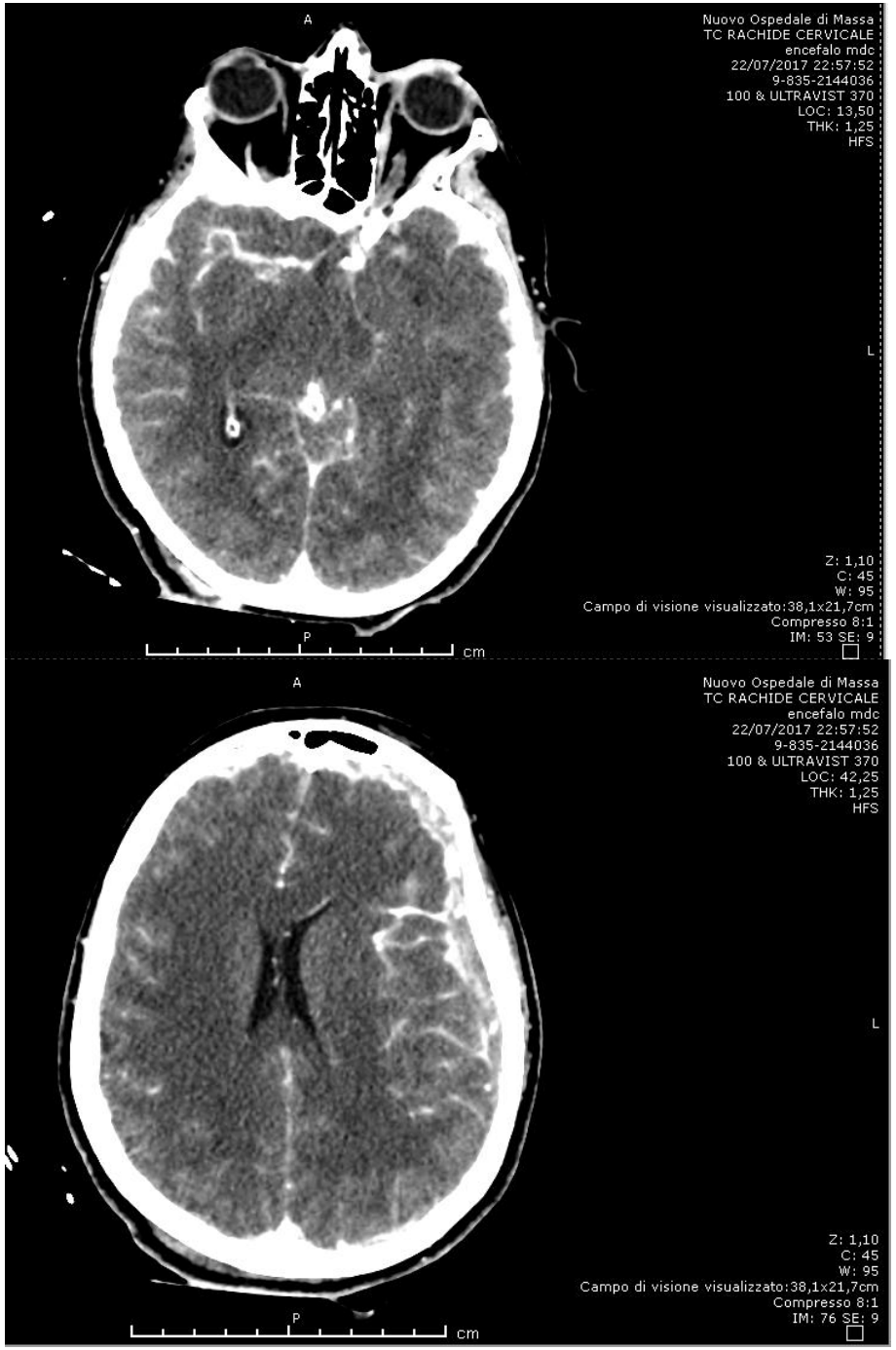
TC CRANIO-ENCEFALO

Frattura della teca cranica in sede occipitale destra che si estende sino al foro occipitale; presenza di falda di iperdensità periencefalica da riferire ad ematoma subdurale in sede fronto-temporo-parietale sinistra dello spessore max di 6mm, omolateralmente si associa ESA in sede frontale e temporale e focalità iperdensa di 4mm a localizzazione corticale in sede parietale. A destra si apprezza piccola falda di ematoma subdurale dello spessore max di 6mm in sede parietale, ESA in sede fronto-temporo-parietale. Iperdensità emorragica del tentorio cerebellare e della grande falce cerebrale. Lieve shift della linea mediana a destra (3mm).

In sede sottotentoriale si rileva minuta e sfumata iperdensità nel contesto dell'emisfero cerebellare di destra, reperto di non univoca interpretazione.

Sistema ventricolo-cisternale nei limiti

Non segni di frattura del rachide cervicale, si segnala piccola bolla gassosa in corrispondenza dell'artecolazione atlantooccipitale sinistra.



TC DEL TORACE SENZA E CON MDC TC DELL' ADDOME COMPLETO SENZA E CON MDC

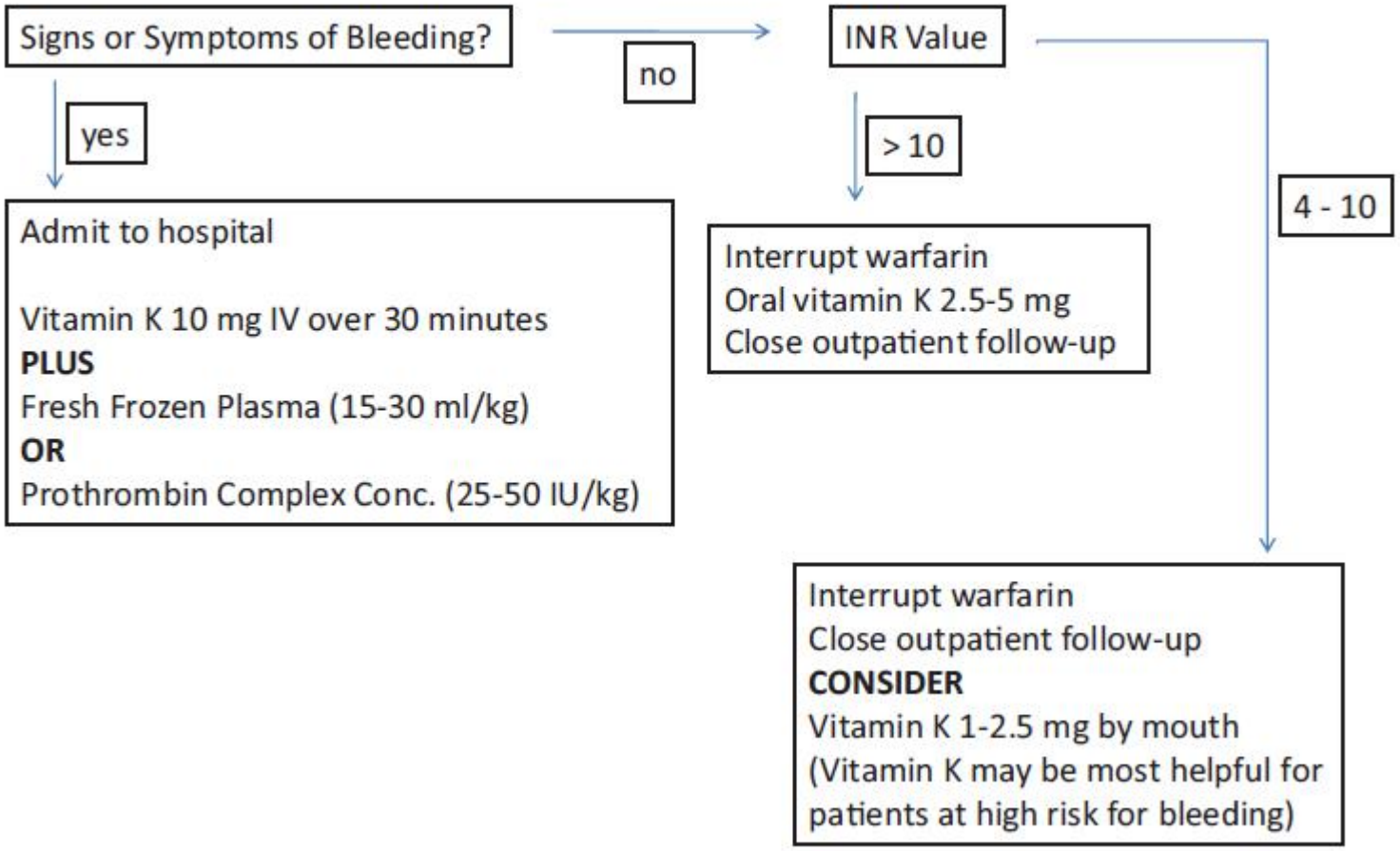
A carico del polmone destro si apprezza falda di PNX dello spessore massimo di 20 mm in sede basale e versamento pleurico nel cui contesto si apprezzano piccoli spot iperdensi in fas a più evidenti nelle fasi venose portale e tardiva da riferire a stravaso em
Aree di consolidame alozazione mantellare in sede dorsale bilateralm di addensamento polmonare e strie di consoli o medio e nel lobo superiore destro.
Multiple fratture costali a destra, anche scomp di enfisema sottocutaneo più rappresentato anteriormente. Frattura del VI, VII e VIII costa a sinistra.
In ambito addominale si apprezza tumefazione di entrambi i muscoli psoas nel cui contesto si apprezza spandimento di MdC in fase arteriosa.
Frattura del soma di D12 con regolare muro posteriore, frattura del suo processo trasverso di destra ; frattura a più linee del soma di L2 estesa al muro posteriore che risulta prospiciente a livello del canale rachideo riducendone significativamente l'ampiezza. Frattura della lamina sinistra e del processo trasverso sinistro di L2. Frattura del processo trasverso destro di L1 e del suo processo spinoso

Indicazione a drenaggio toracico

Rescue?

Warfarin
Heparin
Fondaparinux
Dabigratan
Rivaroxaban
Apixaban
Edoxaban

Management of a warfarin-treated patient whose INR exceeds 4. A suggested algorithm



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Controllare INR dopo 15' dall'infusione e se >1,5 ripetere lo schema di terapia partendo dal valore di INR per ripetere lo schema

- Infondere Plasma (15 mL/Kg)
- Trasfusione di piastrine se < 60000

LG

FCSA 2014

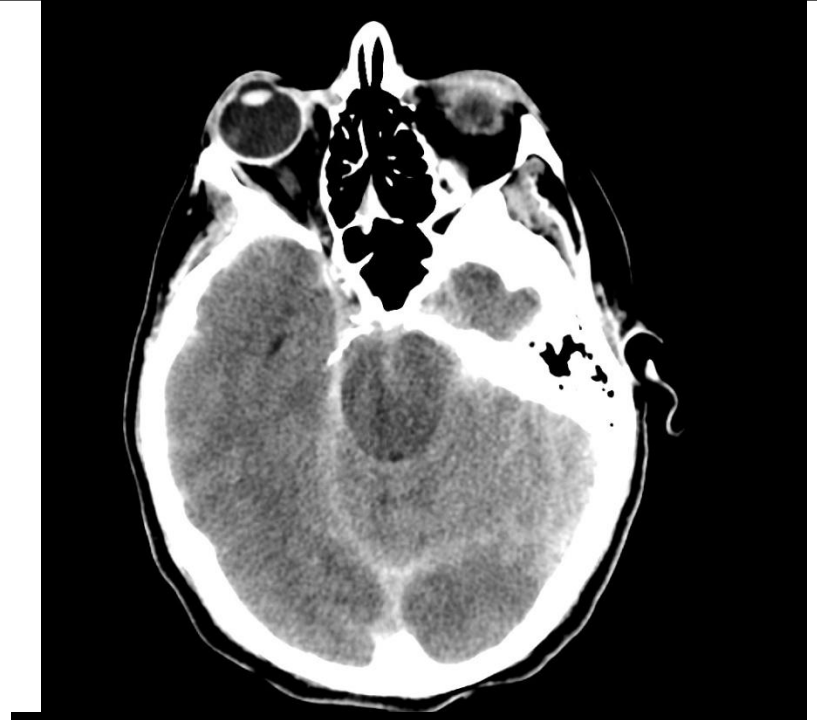
Contattato il laboratorio: INR non ancora disponibile (sarà disponibile tra circa 20 minuti)

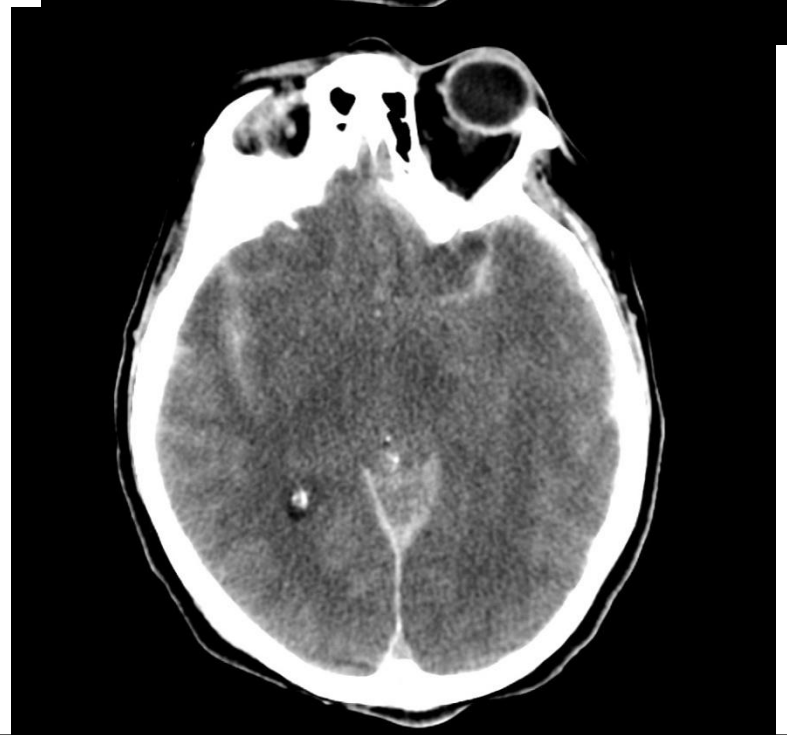
Vista la necessità di centralizzazione con Elisoccorso per procedura NCH, si decide di procedere al posizionamento di drenaggio toracico senza esami di laboratorio:

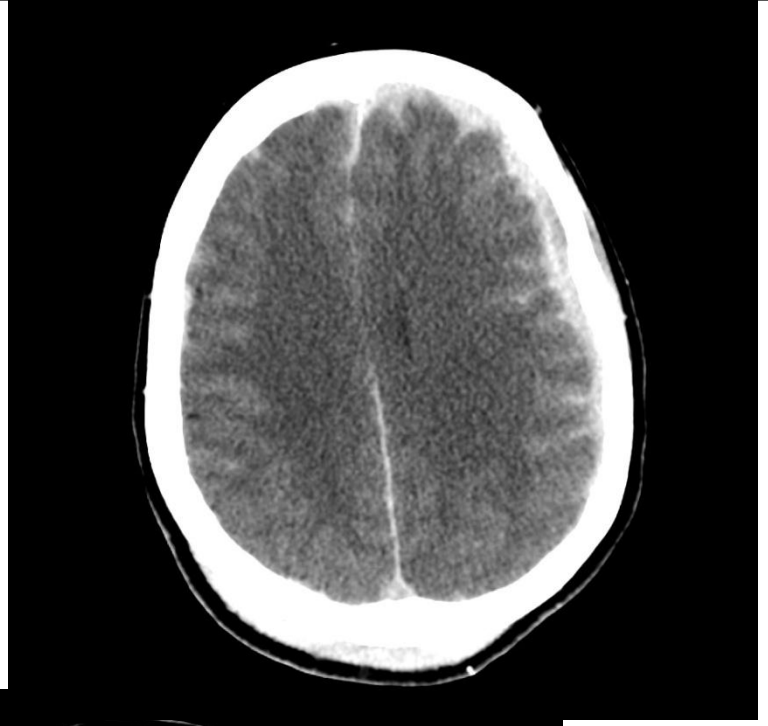
Peso stimato 90 Kg
INR stimato: elevato
Somministrato PCC 4500 UI

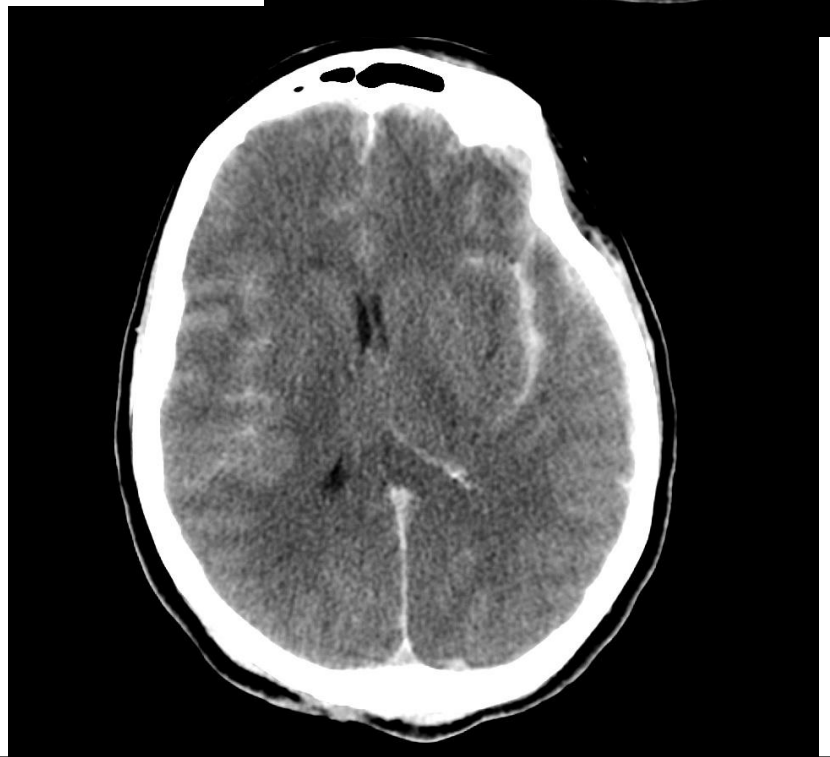
Si procede con posizionamento drenaggio toracico e rapida centralizzazione in NCH Cisanello, AOUP, Pisa

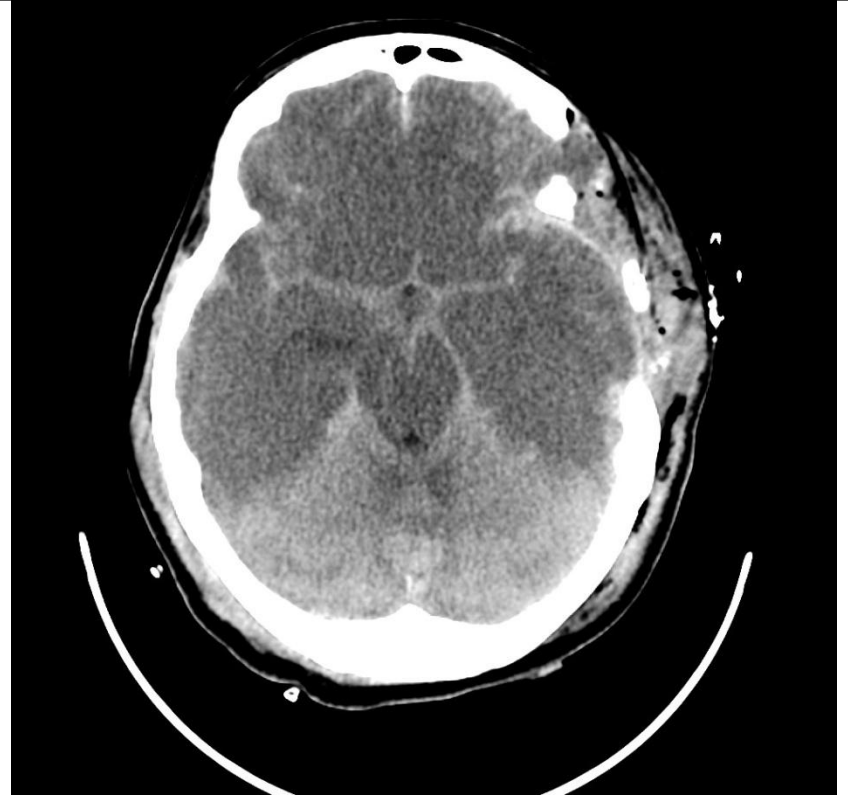
TC a 24 h

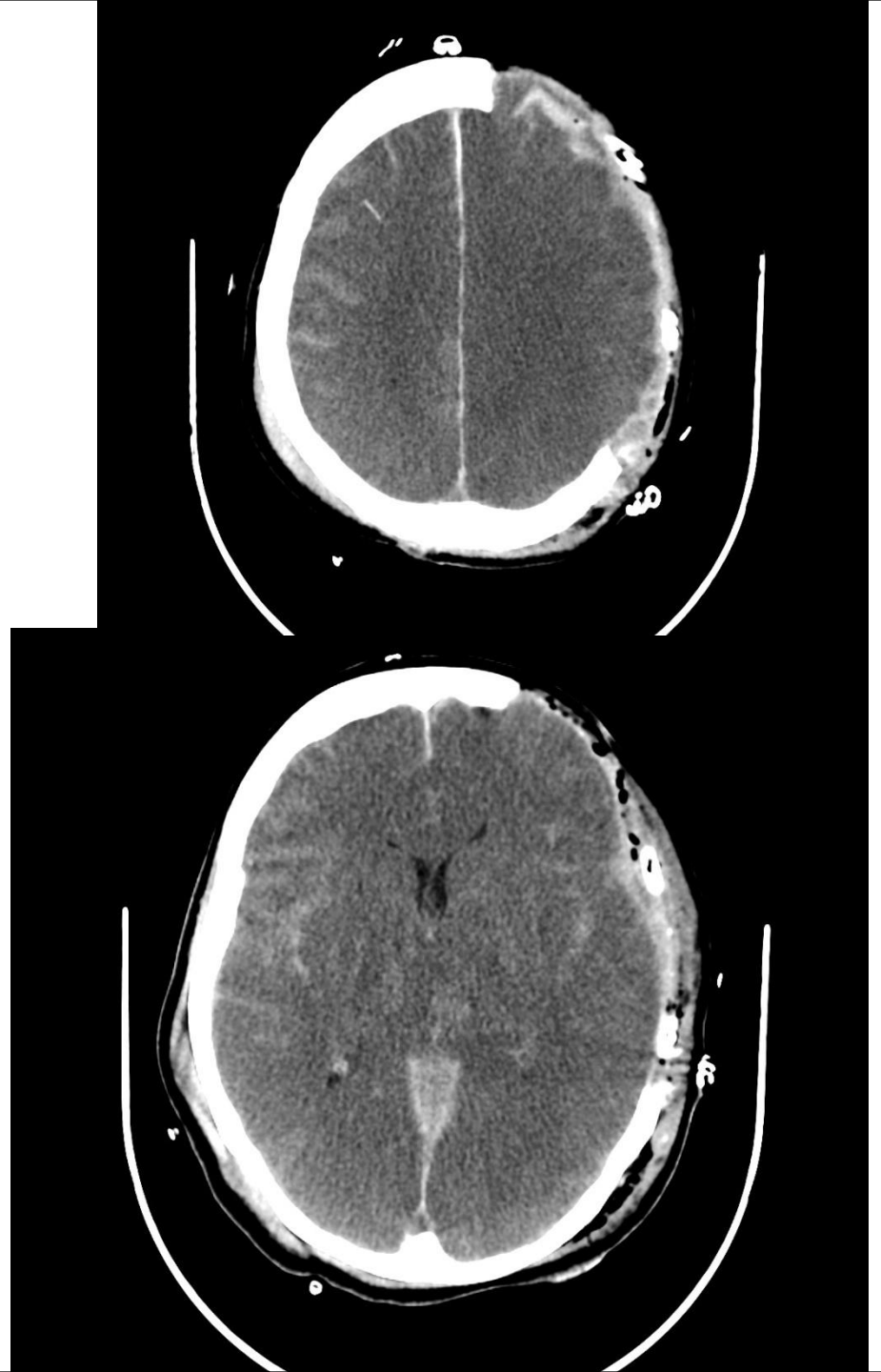












TC Cranio post
intervento chirurgico

Cade dal palco durante lo spettacolo, muore attrice

Stava recitando quando ha fatto un volo di tre metri: la commedia è stata sospesa e la donna trasportata in ospedale, dove è deceduta

SPETTACOLI INCIDENTI

MONTIGNOSO. Un malore, oppure un capogiro, le ha fatto perdere l'equilibrio e l'ha fatta precipitare giù dal balconcino del palco dove stava recitando insieme ai suoi amici del Gruppo folcloristico Montignoso. Lorena Baldi, 56 anni, ha fatto un volo di circa tre metri, terminato rovinosamente sull'asfalto. Lasciando una macchia di sangue che non faceva presagire nulla di buono. La donna è stata portata d'urgenza al Noa in ambulanza, poi è stato deciso di trasferirla a Cisanello in elicottero. Una viaggio disperato, di notte, che non è servito a salvarle la vita, dato che l'attrice amatoriale è deceduta nel primo pomeriggio di domenica a Pisa. A causa di un'emorragia irreversibile che non

Prendeva un farmaco, per curare una patologia che la tormentava da un paio di anni, che ha impedito al sangue di coagularsi. Una beffa del destino.

Sei in: MASSA-CARRARA > CRONACA > CADE DAL PALCO DURANTE LO SPETTACOLO,...

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Riflessioni:
con altro anticoagulante sarebbe stato diverso…
soprattutto con anticoagulante e disponibilità di reversal agent…

di Grazia

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Quando il “Reversal Management”
E quando il singolo Reversal Agent?

Topic

Guidelines for reversal of anticoagulants

NAMES	ELIMINATION HALF-LIFE	REMOVED BY HD	STRATEGIES TO REVERSE OR MINIMIZE DRUG EFFECT
apixaban *(Eliquis)*	8-15 hours (longer in renal impairment)	NO	• Drug activity can be assessed with anti-factor Xa activity assay (UWMedicine: apixaban assay [APIXN1]) • If ingested within 2 hours, administer activated charcoal • *Consider 4-factor PCC (KCentra) 50 units/kg (maximum 5000 units)* *(25 unit/kg, maximum 2500 units for intraparenchymal hemorrhage)* **NOTE:** PCC may partially correct PT/aPTT but will not affect anti-factor Xa activity and will not increase drug clearance; correlation of shortening PT/aPTT with reduction in bleeding risk is unknown
dabigatran *(Pradaxa)*	14-17 hours (up to 34 hrs in severe renal impairment)	~ 65%	• Drug activity can be assessed with aPTT and/or plasma-diluted thrombin time (UWMedicine: dabigatran assay [DABIG]) • If ingested within 2 hours, administer activated charcoal • *For life-threatening bleeding or emergency surgery, consider idarucizumab (Praxbind) 5gm IV* **NOTE:** Idarucizumab will likely correct aPTT and plasma-diluted thrombin time but the correlation of lab results with improved outcomes is not established **NOTE**: Plasma dabigatran concentrations can increase more than 12-24 hours after idarucizumab, likely due to re-distribution from the extravascular compartment. **NOTE**: The risks and benefits of repeat idarucizumab administration are not known.
Edoxaban (Savaysa)	10-14 hours (longer in renal impairment)	~ 25%	• There is no assay for edoxaban at this time. • If ingested within 2 hours, administer activated charcoal • *Consider 4-factor PCC (KCentra) 50 units/kg (maximum 5000 units)* *(25 unit/kg, maximum 2500 units for intraparenchymal hemorrhage)* **NOTE:** PCC may partially correct PT/aPTT but will not affect anti-factor Xa activity and will not increase drug clearance; correlation of shortening PT/aPTT with reduction in bleeding risk is unknown
Rivaroxaban *(Xarelto)*	Healthy: 5-9 hrs Elderly: 11-13 hrs (longer in renal impairment)	NO	• Drug activity can be assessed with anti-factor Xa activity (UWMedicine: rivaroxaban assay [RIVAR1]) • If ingested within 2 hours, administer activated charcoal • *Consider 4-factor PCC (KCentra) 50 units/kg (maximum 5000 units)* *(25 unit/kg, maximum 2500 units for intraparenchymal hemorrhage)* **NOTE:** PCC may partially correct PT/aPTT but will not affect anti-factor Xa activity and will not increase drug clearance; correlation of shortening PT/aPTT with reduction in bleeding risk is unknown

Product for bleeding management of a DOACs-treated patient

Product	Time to Effect (After Administration)	Duration of Effect	Evidence of Efficacy for Warfarin Revesal	Risk of Thrombosis
Fresh frozen plasma	Immediate	12–24 h	++	NS
PCC	Immediate	12–24 h	+++	+ (Higher with activated PCC)
Recombinant factor VIIa	Immediate	2–6 h	+	++

Garcia DA, Crowther MA. Circulation 2012; 125:2944-2947.

NOAC reversal agents are in development

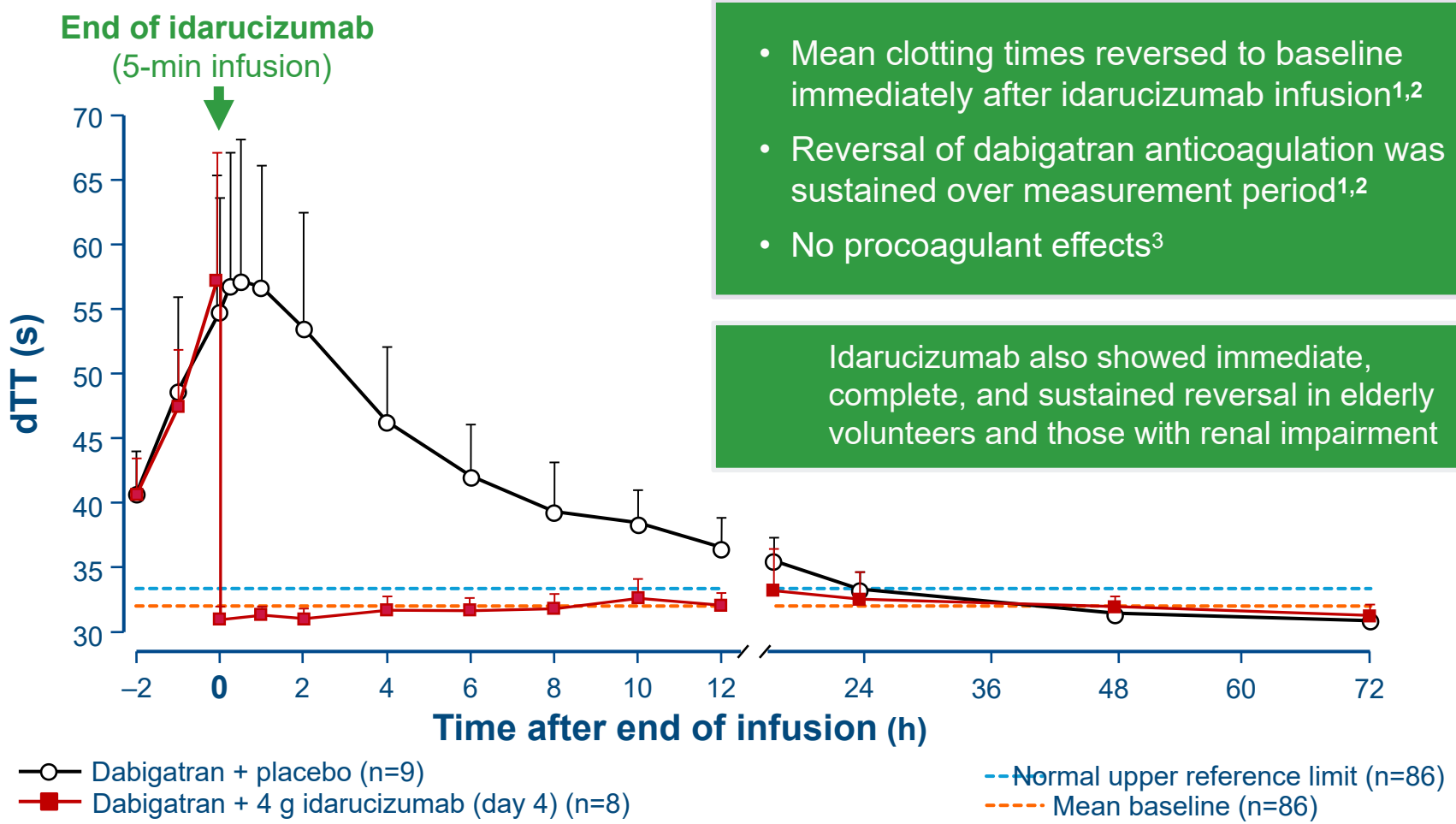
NOAC reversal agent	Target	Mechanism of action
Idarucizumab[1]	Dabigatran	Humanized Fab: specifically binds dabigatran with high affinity[2]
Andexanet alfa (PRT064445)[1]	FXa inhibitors	Recombinant modified FXa: competitive affinity for direct FXa inhibitors[3]
Ciraparantag (PER977)[1]	Universal	Synthetic small molecule: hydrogen bonds (NOACs); charge–charge interactions (heparin)[4]

FXa, activated Factor X

1. Greinacher et al. Thromb Haemost 2015; 2. Schiele et al. Blood 2013; 3. Lu et al. Nat Med 2013;
4. Ansell et al. N Engl J Med 2014

Overview of key differentiators

	Idarucizumab	Andexanet alfa
Approval and availability	**Approved by FDA, and EMEA**	**Recently approved by FDA, waiting for EMEA**
Type of agent	Humanized Fab fragment	Recombinant modified FXa
Specificity	Specific to dabigatran	Targets direct and indirect FXa inhibitors
Reversal in volunteers and patients	Immediate, complete, sustained reversal	Immediate but sustained only with continuous infusion
Safety in volunteers	No safety concerns, and no procoagulant or prothrombotic effects	Transient procoagulant signal observed
Patient study design	Representative of clinical practice in urgent surgery and life-threatening bleeding	Highly selected to exclude patients requiring urgent surgery and those with reduced life expectancy
Ease of use	Fixed dose; ready-to-use solution; single injection	Variable dose; lyophilized; bolus plus infusion
Use with other bleeding management strategies	Tested in RE-VERSE AD™	Recently evaluated
Restarting anticoagulation	Dabigatran after 24 hrs, others (including heparin) at any time	Rapidly cleared; FXa inhibitors can likely be restarted soon after reversal,

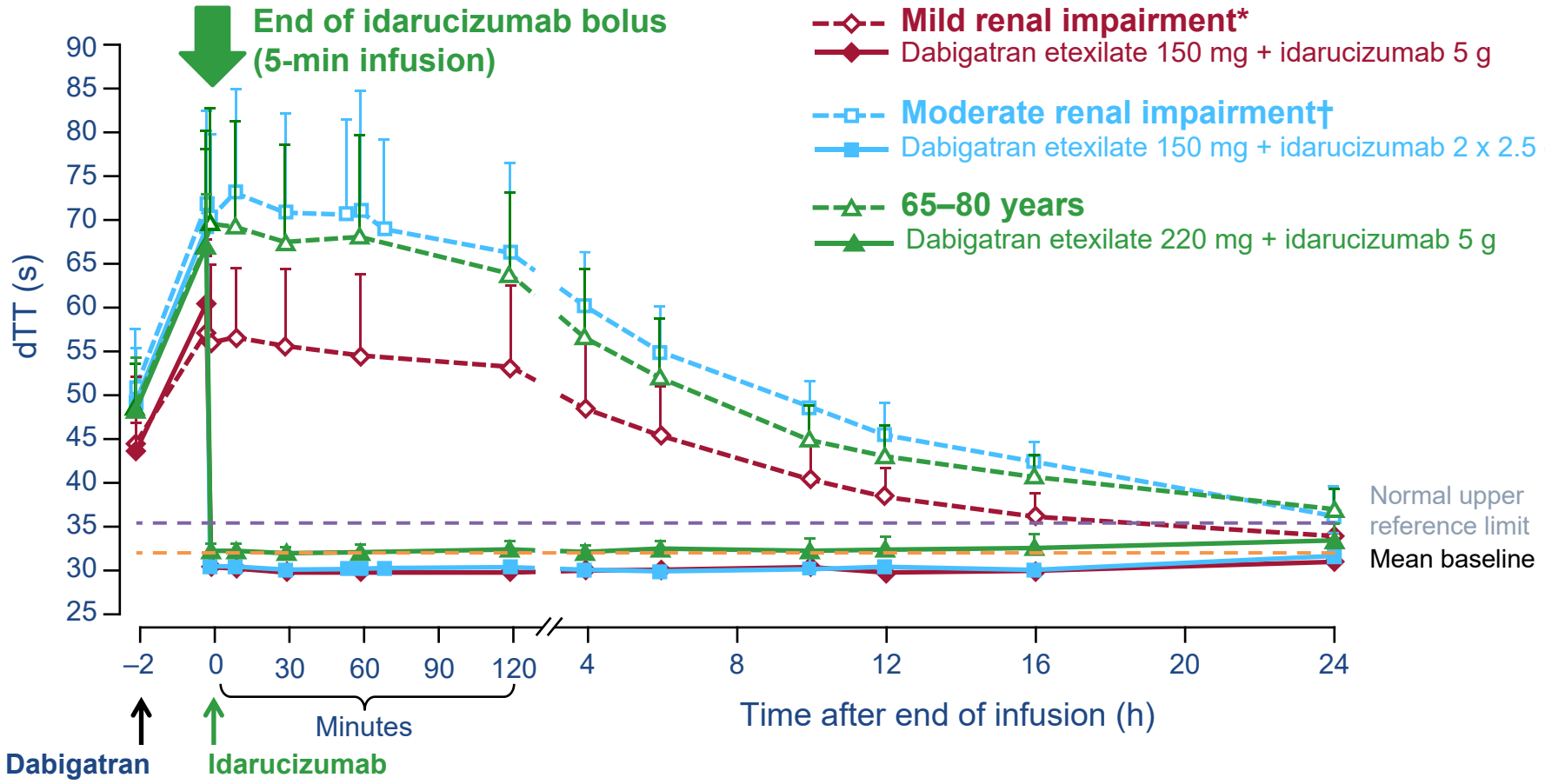


- Mean clotting times reversed to baseline immediately after idarucizumab infusion[1,2]
- Reversal of dabigatran anticoagulation was sustained over measurement period[1,2]
- No procoagulant effects[3]

Idarucizumab also showed immediate, complete, and sustained reversal in elderly volunteers and those with renal impairment

dTT, diluted thrombin time. 1. Glund S et al. Lancet 2015; 2. Glund S et al. Thromb Haemost 2015; 3. Glund S et al. ASH 2014

Idarucizumab shows **immediate, complete, and sustained** reversal in healthy elderly subjects and those with mild or moderate renal impairment

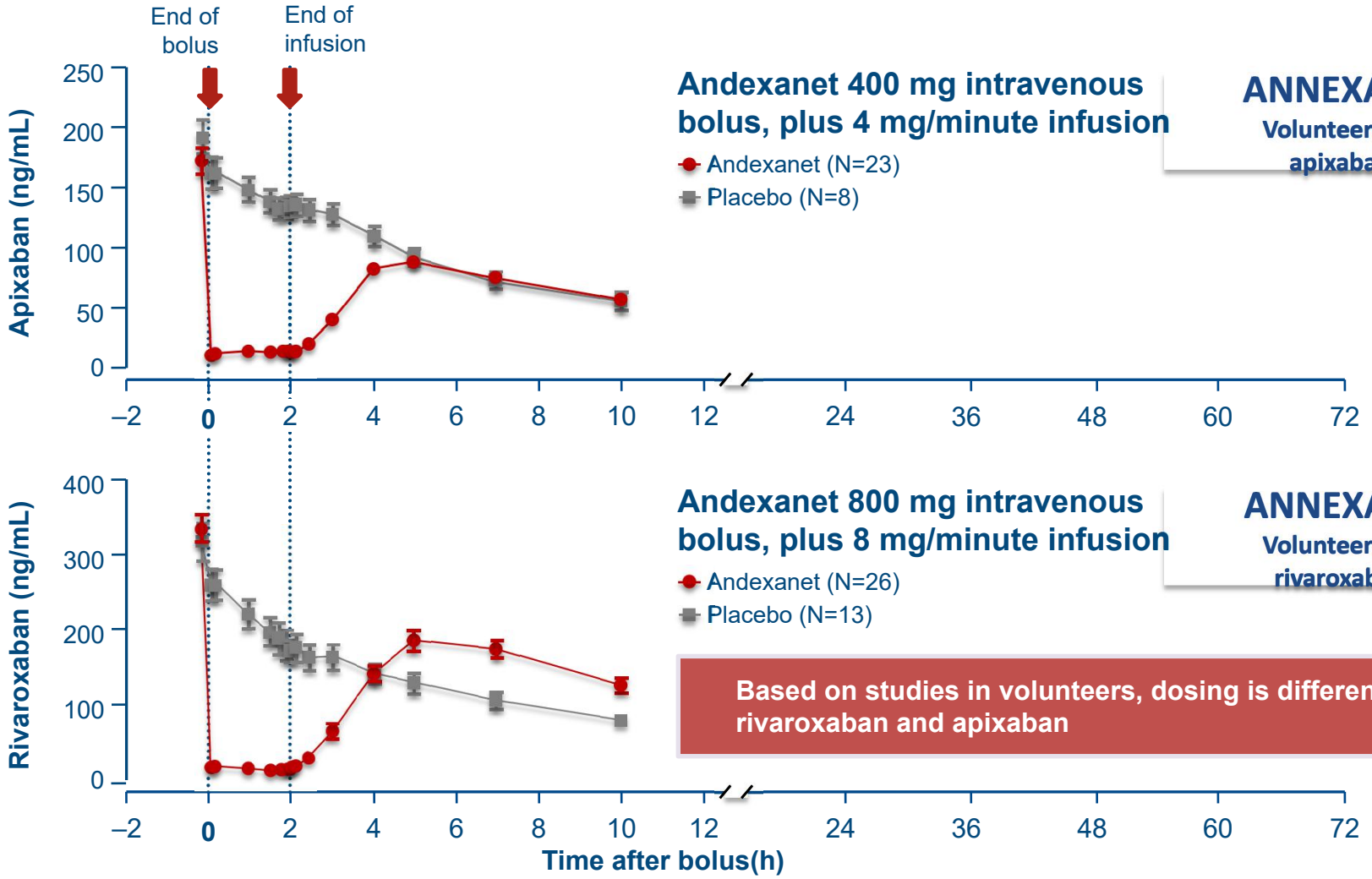


*CrCl ≥60–<90 mL/min; †CrCl ≥30–<60 mL/min; dTT, diluted thrombin time

Glund S et al. Clin Pharmacokinet 2016

Andexanet alfa

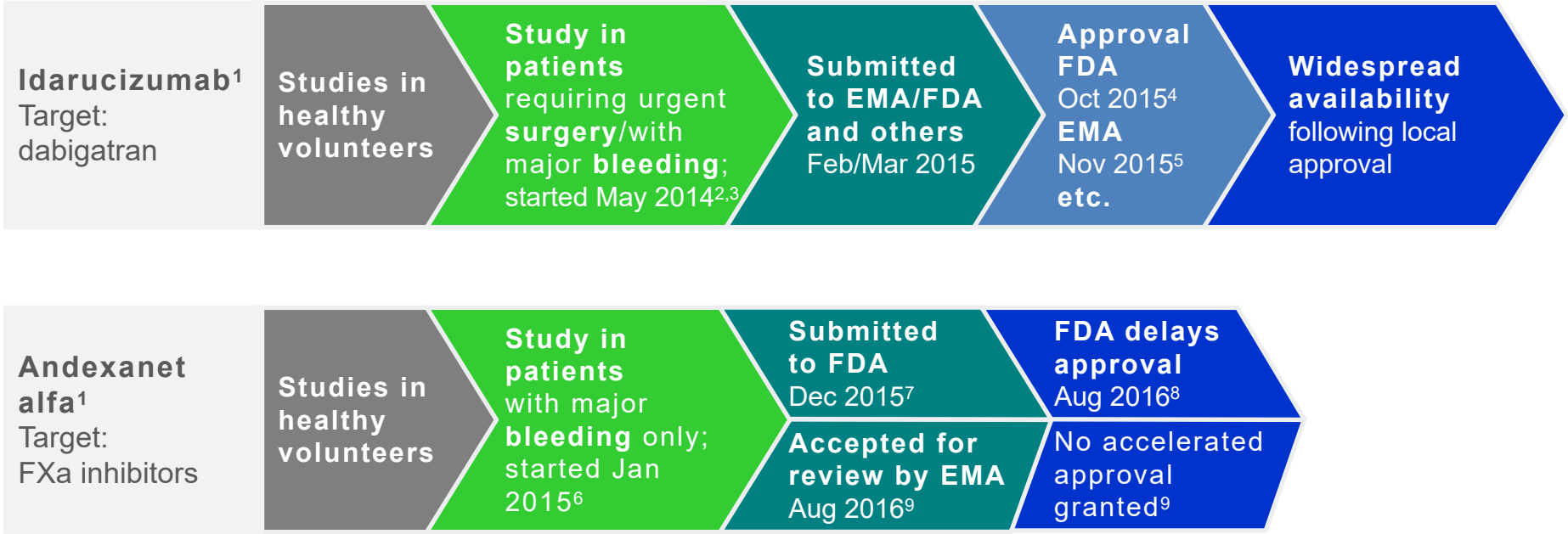
In healthy volunteers, the reversal effects of andexanet alfa were not sustained beyond the 2-hour infusion



Based on studies in volunteers, dosing is different for rivaroxaban and apixaban

1. Siegal DM et al. N Engl J Med 2015

What specific reversal agents for NOACs are available?



1. Adapted from Greinacher A et al. Thromb Haemost 2015;
2. Pollack C et al. N Engl J Med 2015;
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4. US FDA 2015 press release, 16 October 2015;
5. European Commission Community Register of Medicinal Products for Human Use 2015;
6. ClinicalTrials.gov Identifier: NCT02329327;
7. Portola Pharmaceuticals press release, 18 Dec 2015;
8. Portola Pharmaceuticals press release 17 August 2016;
9. Portola Pharmaceuticals press release 19 August 2016

Caso clinico 3

ore 23.00 domenica:
Femmina di 86 anni
Codice di accesso in PS: GIALLO

Motivo: Riferito episodio di rettorragia massiva. Analogo episodio una settimana prima risoltosi spontaneamente; nei giorni successivi spot emorragici di lieve entità.

Parametri d'ingresso:
PA 90/65 mmHg, FC 105 bpm, aritmico, Sat.O2 98% in FiO2 21%

Caso clinico 3

APR:

pz allettata per esiti di ictus ischemico da circa 1 anno

Fibrillazione atriale permanente

Diabete mellito

Pregressi interventi di protesi ginocchio dx e sx

TD:

Bisoprolo 1,25 mg cpx2

Pantoprazolo 20 mg cp ore 8

Keppra 500 mg cp x3

Novonorm 0,5 mg cp x2

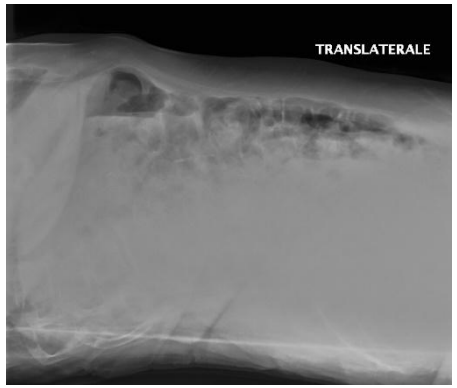
Pradaxa 110 mg cp x2

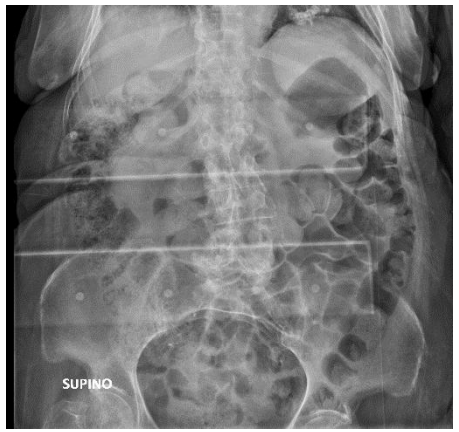
Caso clinico 3

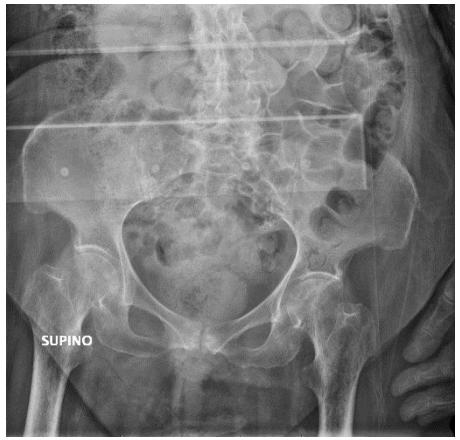
Esame obiettivo:
Pz vigile, poco collaborante, emiplegia destra
Azione cardiaca aritmica, tendenzialmente tachifrequente
MV ridotto, non grossolani rumori respiratori aggiunti
Addome trattabile, non dolente, dolorabile alla palpazione profonda nei quadranti di sinistra
Non edemi declivi
All'esplorazione rettale sangue rosso vivo misto a feci

Dopo expander con Soluzione fisiologica 1000 mL
PA 105/70, FC 85, sat 98% in AA

Emogas analisi Hb 11 gr/dL

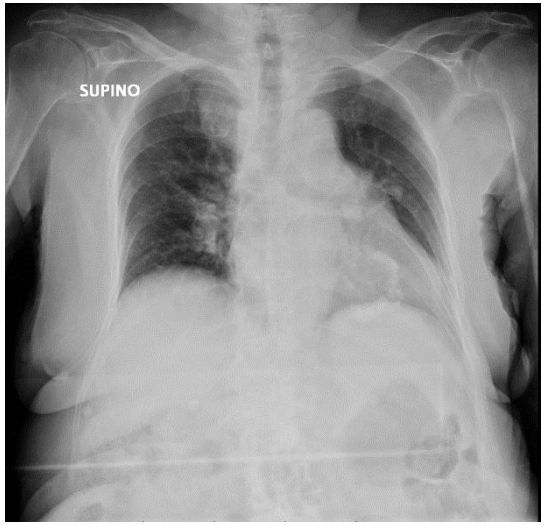






RX TORACE A LETTO

Non alterazioni parenchimali
con carattere di focolaio in atto.
Aumento del diametro trasverso cardiaco.
Non segni di versamento pleurico.



RX ESAME DIRETTO DELL'ADDOME

Non segni di aria libera subfrenica.
Non significativi livelli idroaerei.
Coprostasi colica ed in ampolla.

ECOGRAFIA ADDOME

Fegato di dimensioni nei limiti, indenne da alterazioni focali rilevabili.
Colecisti a contenuto litiasico con aggregato del diametro massimo di circa 2 cm. Vie biliari non dilatate.
Pancreas ad ecostruttura regolare con Wirsung sottile.
Milza di dimensioni nei limiti.
Aorta addominale di calibro regolare.
Reni nella norma per morfovolumetria con rapporto cortico-midollare discretamente conservato. Non idronefrosi.
Vescica scarsamente distesa a profili parietali regolari, indenne da formazioni endoluminali.
Utero con formazione fibromiomatosa esofitica del fondo di circa 6 cm.
Non versamento endoaddominale.

Esami di laboratorio

ora	Hb	GR	GB	Creat	INR	PT	aPTT	aPTT Ratio
23,30	11,5	4,22	7,48	0,57	1,27	69	24	0,8

Ore 00.30 Rivalutazione paziente

Clinicamente stabile
PA 105/70 mmHg
FC 85 bpm
Hb 11,5 gr/dL
Non ulteriori episodi di sanguinamento

Emorragia Maggiore o Minore?

- Sede: Tubo digerente (non è un sito critico)
- Hb: 11.5 gr/dL
- Iniziale instabilità emodinamica con rapida risposta a terapia expander di volemia

Ho valutato tutto?

LA TERAPIA!!!

Bisoprolo 1,25 mg cpx2
Pantoprazolo 20 mg cp ore 8
Keppra 500 mg cp x3
Novonorm 0,5 mg cp x2
Pradaxa 110 mg cp x2

Algorithm for management of dabigatran-treated patients with bleeding or requiring urgent surgery

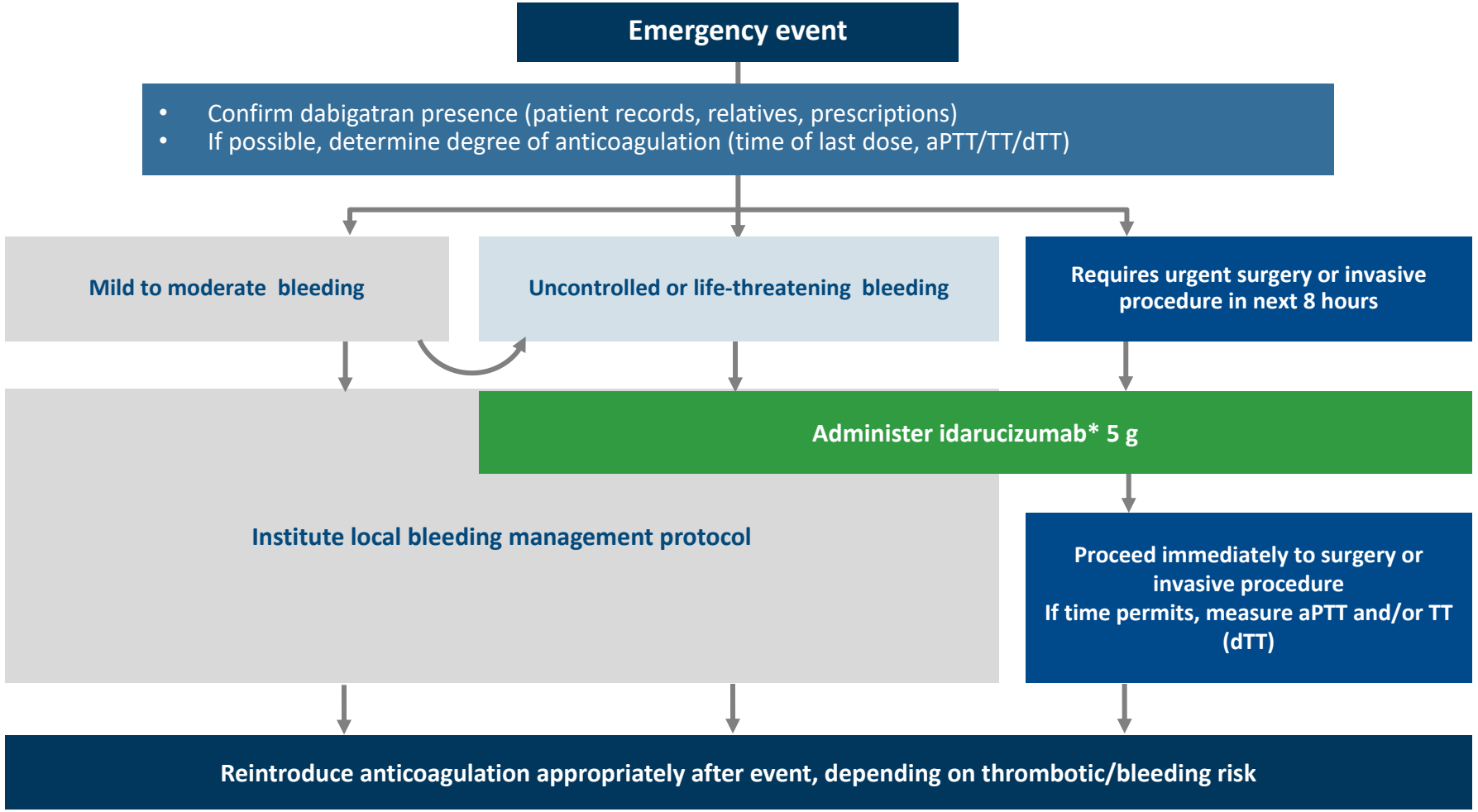


Figure ad m. Et al. *Circulation*. 2015;132:2412-2422

Caso clinico 3

ore 23.00 domenica:
Femmina di 86 anni
Codice di accesso in PS: GIALLO

Motivo: Riferito episodio di rettorragia r

Ore 00.30 Rivalutazione paziente

Clinicamente stabile
PA 105/70 mmHg
FC 85 bpm
Hb 11,5 gr/dL
Non ulteriori episodi di sanguinamento

Esami di laboratorio

	GR	GB	Creat	INR	PT	aPTT	aPTT Ratio
5	4,22	7,48	0,57	1,27	69	24	0,8

ULTIMA ASSUNZIONE DI DABIGATRAN???

La figlia riferisce ultima somministrazione ore 8 della mattina

Guidelines for reversal of anticoagulants

NAMES	ELIMINATION HALF-LIFE	REMOVED BY HD	STRATEGIES TO REVERSE OR MINIMIZE DRUG EFFECT
apixaban *(Eliquis)*	8-15 hours (longer in renal impairment)	NO	• Drug activity can be assessed with anti-factor Xa activity assay (UWMedicine: apixaban assay [APIXN1]) • If ingested within 2 hours, administer activated charcoal • *Consider 4-factor PCC (KCentra) 50 units/kg (maximum 5000 units)* *(25 unit/kg, maximum 2500 units for intraparenchymal hemorrhage)* **NOTE:** PCC may partially correct PT/aPTT but will not affect anti-factor Xa activity and will not increase drug clearance; correlation of shortening PT/aPTT with reduction in bleeding risk is unknown
dabigatran *(Pradaxa)*	14-17 hours (up to 34 hrs in severe renal impairment)	~ 65%	• Drug activity can be assessed with aPTT and/or plasma-diluted thrombin time (UWMedicine: dabigatran assay [DABIG]) • If ingested within 2 hours, administer activated charcoal • *For life-threatening bleeding or emergency surgery, consider idarucizumab (Praxbind) 5gm IV* **NOTE:** idarucizumab will likely correct aPTT and plasma-diluted thrombin time but the correlation of lab results with improved outcomes is not established **NOTE**: Plasma dabigatran concentrations can increase more than 12-24 hours after idarucizumab, likely due to re-distribution from the extravascular compartment. **NOTE**: The risks and benefits of repeat idarucizumab administration are not known.
Edoxaban (Savaysa)	10-14 hours (longer in renal impairment)	~ 25%	• There is no assay for edoxaban at this time. • If ingested within 2 hours, administer activated charcoal • *Consider 4-factor PCC (KCentra) 50 units/kg (maximum 5000 units)* *(25 unit/kg, maximum 2500 units for intraparenchymal hemorrhage)* **NOTE:** PCC may partially correct PT/aPTT but will not affect anti-factor Xa activity and will not increase drug clearance; correlation of shortening PT/aPTT with reduction in bleeding risk is unknown
Rivaroxaban *(Xarelto)*	Healthy: 5-9 hrs Elderly: 11-13 hrs (longer in renal impairment)	NO	• Drug activity can be assessed with anti-factor Xa activity (UWMedicine: rivaroxaban assay [RIVAR1]) • If ingested within 2 hours, administer activated charcoal • *Consider 4-factor PCC (KCentra) 50 units/kg (maximum 5000 units)* *(25 unit/kg, maximum 2500 units for intraparenchymal hemorrhage)* **NOTE:** PCC may partially correct PT/aPTT but will not affect anti-factor Xa activity and will not increase drug clearance; correlation of shortening PT/aPTT with reduction in bleeding risk is unknown

TRATTAMENTO

- Trattenuta in oservazione OBI
- PROGRAMMATA COLONSCOPIA
- TRATTAMENTO CONSERVATIVO
- TERAPIA: Sospensione Dabigratran

  Introduzione EBPM (programmata)

  Acido tranexamico

  Idratazione

  Terapia domiciliare

Riflessioni:

Sarebbe stato diverso se il farmaco fosse stato assunto da 2 ore, o da < di 8 ore…

di Grazia

ading of
st,
.

Quando il “Reversal Management”
E quando il singolo Reversal Agent?

Topic

Caso clinico 4

ore 20.00 mercoledì:
Femmina di 80 anni
Codice di accesso in PS: ROSSO

Motivo: politrauma, shock ipovolemico, GCS 12 (O4V3M5).

Parametri d'ingresso:
PA 95/50 mmHg, FC 105 bpm, aritmico, Sat.O2 92% in FiO2 21%

Paziente caduta dalle scale con trauma toracospinale

APR: Fibrillazione atriale permanente
TD: Pradaxa 110 mg x2, Nebivololo, Amiodarone, lasix

Esami ed Obiettività

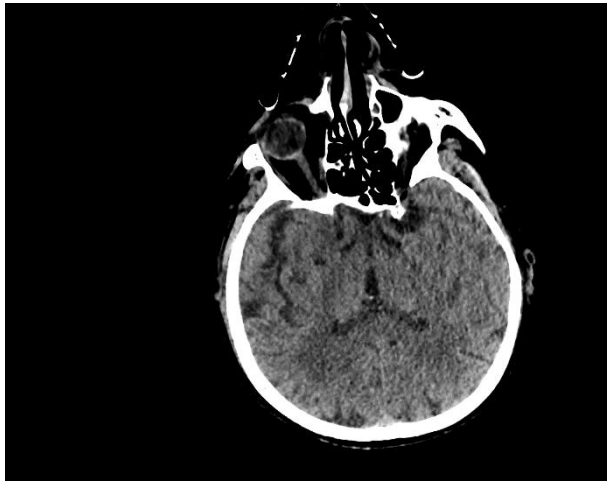
Emogas analisi:
ph 7,39 PO2 67 mmHg, pCO2 38 mmHg HCO3 23 mmol/L Hb 10.5 g dL

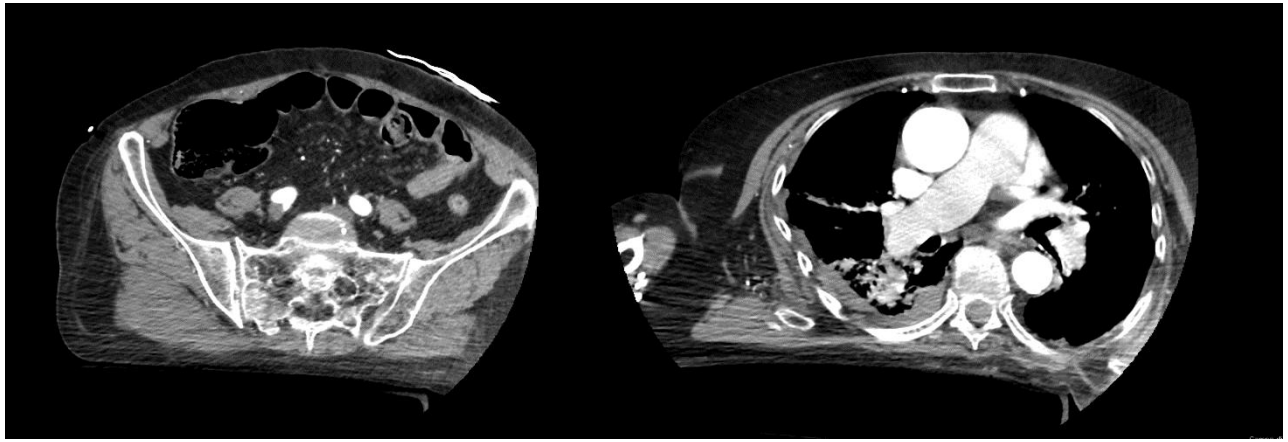
Paziente su tavola spinale, collare cervicale.
Occhi aperti, miotica, risponde allo stimolo verbale con lamenti, localizza il dolore
Azione cardiaca aritmica, tachifrequente
Murmure vescicolare ridotto diffusamente, non rumori respiratori aggiunti
Addome ndn Non grossolane escoriazioni

Trattamento:
Inizia colloidi 1000 ml e Cristalloidi 2000 ml
Linea arteriosa per monitoraggio continuo
Ventimask 50% O2 12 litri min
Richieste 3 Unità GRC

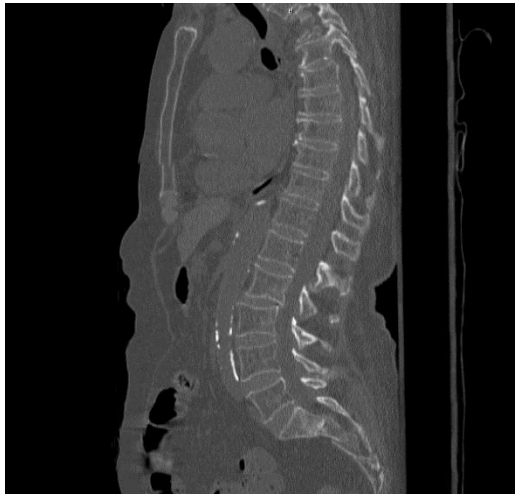
Progressiva stabilizzazione clinica: PA 105/65, FC 100

Ore 21,20: ESECUZIONE TC TORACE E ADDOME CON E SENZA MdC, RACHIDE IN TOTO, CRANIO-ENCEFALO





Addensamento parenchimale di verosimile natura post-contusiva a carico del polmone di destra, più evidente in sede dorsale. Si associa **modesto versamento pleurico** dorso-basale a densità sovraidrica, possibile emotorace.
Non evidenti alterazioni a carattere post-traumatico a carico delle strutture mediastiniche esaminate. Non evidenti alterazioni a carattere post-traumatico a carico delle strutture addominali esaminate. Non liquido libero né segni di perforazione.



Crollo vertebrale di D4 con deformazione a cuneo del soma, lieve retrolistesi rispetto al soma sovrastante ed irregolarità del profilo osseo posteriore.
Irregolarità del muro posteriore con lieve retropulsione anche a livello del soma di D5 che non presenta evidente riduzione di altezza. **Frattura del processo trasverso di destra di D9.**
Multiple fratture costali scomposte dalla III alla XII costa.
Frattura scomposta del corpo della scapola bilateralmente. A destra si evidenzia **ematoma dei tessuti muscolari profondi in assenza di evidenti segni di sanguinamento in atto**. **Frattura composta del corpo dello sterno**.
Al momento, non si evidenziano raccolte ematiche in sede periencefalica od intracerebrale.
Non alterazioni focali riferibili a lesioni ischemiche recenti. Strutture della linea mediana in asse.

Esami di laboratorio

ora	Hb	GR	GB	Creat	INR	PT	aPTT	aPTT Ratio
21.00	10,7	3,44	20,88	1,25	1,43	60	50	1,69

CONSULENZA ORTOPEDICA: trattamento incruento delle lesioni ossee

CONSULENZA NCH: non indicazione con carattere d'urgenza

Ore 22,50
Peggioramento delle condizioni cliniche, obnubilamento del sensorio
Instabilità emodinamica
PA 95/60 mmHg,
FC 108 bpm

Consulenza rianimatoria con IOT

All’emogas analisi Hb 8.1 gr/dL

Ore 22,50
Peggioramento delle condizioni cliniche, obnubilamento del sensorio
Instabilità emodinamica
PA 95/60 mmHg,
FC 108 bpm

Consulenza rianimatoria con IOT

Emogas Hb 8.1 g/dL

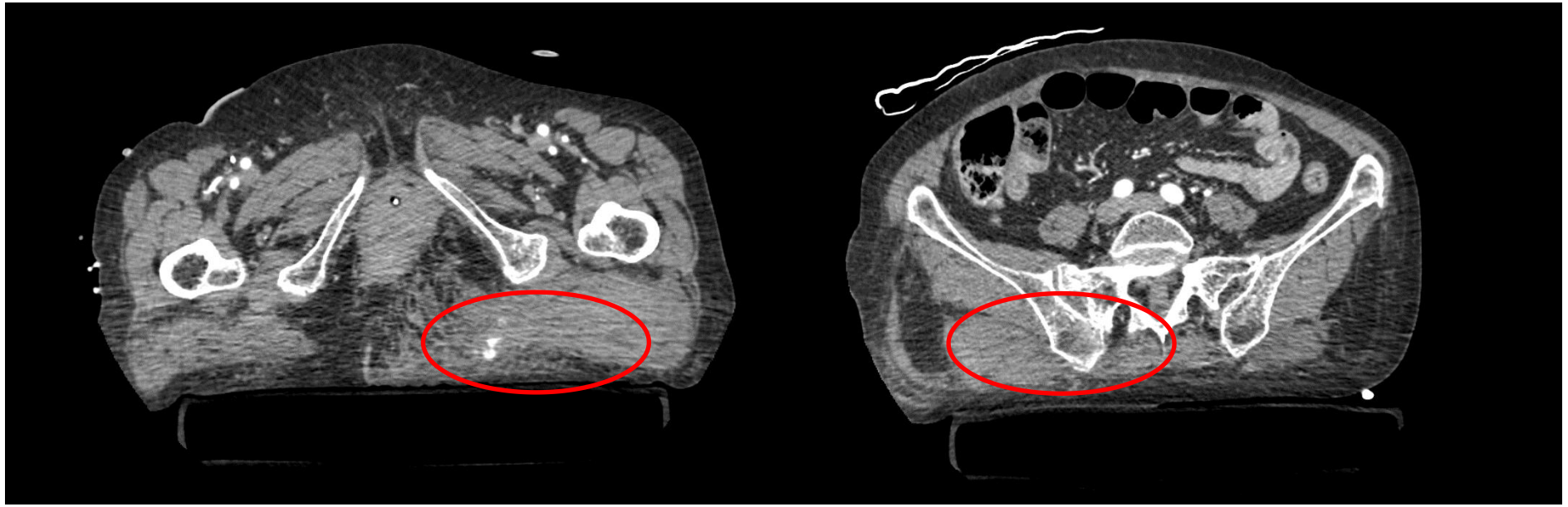
…nuovo esame
TC total-body

L'incredulità di San Tommaso

Michelangelo Merisi da Caravaggio,
1600-1601
Bildergalerie, Potsdam

Ore 23.10: TC TORACE E ADDOME CON E SENZA MdC

Esame ripetuto per relativa riduzione dei valori di emoglobina.
Il controllo attuale mette in evidenza segni di sanguinamento attivo in corrispondenza del profilo postero-superiore dell'ala iliaca di destra, sede di verosimile piccola rima di frattura ed in sede glutea a sinistra.
Tubo endotracheale in sede.
Sostanzialmente invariato il resto del quadro.



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Algorithm for management of dabigatran-treated patients with bleeding or requiring urgent surgery

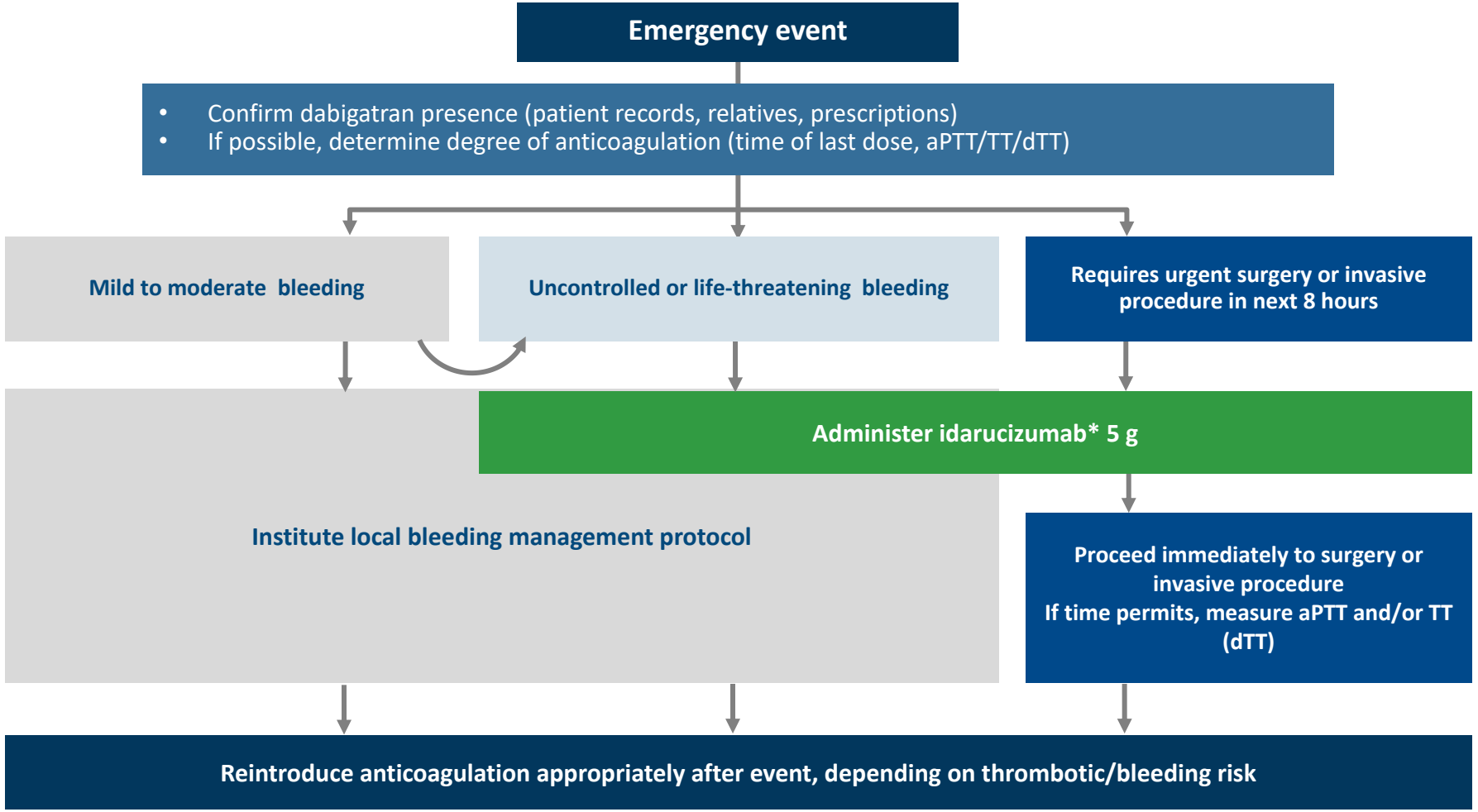


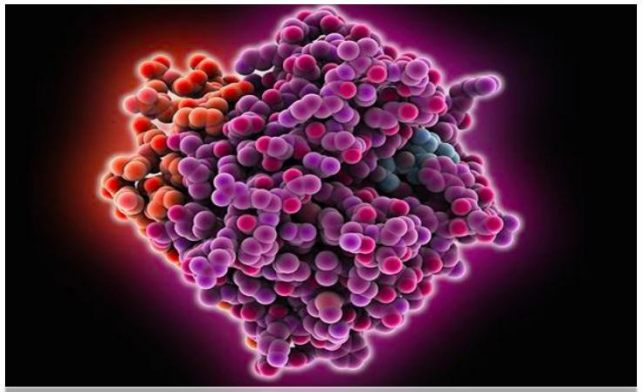
Figure ad m. Et al. *Circulation*. 2015;132:2412-2422

Somministrazione dell’antidoto

Ore 23.40:
inizia, previo consenso informato:
PROTOCOLLO IDARUCIZUMAB

Ore 23.45 PA 90/60mmHg, eseguita 1ª fiala **Idarucizumab 2,5 gr**
Ore 00.00 PA 95/60 mmHg, eseguita 2ª fiala **Idarucizumab 2,5 gr**

Ore 00.15 PA **110/70 mmHg**. Paziente sostanzialmente stabile per clinica

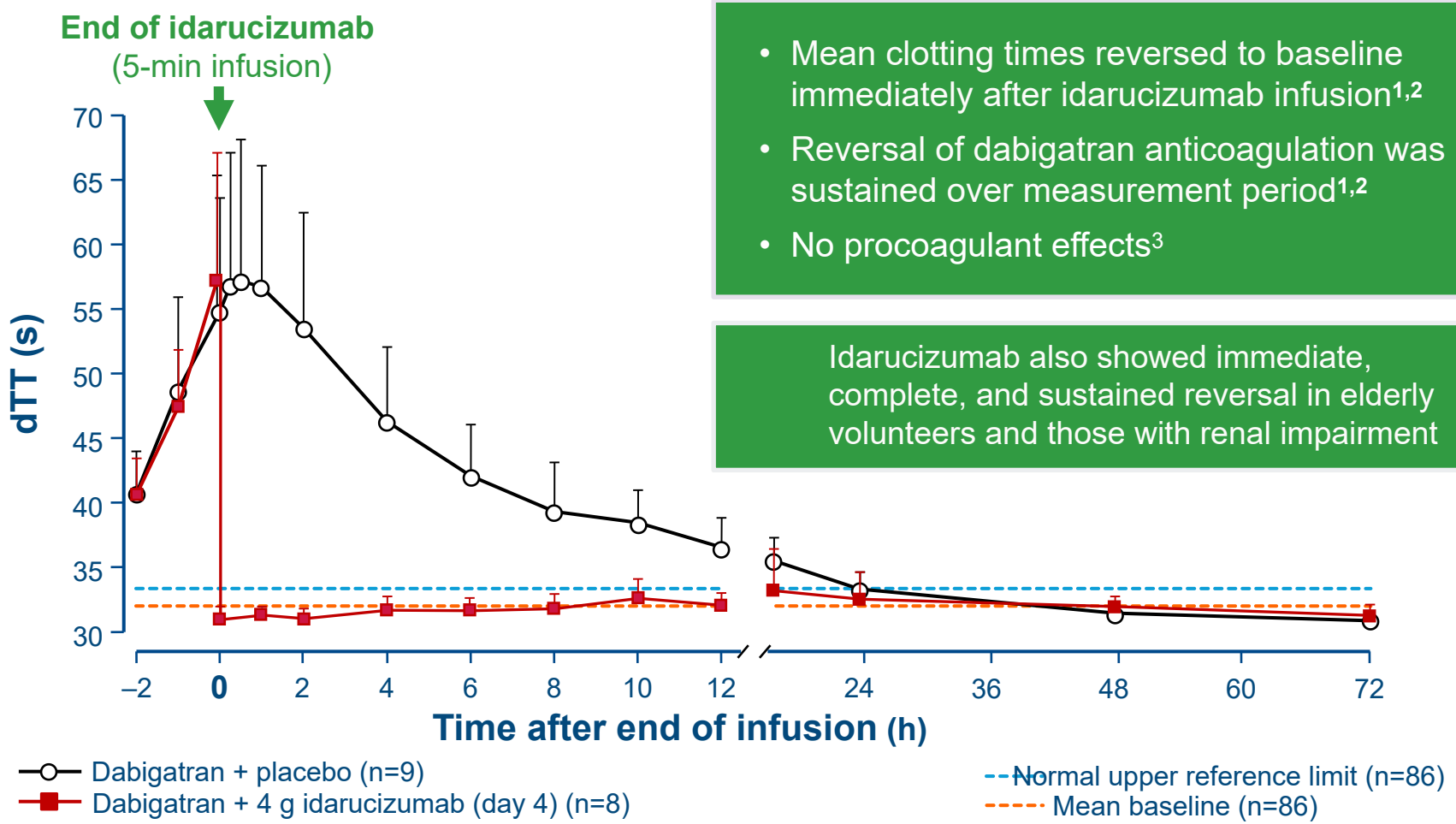


NOAC reversal agents are in development

NOAC reversal agent	Target	Mechanism of action
Idarucizumab[1]	Dabigatran	Humanized Fab: specifically binds dabigatran with high affinity[2]
Andexanet alfa (PRT064445)[1]	FXa inhibitors	Recombinant modified FXa: competitive affinity for direct FXa inhibitors[3]
Ciraparantag (PER977)[1]	Universal	Synthetic small molecule: hydrogen bonds (NOACs); charge–charge interactions (heparin)[4]

FXa, activated Factor X

1. Greinacher et al. Thromb Haemost 2015; 2. Schiele et al. Blood 2013; 3. Lu et al. Nat Med 2013;
4. Ansell et al. N Engl J Med 2014

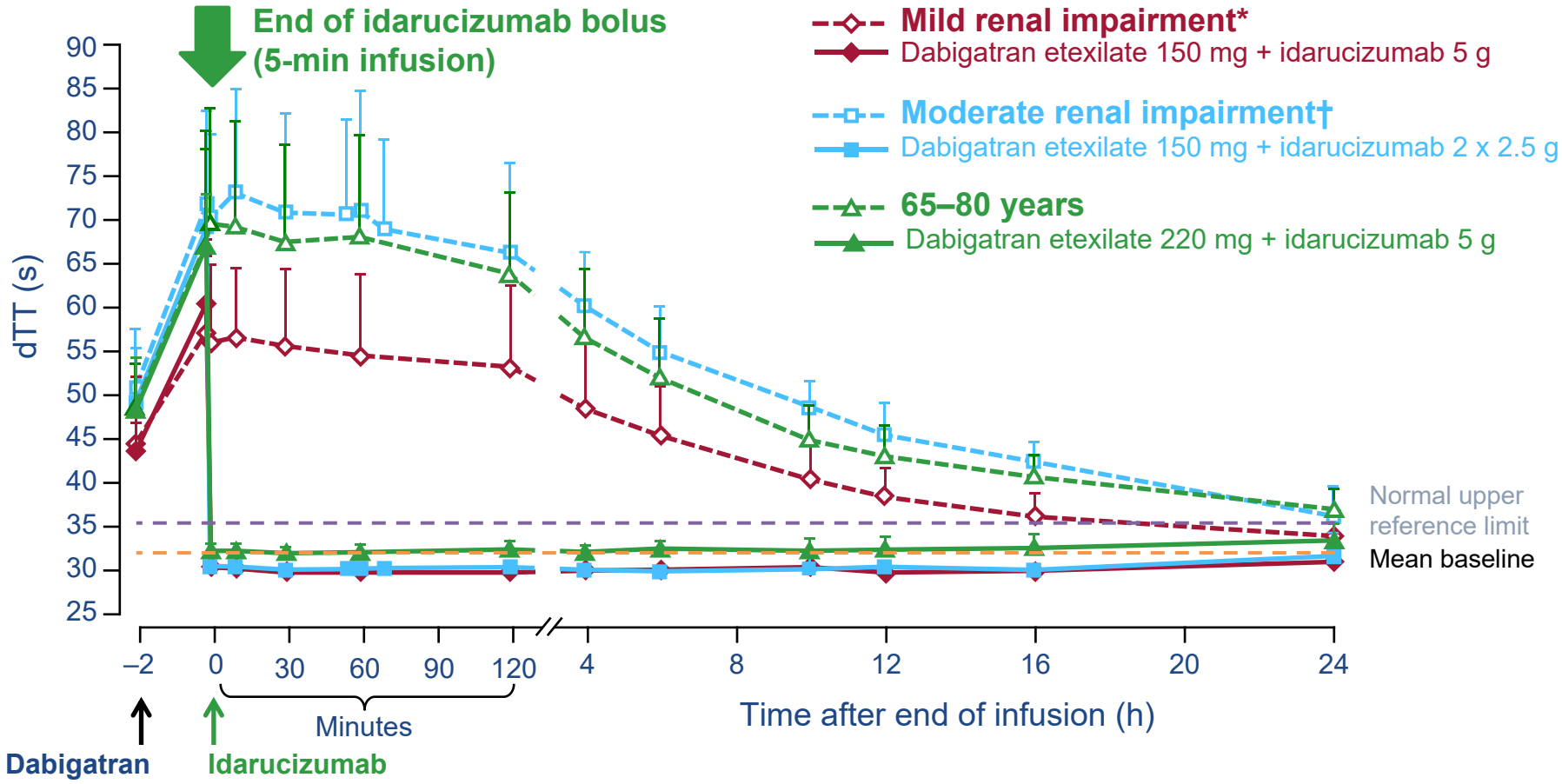


- Mean clotting times reversed to baseline immediately after idarucizumab infusion[1,2]
- Reversal of dabigatran anticoagulation was sustained over measurement period[1,2]
- No procoagulant effects[3]

Idarucizumab also showed immediate, complete, and sustained reversal in elderly volunteers and those with renal impairment

dTT, diluted thrombin time. 1. Glund S et al. Lancet 2015; 2. Glund S et al. Thromb Haemost 2015; 3. Glund S et al. ASH 2014

Idarucizumab shows **immediate, complete, and sustained** reversal in healthy elderly subjects and those with mild or moderate renal impairment



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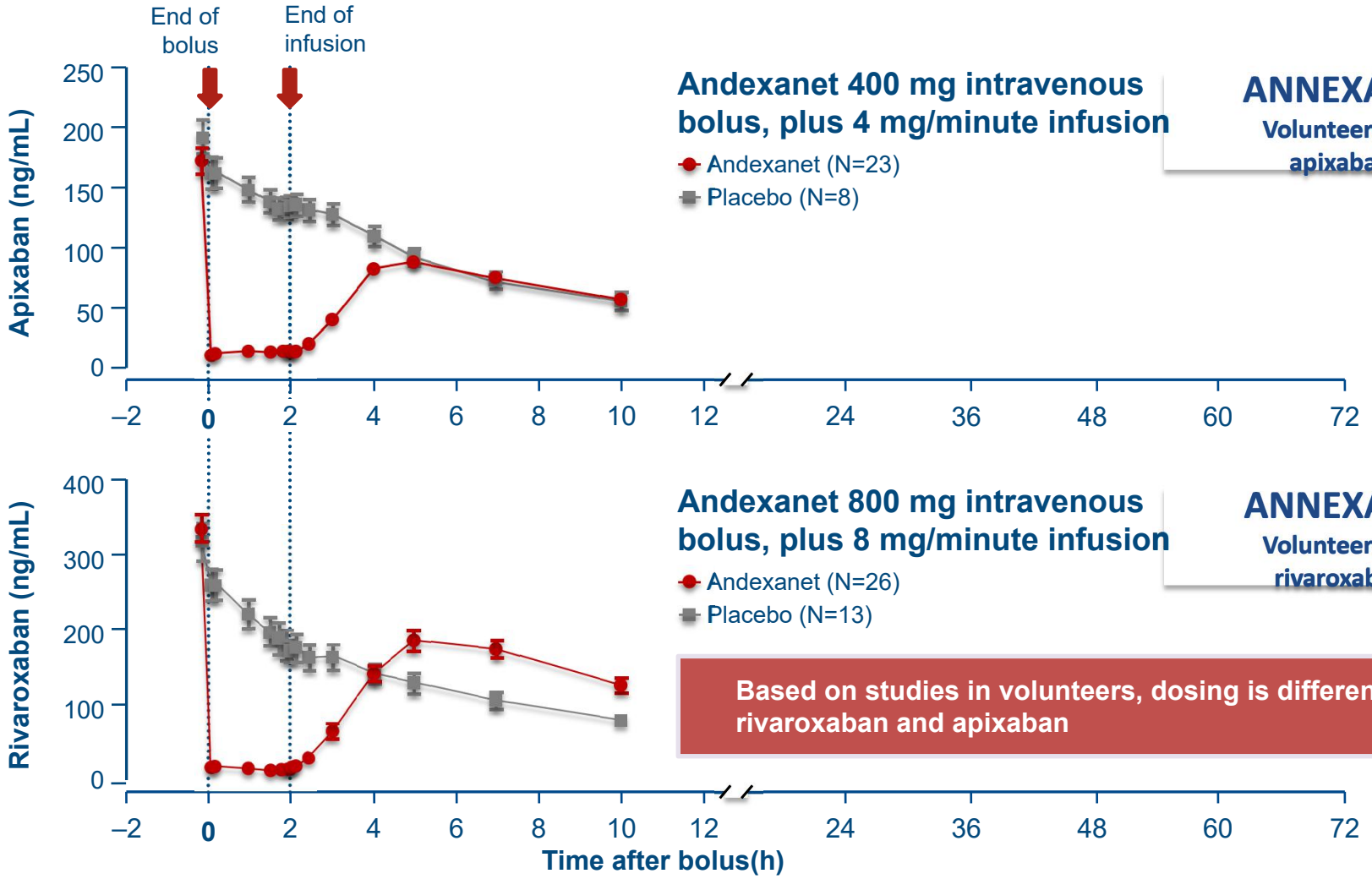
Glund S et al. Clin Pharmacokinet 2016

Andexanet alfa

In healthy volunteers, the reversal effects of andexanet alfa were not sustained beyond the 2-hour infusion



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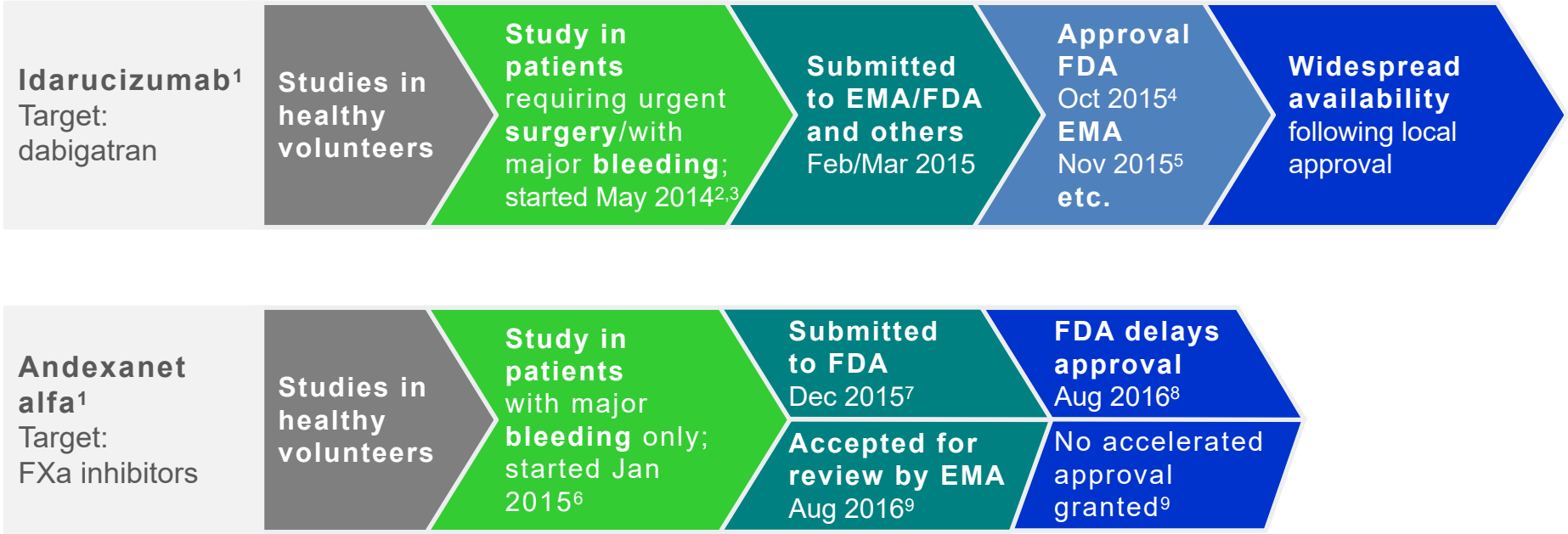
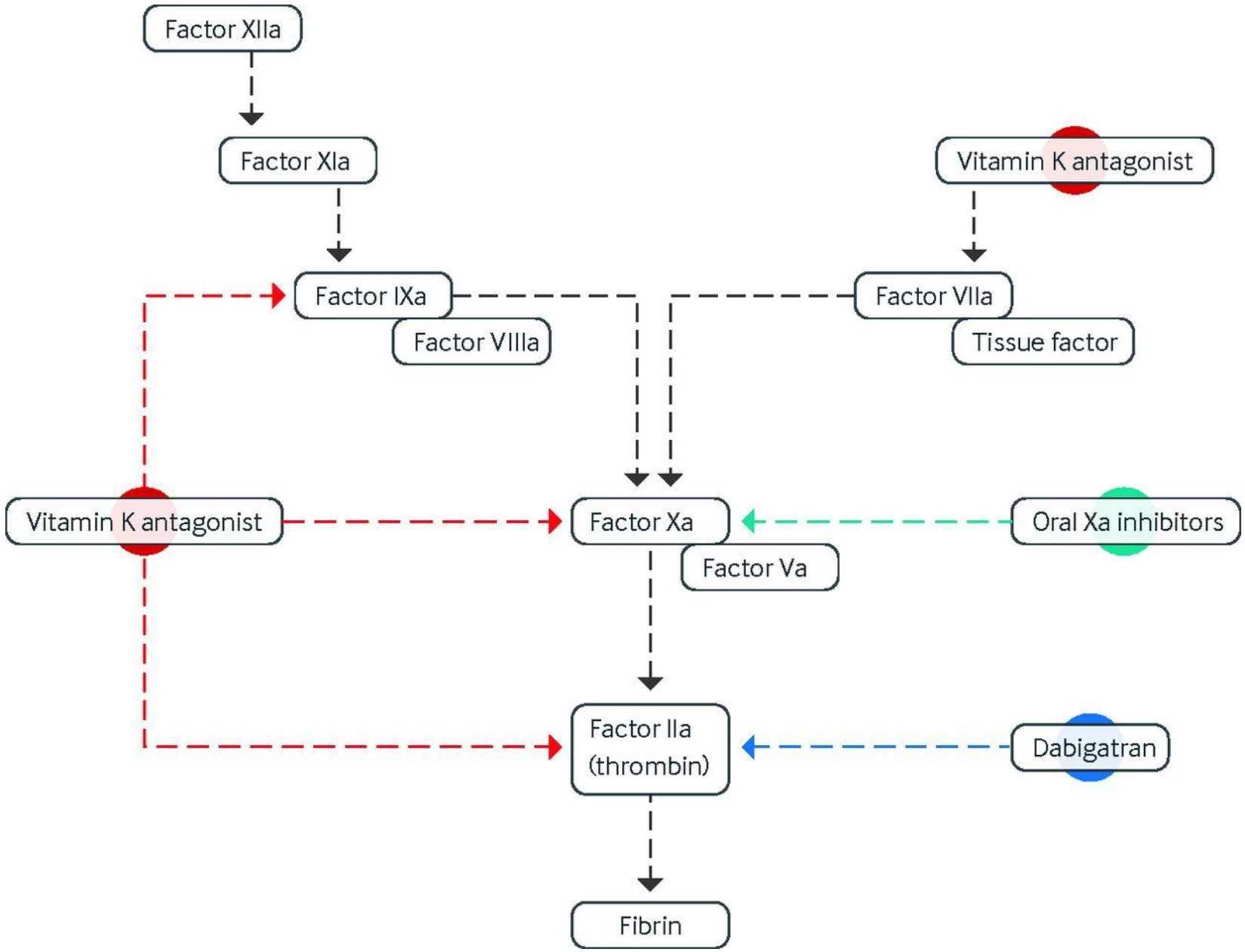
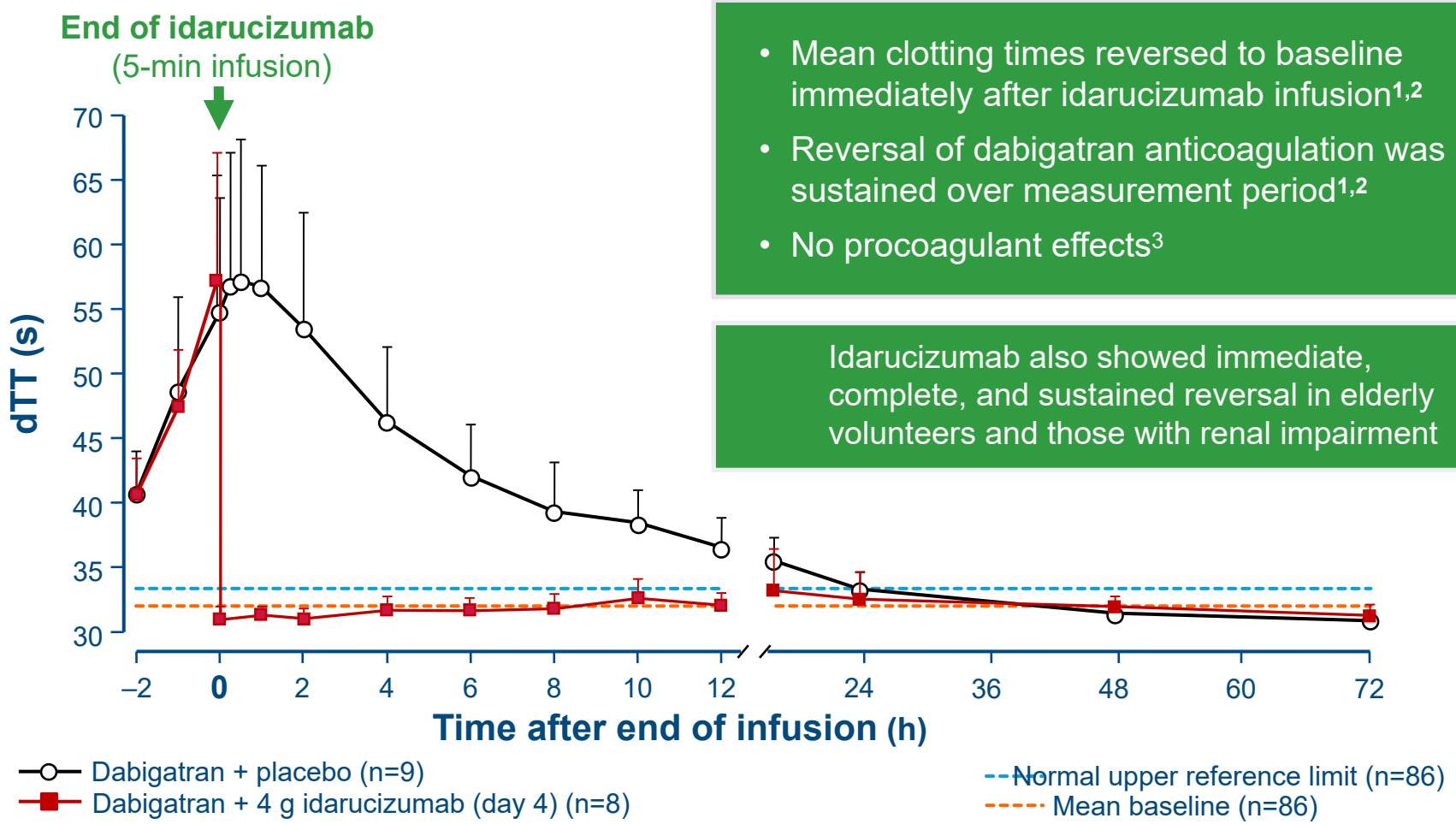
What specific reversal agents for NOACs are available?



1. Adapted from Greinacher A et al. Thromb Haemost 2015;
2. Pollack C et al. N Engl J Med 2015;
3. Pollack C et al. Thromb Haemost 2015;
4. US FDA 2015 press release, 16 October 2015;
5. European Commission Community Register of Medicinal Products for Human Use 2015;
6. ClinicalTrials.gov Identifier: NCT02329327;
7. Portola Pharmaceuticals press release, 18 Dec 2015;
8. Portola Pharmaceuticals press release 17 August 2016;
9. Portola Pharmaceuticals press release 19 August 2016

Coaugulation cascade





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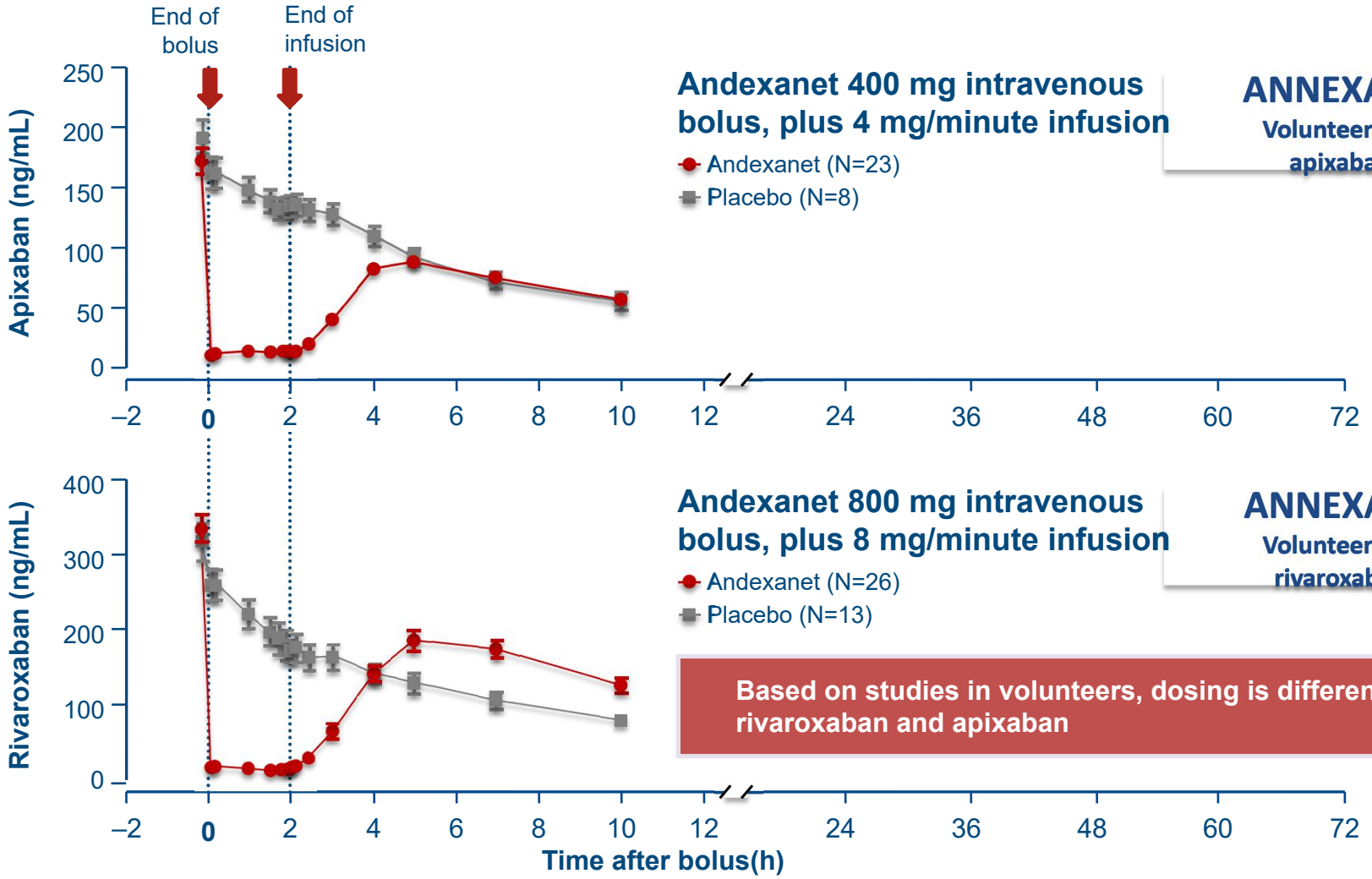
Andexanet alfa

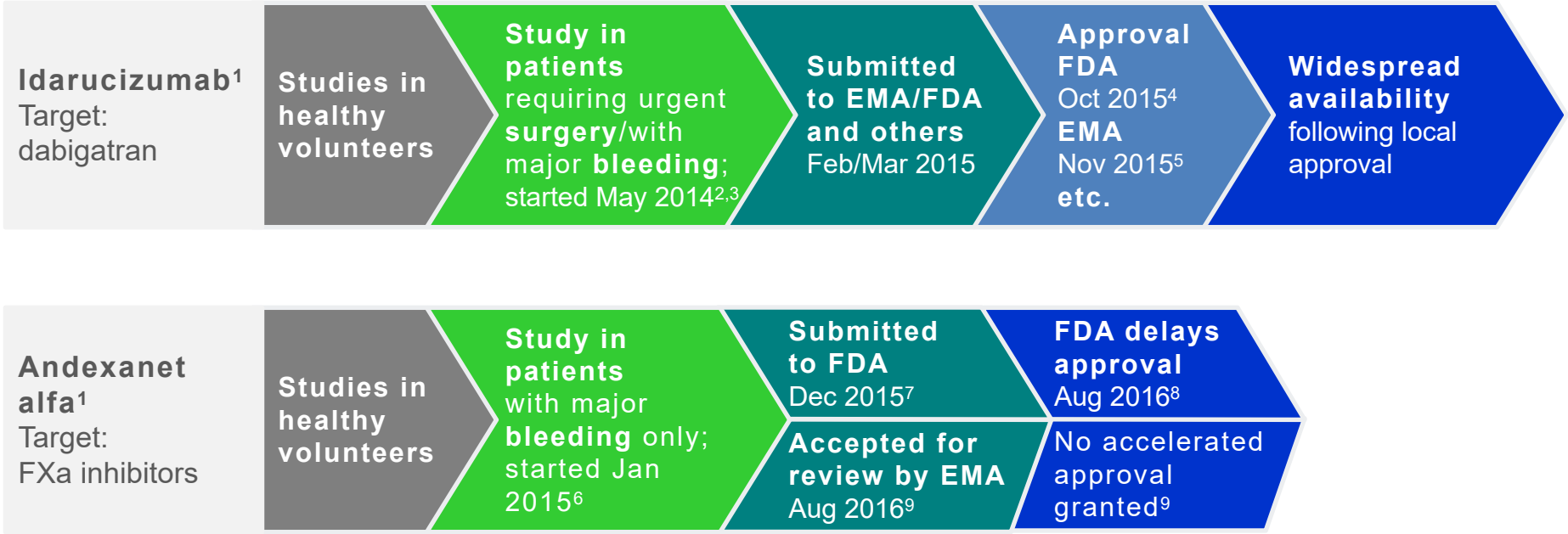
In healthy volunteers, the reversal effects of andexanet alfa were not sustained beyond the 2-hour infusion



Based on studies in volunteers, dosing is different for rivaroxaban and apixaban

1. Siegal DM et al. N Engl J Med 2015

What specific reversal agents for NOACs are available?



1. Adapted from Greinacher A et al. Thromb Haemost 2015;
2. Pollack C et al. N Engl J Med 2015;
3. Pollack C et al. Thromb Haemost 2015;
4. US FDA 2015 press release, 16 October 2015;
5. European Commission Community Register of Medicinal Products for Human Use 2015;
6. ClinicalTrials.gov Identifier: NCT02329327;
7. Portola Pharmaceuticals press release, 18 Dec 2015;
8. Portola Pharmaceuticals press release 17 August 2016;
9. Portola Pharmaceuticals press release 19 August 2016

Overview of key differentiators

	Idarucizumab	Andexanet alfa
Approval and availability	Approved in many countries and widely available	If approved, initial availability will be limited by supply
Type of agent	Humanized Fab fragment	Recombinant modified FXa
Specificity	Specific to dabigatran	Targets direct and indirect FXa inhibitors
Reversal in volunteers and patients	Immediate, complete, sustained reversal	Immediate but sustained only with continuous infusion
Safety in volunteers	No safety concerns, and no procoagulant or prothrombotic effects	Transient procoagulant signal observed
Patient study design	Representative of clinical practice in urgent surgery and life-threatening bleeding	Highly selected to exclude patients requiring urgent surgery and those with reduced life expectancy
Ease of use	Fixed dose; ready-to-use solution; single injection	Variable dose; lyophilized; bolus plus infusion
Use with other bleeding management strategies	Tested in RE-VERSE AD™	Unknown
Restarting anticoagulation	Dabigatran after 24 hrs, others (including heparin) at any time	Rapidly cleared; FXa inhibitors can likely be restarted soon after reversal, however this has not been tested under controlled conditions in any study to date

Somministrazione dell’antidoto

Terapia:

Praxbind 2 Flaconi a distanza 5 minuti, ev

Successivo trasferimento del paziente in radiologia interventistica per procedura di embolizzazione arteriosa selettiva e successivo ricovero in Terapia Intensiva.

La paziente è stata dimessa dopo una settimana in condizioni di buona salute.
Ripresa terapia Pradaxa

XI congresso nazionale
simeu
ROMA 24-26 MAGGIO 2018

Update on Antithrombotics and Bleeding
Case-Load & Case-Mix in the ED

Il sanguinamento maggiore tra
definizioni, gestione dell'urgenza
ed outcome clinico del paziente

Gli studi di vita reale hanno confermato la sicurezza di Pradaxa dimostrata nello studio RE-LY. L'ultimo registro pubblicato è GLORIA AF, ampio registro prospettico la cui FASE II ha confermato e superato I solidi dati di sicurezza dello studio RE-LY e dell'analisi post hoc EU LABLE RE-LY confermando sicurezza ed efficacia di Pradaxa

The Changing Landscape for Stroke Prevention in AF

Findings From the GLORIA-AF Registry Phase 2

Menno V. Huisman, MD, PhD,[a] Kenneth J. Rothman, Dr PH,[b] Miney Paquette, MSc,[c] Christine Teutsch, MD,[d] Hans-Christoph Diener, MD,[e] Sergio J. Dubner, MD,[f] Jonathan L. Halperin, MD,[g] Chang Sheng Ma, MD,[h] Kristina Zint, PhD,[i] Amelie Elsaesser, PhD,[j] Dorothee B. Bartels, PhD,[k,l] Gregory Y.H. Lip, MD,[m] on behalf of the GLORIA-AF Investigators

ABSTRACT

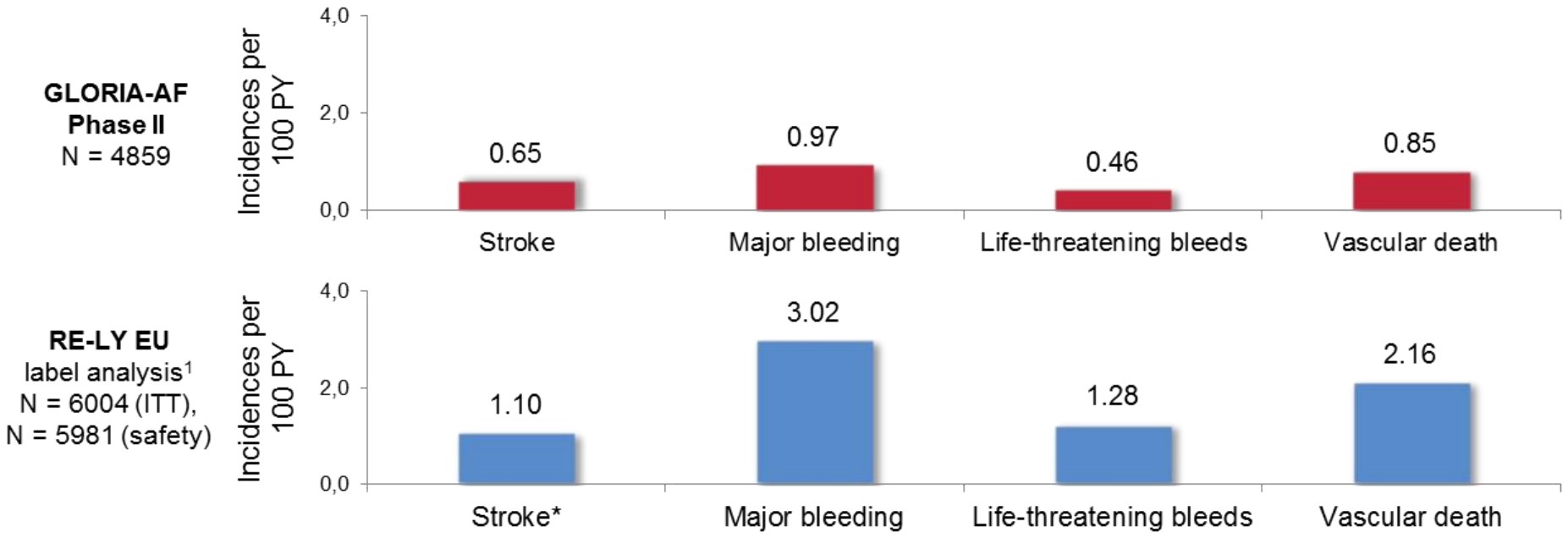
BACKGROUND GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation) is a prospective, global registry program describing antithrombotic treatment patterns in patients with newly diagnosed nonvalvular atrial fibrillation at risk of stroke. Phase 2 began when dabigatran, the first non–vitamin K antagonist oral anticoagulant (NOAC), became available.

OBJECTIVES This study sought to describe phase 2 baseline data and compare these with the pre-NOAC era collected during phase 1.

METHODS During phase 2, 15,641 consenting patients were enrolled (November 2011 to December 2014); 15,092 were eligible. This pre-specified cross-sectional analysis describes eligible patients' baseline characteristics. Atrial fibrillation disease characteristics, medical outcomes, and concomitant diseases and medications were collected. Data were analyzed using descriptive statistics.

RESULTS Of the total patients, 45.5% were female; median age was 71 (interquartile range: 64, 78) years. Patients were from Europe (47.1%), North America (22.5%), Asia (20.3%), Latin America (6.0%), and the Middle East/Africa (4.0%). Most had high stroke risk (CHA_2DS_2-VASc [Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke, Vascular disease, Age 65 to 74 years, Sex category] score ≥2; 86.1%); 13.9% had moderate risk (CHA_2DS_2-VASc = 1). Overall, 79.9% received oral anticoagulants, of whom 47.6% received NOAC and 32.3% vitamin K antagonists (VKA); 12.1% received antiplatelet agents; 7.8% received no antithrombotic treatment. For comparison, the proportion of phase 1 patients (of N = 1,063 all eligible) prescribed VKA was 32.8%, acetylsalicylic acid 41.7%, and no therapy 20.2%. In Europe in phase 2, treatment with NOAC was more common than VKA (52.3% and 37.8%, respectively); 6.0% of patients received antiplatelet treatment; and 3.8% received no antithrombotic treatment. In North America, 52.1%, 26.2%, and 14.0% of patients received NOAC, VKA, and antiplatelet drugs, respectively; 7.5% received no antithrombotic treatment. NOAC use was less common in Asia (27.7%), where 27.5% of patients received VKA, 25.0% antiplatelet drugs, and 19.8% no antithrombotic treatment.

Real Life GLORIA-AF confirms safety and effectiveness of dabigatran over 2 years of follow-up



No direct comparison is intended as populations may differ. *Ischaemic stroke only in RE-LY analysis, ischaemic plus haemorrhagic stroke in GLORIA-AF analysis. ITT, intention-to-treat, PY, patient-years.

1. Lip GYH et al. Thromb Haemost. 2014;111:933-942 [EU label post hoc analysis].
2. Gloria-ASF Registry Phase 2 JACC 2017

Una sottoanalisi del RELY (Majeed 2013) ha dimostrato come in pazienti dopo un episodio di emorragia maggiore la mortalità con entrambi i dosaggi di Pradaxa sia risultata inferiore rispetto al trattamento con warfarin

Major bleeding on dabigatran etexilate and warfarin: objectives of analysis

- How were major bleeding events on dabigatran vs warfarin treated in pivotal trials?
- What
- What

SOLO COME APPROFONDIMENTO – sottoanalisi MAJEED

Objecti

- Review the management of major bleeding events in five Phase III trials of dabigatran and warfarin (including RE-LY®)
- Compare the use of blood products, length of stay in intensive care and in hospital, and mortality after major bleeding events in the two treatment groups

Majeed A et al. *Circulation.* 2013;128:2325-2332

Major bleeding on dabigatran etexilate and warfarin: patient population for analysis

Phase III trial	Patients	Treatments	Duration of treatment
RE-LY®[1]	18 113 patients with AF (stroke prevention)	• Dabigatran 110 mg • Dabigatran 150 mg BID • Warfarin	Median 2 years
RE-COVER™[2]	2539 patients with VTE	• Dabigatran 150 mg BID	6 months
RE-COVER II™[3]			
RE-MEDY™[4]			
RE-SONATE™[4]	(secondary prevention)	• Placebo	
Patients randomized and treated in these five trials: N=27 419 (dabigatran n=16 755; warfarin n=10 002; placebo n=662)			

SOLO COME APPROFONDIMENTO – sottoanalisi MAJEED

Key criteria for inclusion in bleeding case narrative analysis:[5]
only centrally adjudicated major bleeding within 3 days of the last dose

BID = twice daily; VTE = venous thromboembolism; **1**. Connolly SJ et al. N Engl J Med 2009;361:1139–51; **2**. Schulman S et al. N Engl J Med 2009;361:2342–52; **3**. Schulman S et al. ASH 2011; abstr 205; **4**. Schulman S et al. N Engl J Med 2013;368:709–718 ; **5.** Majeed A et al. Circulation 2013; Epub ahead of print

Major bleeding on dabigatran etexilate and warfarin: methods

- Assessment of resources used for bleeding management
  - Bleeding and serious event narratives from five Phase III trials
  - Case study report forms from RE-LY® database
  - Asse
  - Extr
  - Add
- Statistic
  - Com
    χ^2 or Fisher's test
  - Cumulative risk for death estimated using Kaplan–Meier analysis
  - Odds ratios for mortality calculated by logistic regression to adjust for sex, age, weight, renal function, and additional antithrombotic therapy

SOLO COME APPROFONDIMENTO – sottoanalisi MAJEED

Majeed A et al. *Circulation.* 2013;128:2325-2332

Major bleeding on dabigatran etexilate and warfarin: patient characteristics – five Phase III trials

Patient characteristics	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	P value D* vs W
Patients with major bleeding, n	262	365	407	
Age, years, mean (SD)	75.9 (6.6)	75.1 (7.8)	71.8 (10.3)	<0.0001
Male sex, n (%)				
Body weight, kg				
CrCl, mL/min, r				
ASA, n (%)				
Clopidogrel, n (				
Triple therapy, n (%)	10 (3.8)	13 (3.6)	14 (3.4)	0.93
NSAID, n (%)	39 (15.9)	42 (11.5)	34 (8.4)	0.023

SOLO COME APPROFONDIMENTO – sottoanalisi MAJEED

Patients with major bleeding on dabigatran were older, had lower CrCl, and greater use of ASA and NSAIDs

Data derived based on case narrative analysis using a cut-off interval of 3 days between last dose and onset of bleeding. There was a total of 1121 major bleeding events in 1034 patients

*Data combined from dabigatran 150 mg and 110 mg BID treatment groups; ASA = acetylsalicylic acid; CrCl = creatinine clearance; NSAID = non-steroidal anti-inflammatory drug; SD = standard deviation

Majeed A et al. Circulation 2013; Epub ahead of print

Major bleeding on dabigatran etexilate and warfarin: bleeding events by bleeding sites

	Dabigatran*	Warfarin	P value
Intracranial, n	52	90	<0.001
Gastrointest			
Respiratory,			
Urinary, n			
Genital, n			
Intra-articular, n	9	10	0.19
Intra-muscular, n	11	20	0.002
Other	166	93	0.44
Post-operative	50	27	0.59

SOLO COME APPROFONDIMENTO – sottoanalisi MAJEED

*Data combined from dabigatran 150 mg and 110 mg twice daily treatment groups

Majeed A et al. Circulation 2013; Epub ahead of print

Major bleeding on dabigatran etexilate and warfarin: management strategies – RE-LY®

	Dabigatran*	Warfarin	P value
Patients with major bleeds, n (%)	741 (100)	421 (100)	
Blood tran			
Fresh froz			
Vitamin K,			
Prothroml			
Recombinant Factor VIIa, n (%)	8 (1.1)	3 (0.7)	0.53

SOLO COME APPROFONDIMENTO – sottoanalisi MAJEED

Major bleeds in the dabigatran groups were more frequently treated with blood transfusions than those on warfarin but less frequently with FFP

Data derived based on the randomized set of RE-LY®

*Data combined from dabigatran 150 mg and 110 mg twice daily treatment groups

FFP = fresh frozen plasma

Majeed A et al. *Circulation.* 2013;128:2325-2332

Major bleeding on dabigatran etexilate and warfarin: short-term consequences – RE-LY®

	Dabigatran*	Warfarin	P value
Patients with major bleeds, n (%)	741 (100)	421 (100)	
Hospitalization events,† n (%)	510 (57.0)	273 (56.5)	0.89
Length of stay,			
Nights in ICU/C			
Nights in step-d			
Patients with m			
Patients with major bleed requiring surgery or resulting in death, n (%)	132 (17.8)	94 (22.3)	0.06
Decrease in haemoglobin from baseline to time of bleeding, g/L, mean (SD)	38.0 (27.2)	30.7 (24.7)	0.02

SOLO COME APPROFONDIMENTO – sottoanalisi MAJEED

Length of stay in ICU shorter with dabigatran than with warfarin

Data derived based on the randomized set of RE-LY®; *Data combined from dabigatran 150 mg and 110 mg twice daily treatment groups; †First reported hospitalization is given for a major bleeding event, if admission to hospital was between 1 day before event and 7 days after event; Length of stay, night in ICU/CCU, night in step-down unit was obtained from all hospitalization events (dabigatran = 510; warfarin = 273) BID = twice daily; CCU = coronary care unit; ICU = intensive care unit; SD = standard deviation;

Majeed A et al. Circulation 2013; Epub ahead of print

Major bleeding on dabigatran etexilate and warfarin: prognosis of ICH – RE-LY®

- Data on the initial and final Rankin score evaluations were available for 78 (55%) patients with ICH

Treatment comparison	P value for comparison of change in
Dabigatran*	
Dabigatran 1	
Dabigatran 1	
Dabigatran 150 mg BID vs 110 mg BID	0.78

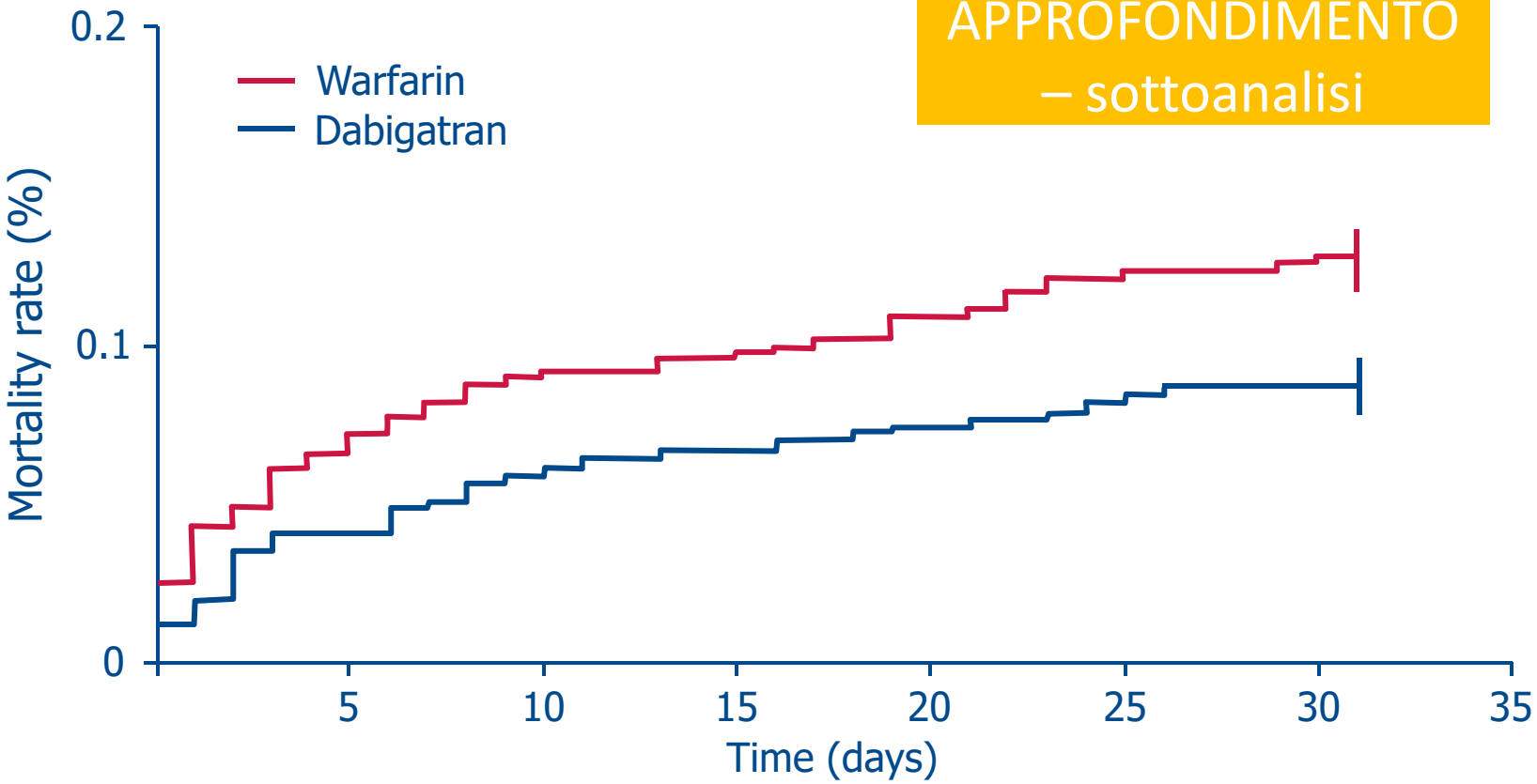
SOLO COME APPROFONDIMENTO – sottoanalisi MAJEED

No significant difference between treatments in modified Rankin scale score for ICH since admission

*Data combined from dabigatran 150 mg and 110 mg BID treatment groups
BID = twice daily; ICH = intracranial haemorrhage
Majeed A et al. Circulation 2013; Epub ahead of print

Major bleeding on dabigatran etexilate and warfarin: mortality after a major bleed – five Phase III trials

APPROFONDIMENTO – sottoanalisi



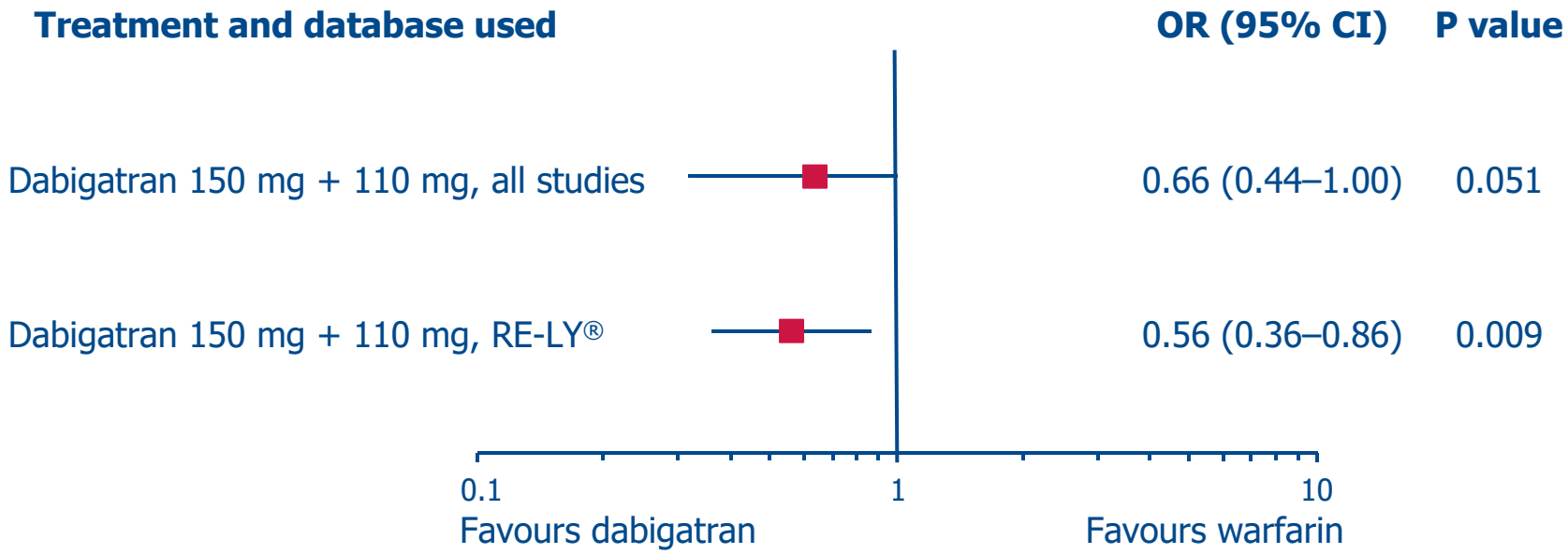
The Kaplan–Meier analysis indicated a trend to reduced risk for death with dabigatran* vs warfarin during 30 days from the bleeding (P=0.052)

Data combined from dabigatran 150 mg and 110 mg BID treatment groups. Only first major bleed included. Analysis not adjusted for covariates

Majeed A et al. Circulation 2013; Epub ahead of print

Major bleeding on dabigatran etexilate and warfarin: adjusted analysis of mortality after major bleed

- Odds ratio (OR) for 30-day mortality adjusted for sex, age, weight, renal function, and additional antithrombotic therapy



Adjusted analysis demonstrates mortality benefit for dabigatran in RE-LY®

Majeed A et al. *Circulation.* 2013;128:2325-2332

new

Major bleeding on dabigatran etexilate and warfarin: conclusions

- For dabigatran, the prognosis after a major bleed trended to be better than after a warfarin-associated bleed and the overall resources required to manage the bleed were not greater
- A better prognosis was observed with dabigatran than with warfarin, despite the absence of a specific antidote for dabigatran
  - In addition, dabigatran-treated patients were at higher risk of bleeding due to older age, poorer renal function and greater use of co-medications
- In the RE-LY population, for dabigatran vs warfarin:
  - patients with major bleeds had a significantly shorter length of stay in the ICU
  - mortality after a major bleed was significantly lower

ICU = intensive care unit

Majeed A et al. Circulation 2013; Epub ahead of print

new

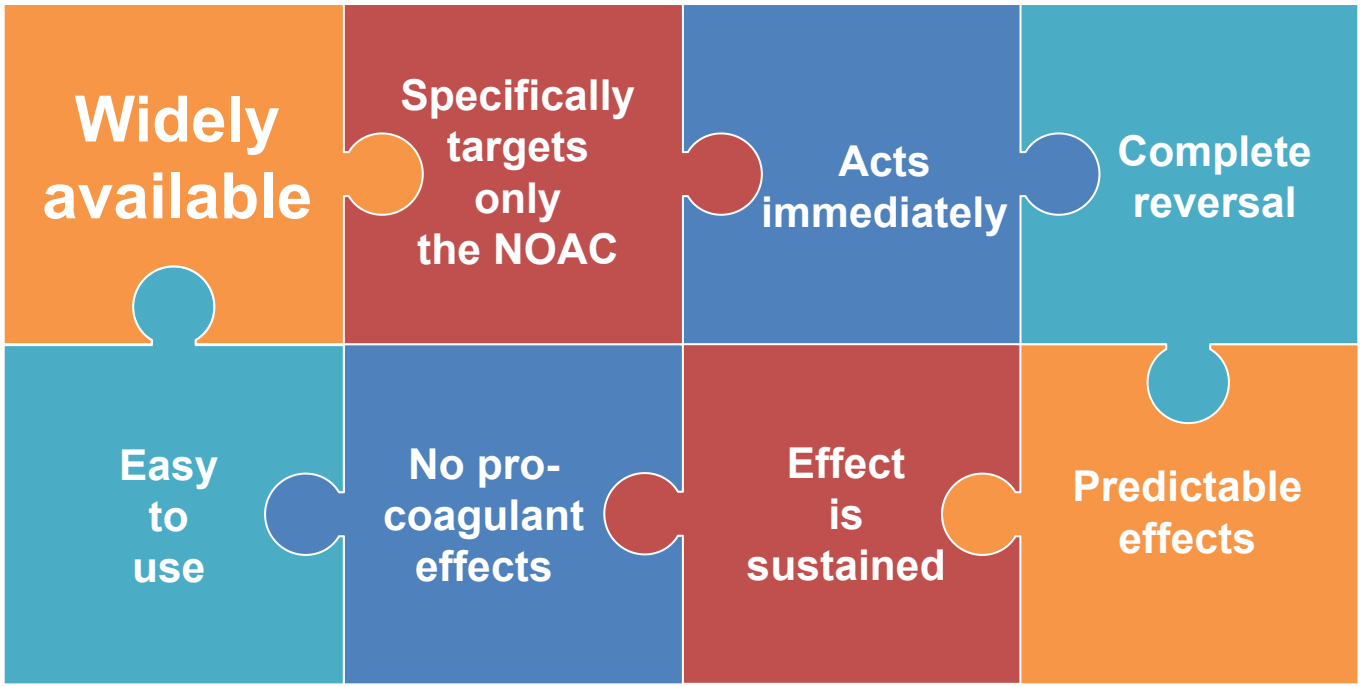
DOPO QUESTE EVIDENZE DI SICUREZZA, SIA SULLA BASSA INCIDENZA DI SANGUINAMENTI MAGGIORI SIA SUL BENEFICIO IN TERMINI DI MORTALITA' VERSO WARFARIN, A COSA CI SERVE AVERE UN ANTIDOTO?

SANGUINAMENTO MAGGIORE: DEFINIZIONE E COMPLICANZE → IMPORTANZA DI AVERE UN ANTIDOTO

PRAXBIND, L'ANTIDOTO IDEALE. DATI DAL REVERSE AD CON FOCALIZZAZIONE SUL PAZIENTE CON "UNCONTROLLED BLEEDING" + RACCOMANDAZIONI DA LINEE GUIDA SULLA GESTIONE DELL'EMERGENZA EMORRAGICA

Dabigratan ...
basso indice di sanguinamento, alta efficacia prevenzione cardioembolismo

Idarucizumab fulfils the characteristics of an ideal reversal agent



Idarucizumab was designed as a specific reversal agent for the anticoagulant activity of dabigatran

Humanized antibody fragment (Fab)

Specific

Bindin
dabig
higher th
to thrombin, resulting in essentially irreversible binding

No endogenous targets

Idarucizumab

Ready to use solutions for IV administration

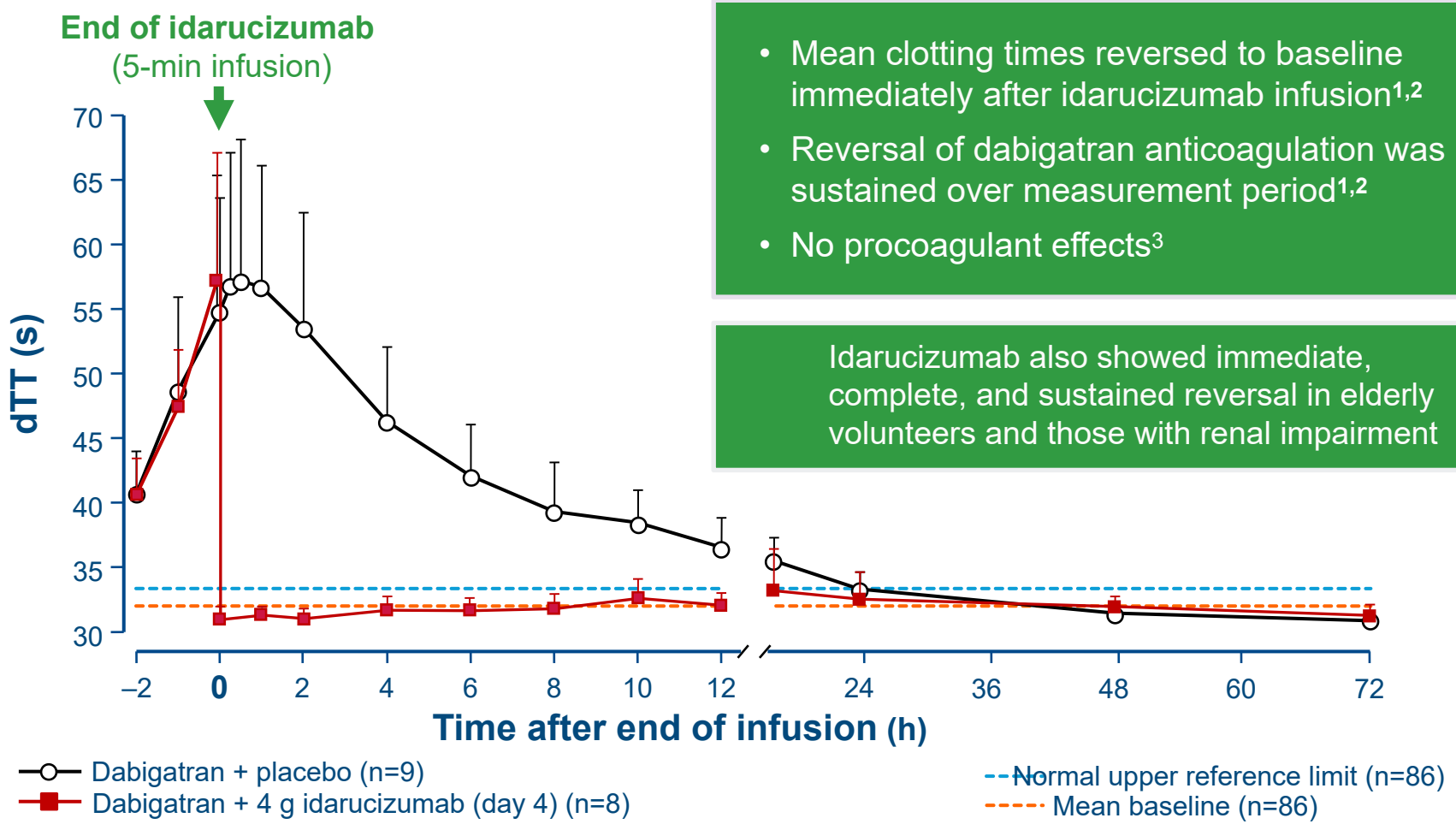
et

or
tivity

Idarucizumab–dabigatran complex is eliminated quickly (within a few hours)

APPROFONDIMENTO

Adapted from Schiele F et al. Blood 2013; Eikelboom J et al. Circulation 2015; Praxbind® EU SPC, 2015; Schmohl M et al. Thromb Haemost 2016

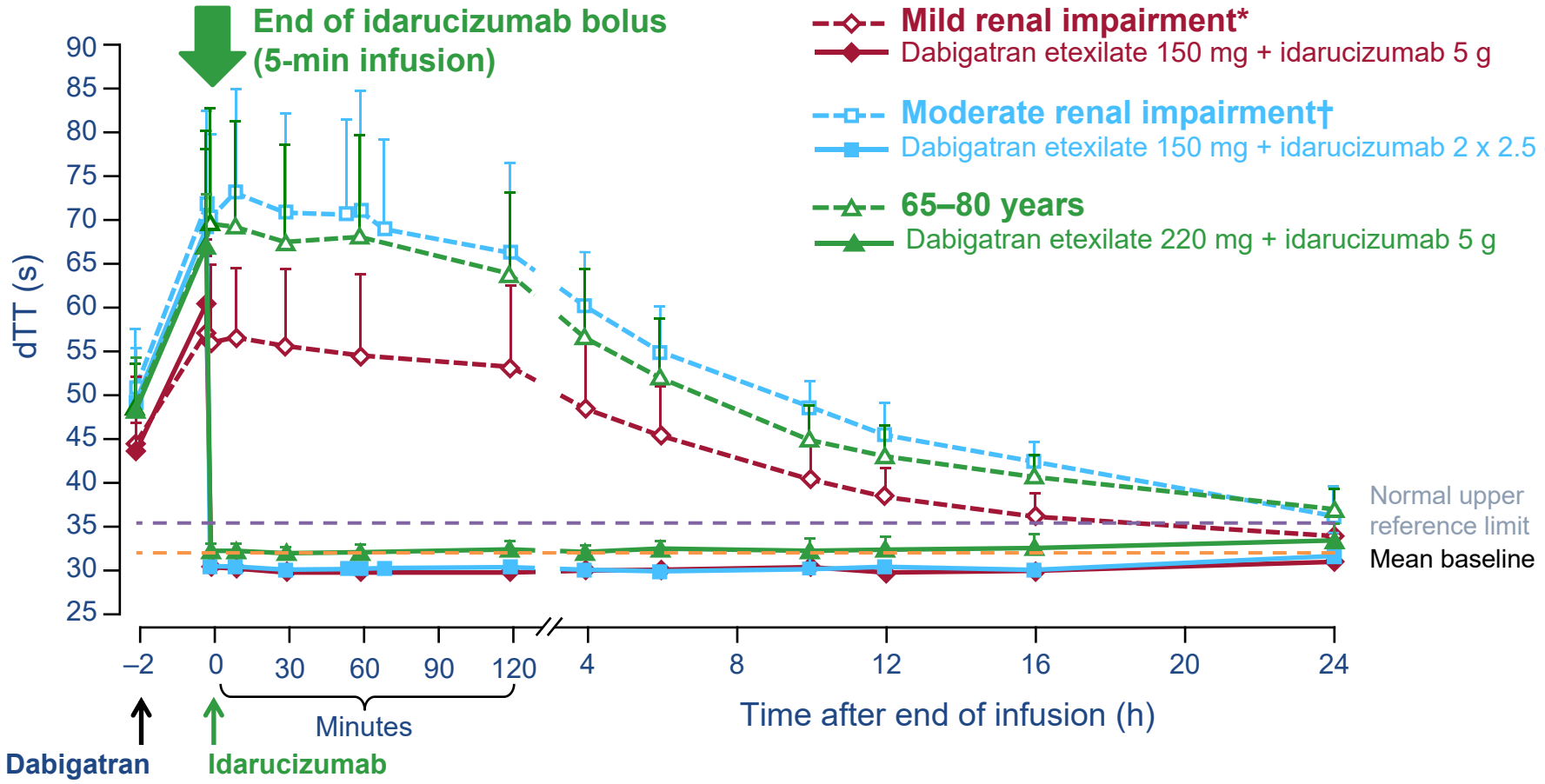


- Mean clotting times reversed to baseline immediately after idarucizumab infusion[1,2]
- Reversal of dabigatran anticoagulation was sustained over measurement period[1,2]
- No procoagulant effects[3]

Idarucizumab also showed immediate, complete, and sustained reversal in elderly volunteers and those with renal impairment

dTT, diluted thrombin time. 1. Glund S et al. Lancet 2015; 2. Glund S et al. Thromb Haemost 2015; 3. Glund S et al. ASH 2014

Idarucizumab shows **immediate, complete, and sustained** reversal in healthy elderly subjects and those with mild or moderate renal impairment



*CrCl ≥60–<90 mL/min; †CrCl ≥30–<60 mL/min; dTT, diluted thrombin time

Glund S et al. Clin Pharmacokinet 2016

Idarucizumab was **well tolerated** across subject groups

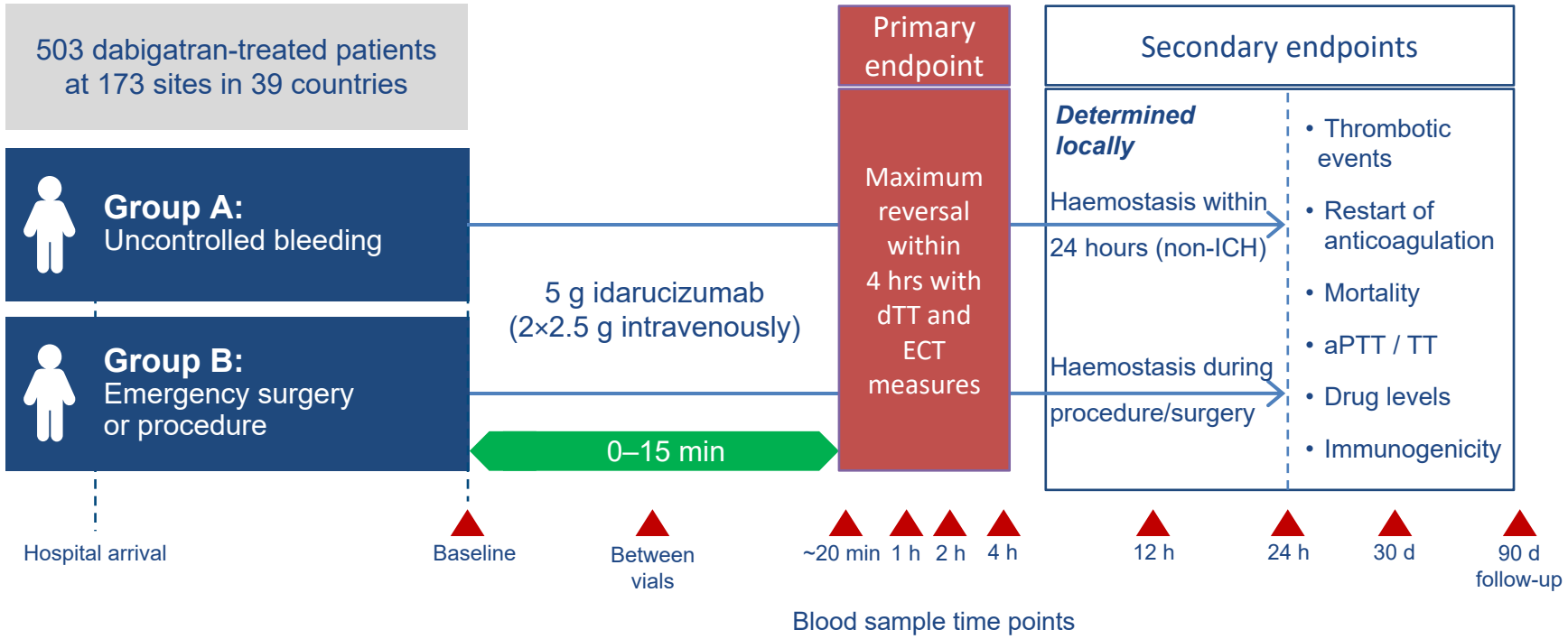
- No serious drug-related AEs reported in total >200 volunteers
- No relevant changes in any of the investigated safety parameters
- No procoagulant effects

APPROFONDIMENTO

AE, adverse event

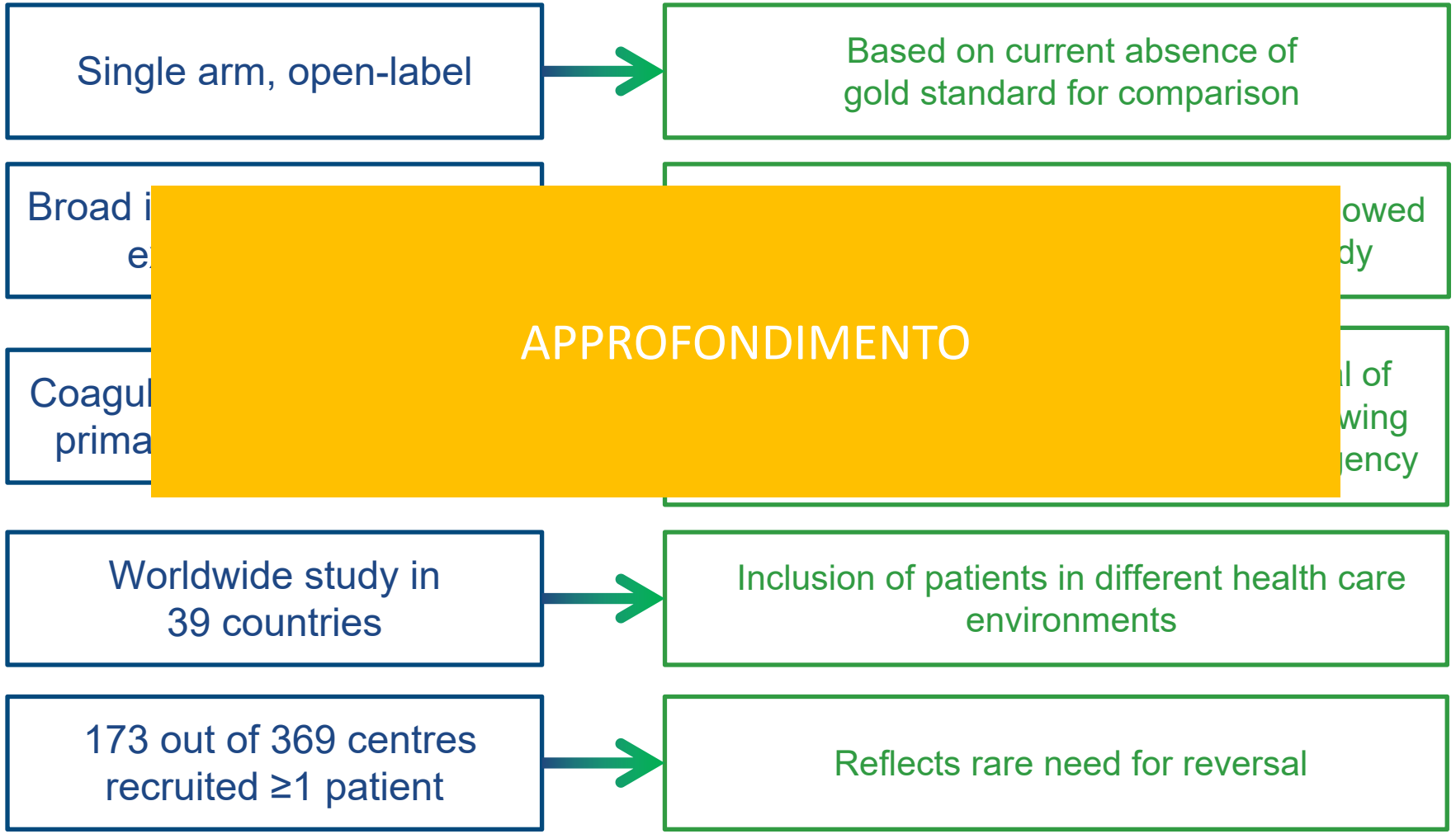
Glund S et al. Clin Pharmacokinet 2016; Eikelboom J et al. Circulation 2015

RE-VERSE AD was a multicentre, open-label, single-arm Phase III trial



aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time; TT, thrombin time;
Pollack C et al. N Eng J Med 2017; Pollack C et al. Thromb Haemost 2015

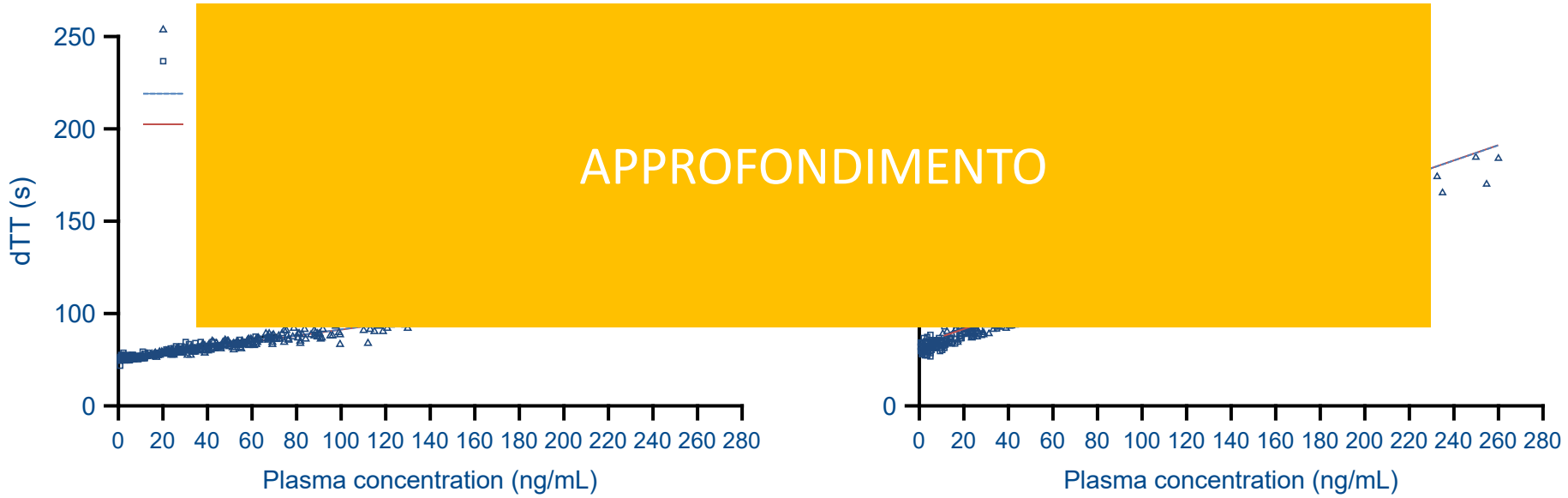
RE-VERSE AD: key study design elements



Pollack C et al. Thromb Haemost 2015; Pollack C et al. N Engl J Med 2017

RE-VERSE AD: the primary endpoint is based on reversal of dabigatran-induced anticoagulation

Maximum % reversal of the anticoagulation effect of dabigatran based on central laboratory assessment of dTT or ECT within 4 hours after idarucizumab administration (each patient has own baseline measurement)



Absence of idarucizumab: dTT = 32.22+0.203*Conc, R^2 = 0.94
Presence of idarucizumab: dTT = 31.60+0.230*Conc, R^2 = 0.86

Absence of idarucizumab: ECT = 42.01+0.518*Conc, R^2 = 0.92
Presence of idarucizumab: ECT = 37.81+0.610*Conc, R^2 = 0.89

dTT and ECT show linear correlations with a wide range of dabigatran concentrations

Glund S et al. Lancet 2015; Pollack C et al. Thromb Haemost 2015

RE-VERSE AD: secondary endpoints include clinical parameters

Clinical secondary endpoints

- Time to recorded cessation of bleeding* in group A: determined by local investigator
- Haemostasis during procedure in group B: assessed by local investigator as normal or mildly, moderately, or severely abnormal
- Adjudica

Laborator

- Time to
- Serial da
- Local an

APPROFONDIMENTO

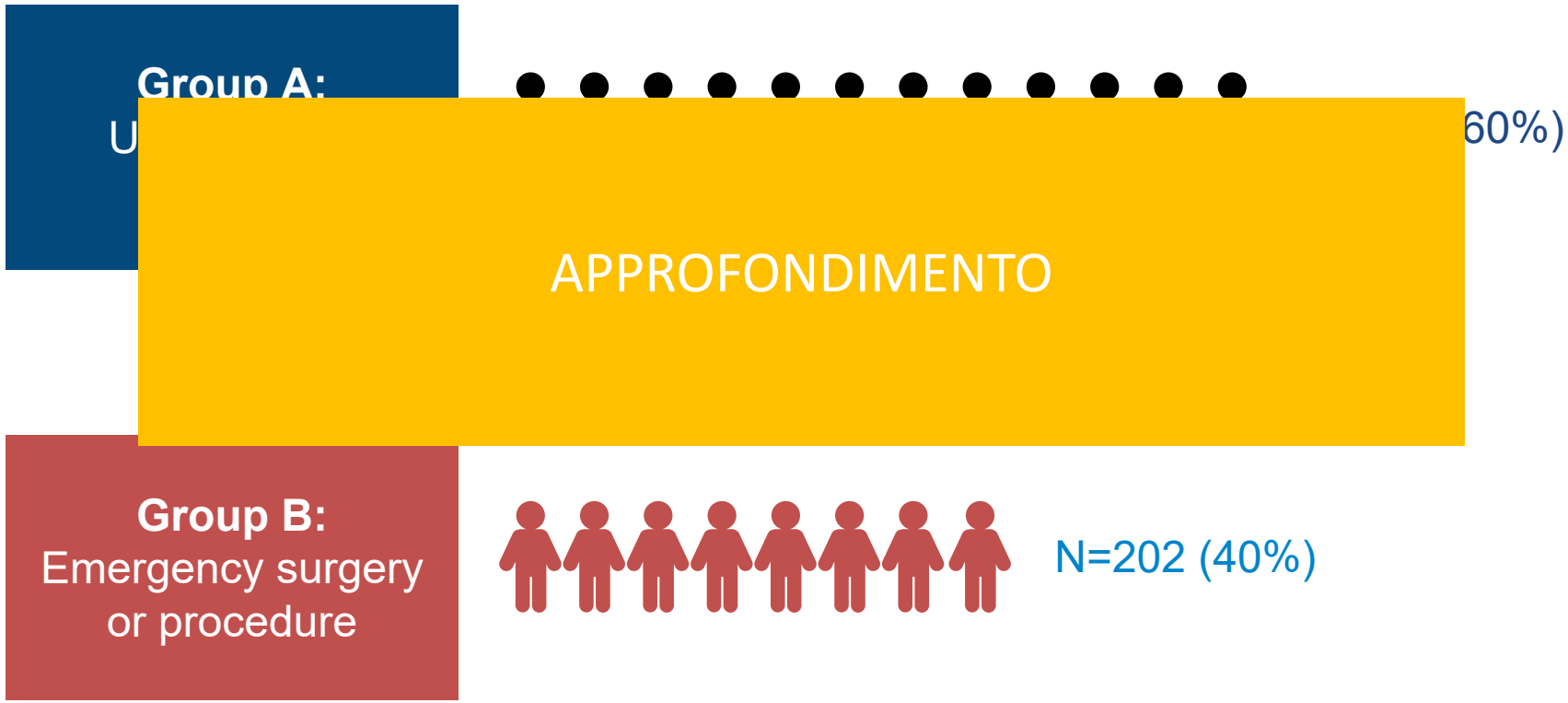
Further endpoints

- Mortality
- Use of blood products and other therapies
- Restart of antithrombotic therapy
- For patients with ICH: serial CT scan to evaluate volume expansion and estimate of blood volume
- Modified Rankin scores (entry and 90 days) for ICH

*No prespecified time points or methodology for assessment

Pollack C et al. Thromb Haemost 2015

RE-VERSE AD: final results from 503 patients were published in the *New England Journal of Medicine* in 2017



Pollack C et al. N Engl J Med 2017

RE-VERSE AD: on average, enrolled patients were elderly with moderate renal impairment

Characteristic		Group A (n=301)	Group B (n=202)	Total (N=503)
Age (yrs)*		79 (24–96)	77 (21–96)	78 (21–96)
Male sex, n (%)		172 (57.1)	102 (50.5)	274 (54.5)
Creatinine clearance (mL/min)*		50.8 (6.1–216.9)	56.0 (7.9–198.7)	52.6 (6.1–216.9)
Comorbiditie				
				(9.3)
Dabigatran,				
	Atrial fibrillation indication	288 (95.7)	190 (94.1)	478 (95.0)
Daily dose	150 mg BID	94 (31.2)	57 (28.2)	151 (30.0)
	110 mg BID	185 (61.5)	126 (62.4)	311 (61.8)
	75 mg BID	16 (5.3)	8 (4.0)	24 (4.8)
Patient-reported time since last dose (hrs)*		14.6 (1.5, 90.4)	18.0 (2.6, 105.8)	15.6 (1.5, 105.8)
Elevated dTT at baseline, n (%)		244 (81.1)	152 (75.2)	396 (78.7)
Elevated dTT or ECT at baseline, n (%)		276 (91.7)	185 (91.6)	461 (91.7)

APPROFONDIMENTO

*Shown as median (range); TIA, transient ischaemic attack

Pollack C et al. N Engl J Med 2017

RE-VERSE AD Group A (n=301): patients were enrolled due to major bleeding events

Type of bleeding*	N (%)
Intracranial	98 (32.6)
Subdural	39
Subarachnoid	26
Gastro	
Intram	
Retroperitoneal	10 (3.3)
Intra-pericardial	7 (2.3)
Intra-articular	5 (1.7)
Intraocular	1 (0.3)
Other	52 (17.3)
Not identified	4 (1.3)

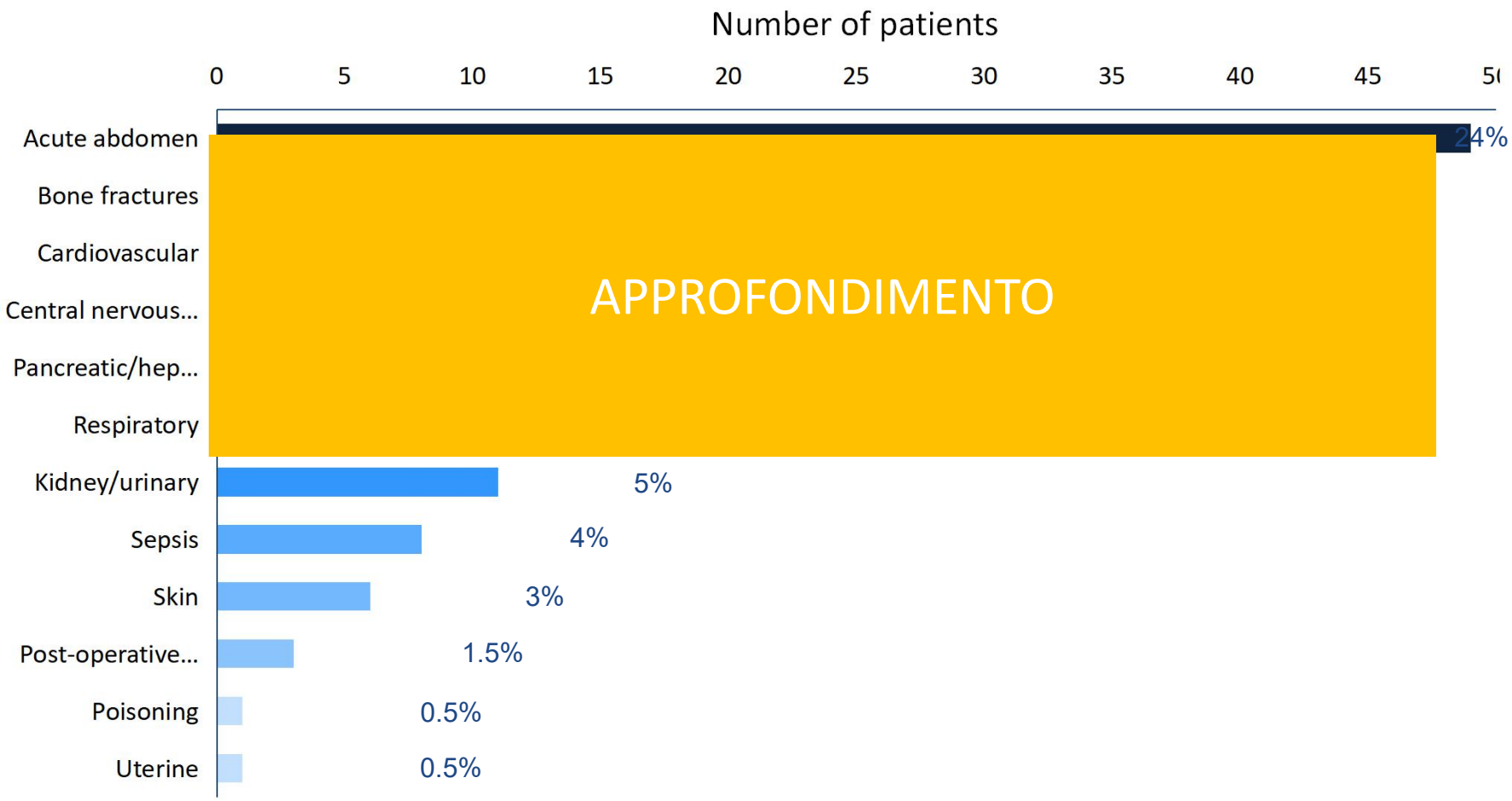
Adjudicated ISTH bleeding severity:

88% Major and life-threatening bleeding

APPROFONDIMENTO

*Bleeding may occur at more than one site; Pollack C et al. N Engl J Med 2017

RE-VERSE AD Group B (n=202): patients were enrolled due to a variety of conditions requiring emergency procedures



RE-VERSE AD: primary endpoint showed immediate reversal of dabigatran-mediated anticoagulation in majority of patients

Median maximum reversal within 4 hours was 100% for both dTT and ECT (95% CI: 100–100)

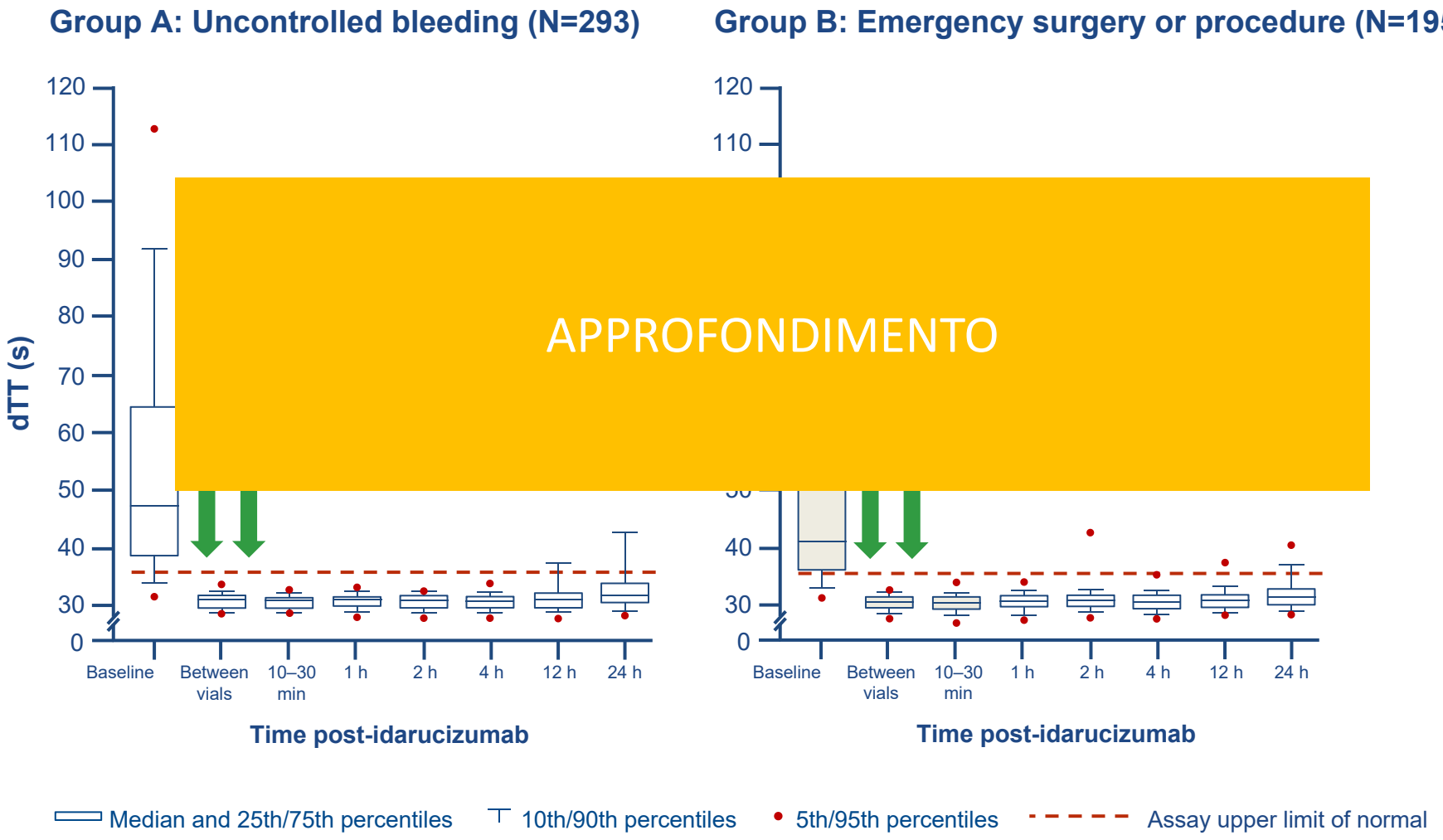
Similar

APPROFONDIMENTO

dTT normalized* within 4 hours in 241/244 patients (98.8%) in Group A and 150/152 patients (98.7%) in Group B

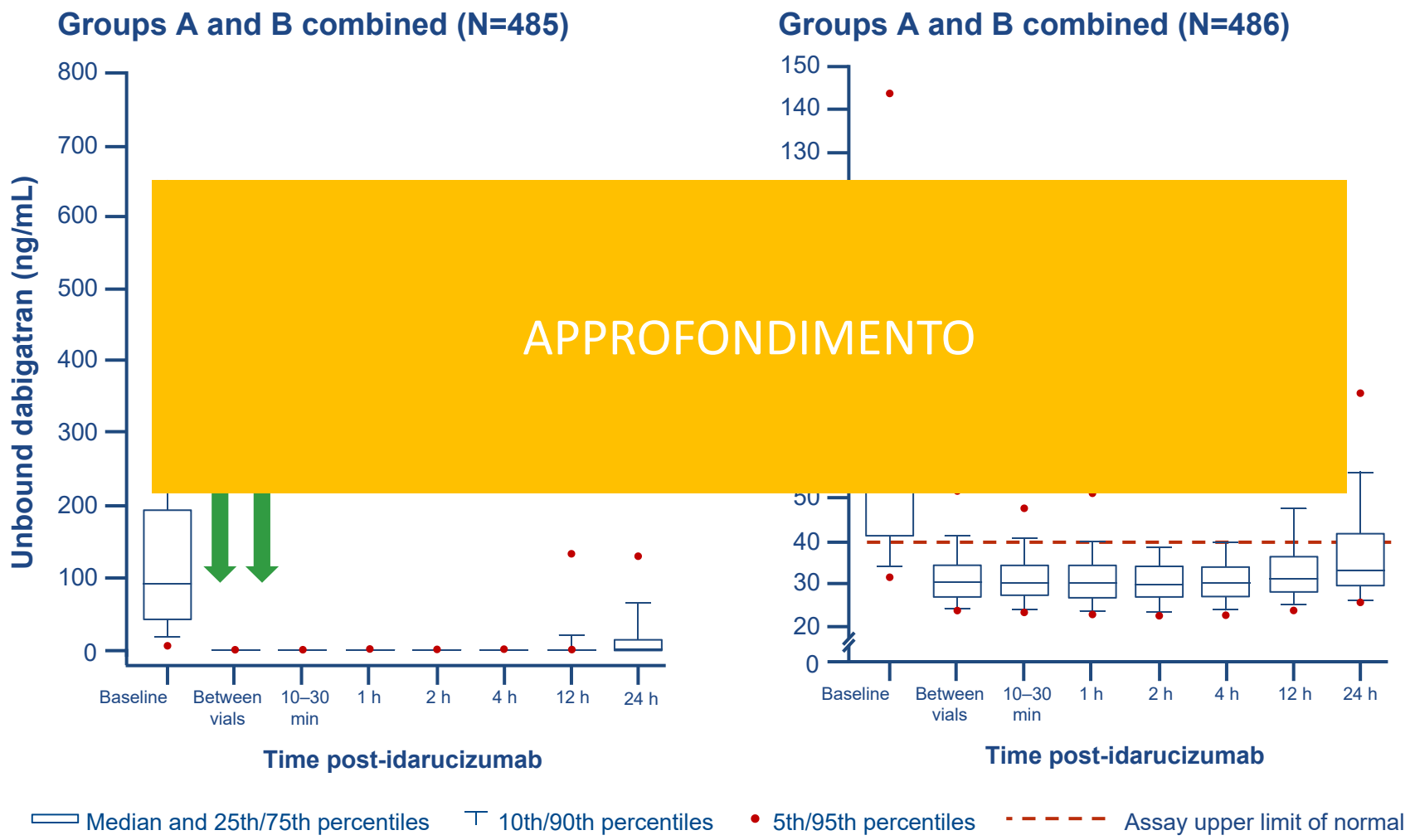
*At or below the upper limit of normal;
All data measured in central laboratory, aPTT and TT outcomes were secondary endpoints
Pollack C et al. N Engl J Med 2017; Pollack et al. Presented at ISTH 2017

RE-VERSE AD: reversal of dabigatran anticoagulation in Groups A and B, based on dTT



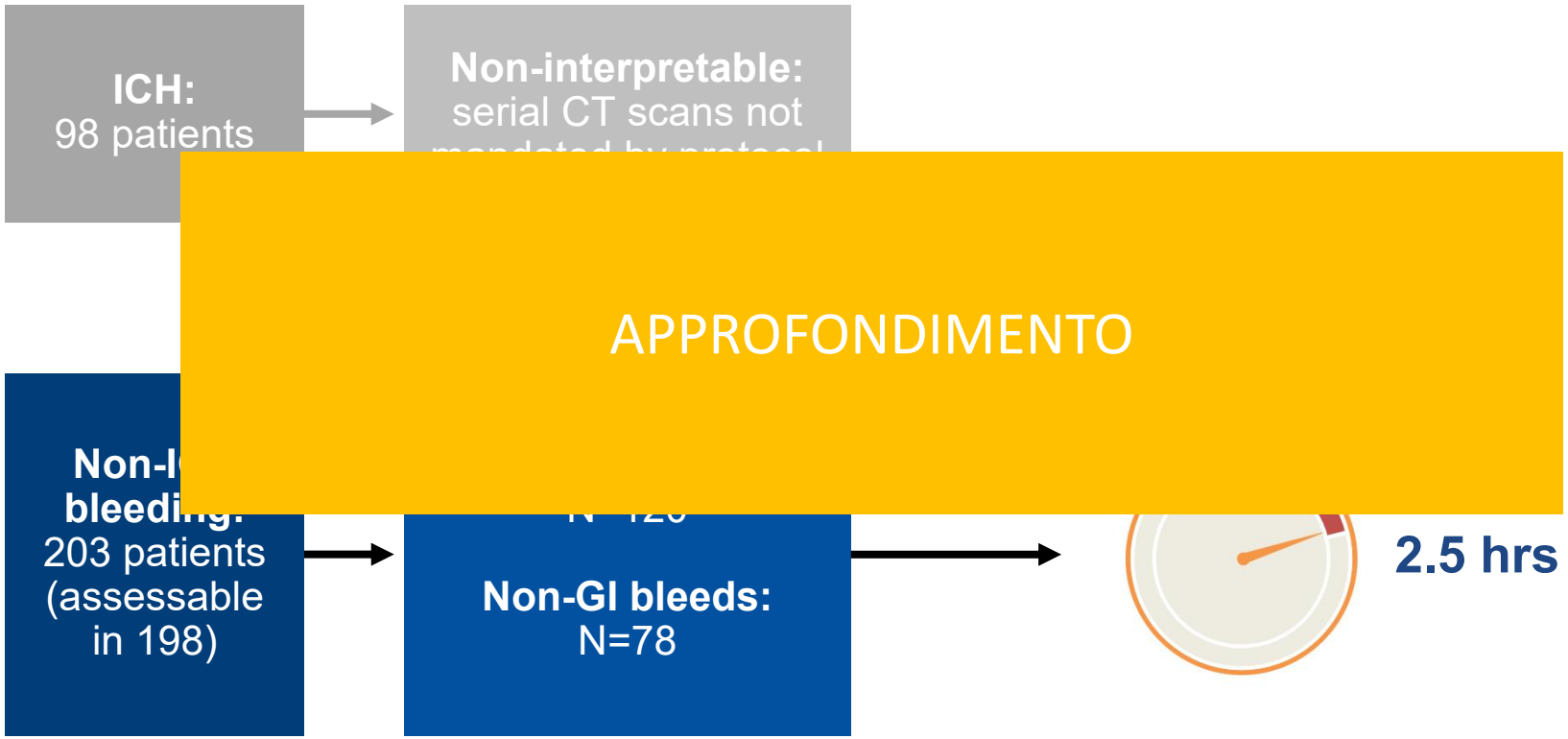
Pollack C et al. N Engl J Med 2017

RE-VERSE AD: dabigatran reversal measured as unbound dabigatran and aPTT



Pollack C et al. N Engl J Med 2017

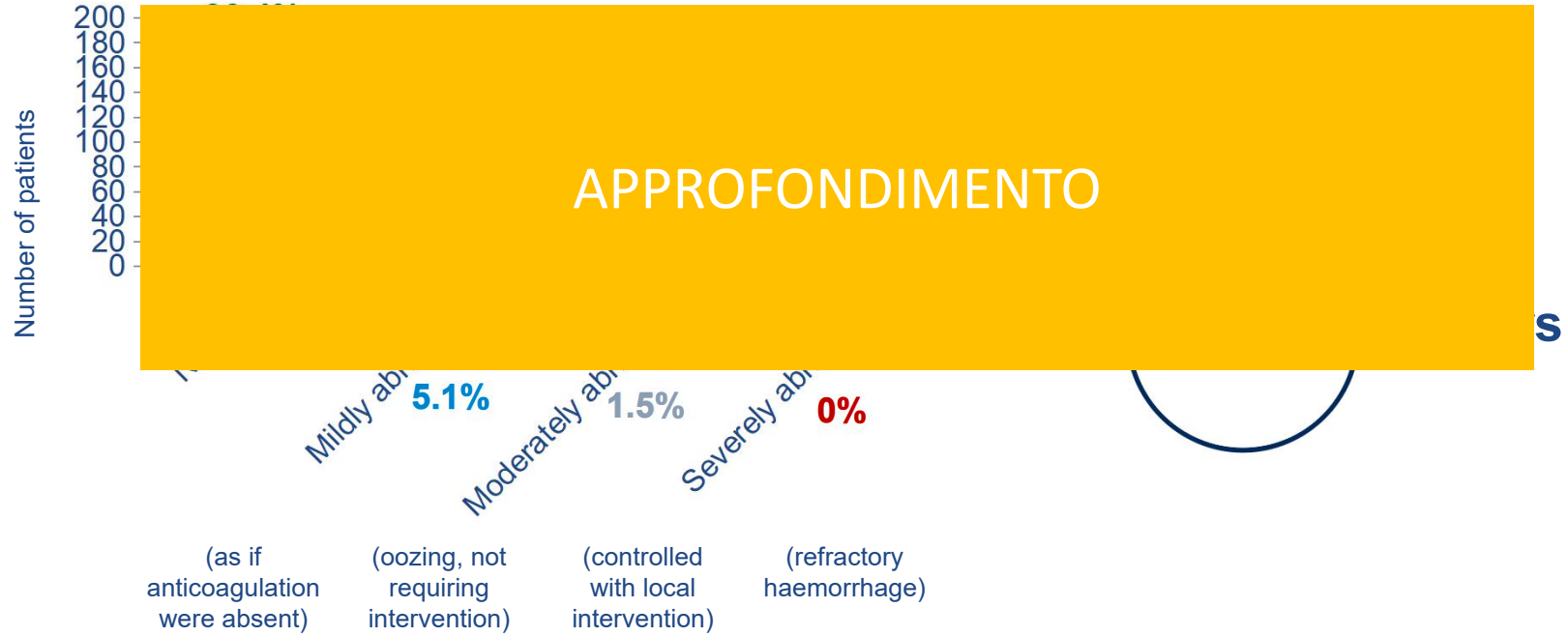
Group A: bleeding stopped within 2.5 hours in patients with extracranial haemorrhage



*Local investigator-determined time to bleeding cessation
Pollack C et al. N Engl J Med 2017

Group B: most patients had normal haemostasis during surgery

197/202 (97.5%) patients underwent surgery/procedure with periprocedural haemostasis classed as:



Pollack C et al. N Engl J Med 2017

RE-VERSE AD: no safety concerns and no evidence of a prothrombotic effect

Events n (%)	Group A (n=301)	Group B (n=202)	Total (n=503)
30 days	14 (4.6)	10 (5.0)	24 (4.8)

APPROFONDIMENTO

- At **72**
  had r
- By **90 days**, antithrombotic therapy had been re-started in 72.8% of Group A and 90.1% of Group B patients
- Patients restarted on dabigatran:
  - 28.9% in Group A (median time 16 days)
  - 61.4% in Group B (median time 6 days)

Pollack C et al. N Engl J Med 2017; Pollack et al. Presented at ISTH 2017

RE-VERSE AD: mortality reflects severity of the underlying diseases

- Within 5 days of idarucizumab treatment, 19 deaths occurred in Group A (6.3%) and 16 deaths occurred in Group B (7.9%)

- Kaplan–Meier rates at 30 and 90 days:

		Group A (n=301)	Group B (n=202)
30 days	Patients at risk, n	254	169
	Mortality, %	13.5	12.6
90 days	Patients at risk, n	152	109
	Mortality, %	18.8	18.9

APPROFONDIMENTO

Pollack C et al. N Engl J Med 2017; Pollack et al. Presented at ISTH 2017

RE-VERSE AD: key results in a cohort of multi-morbid elderly patients presenting with life-threatening emergencies

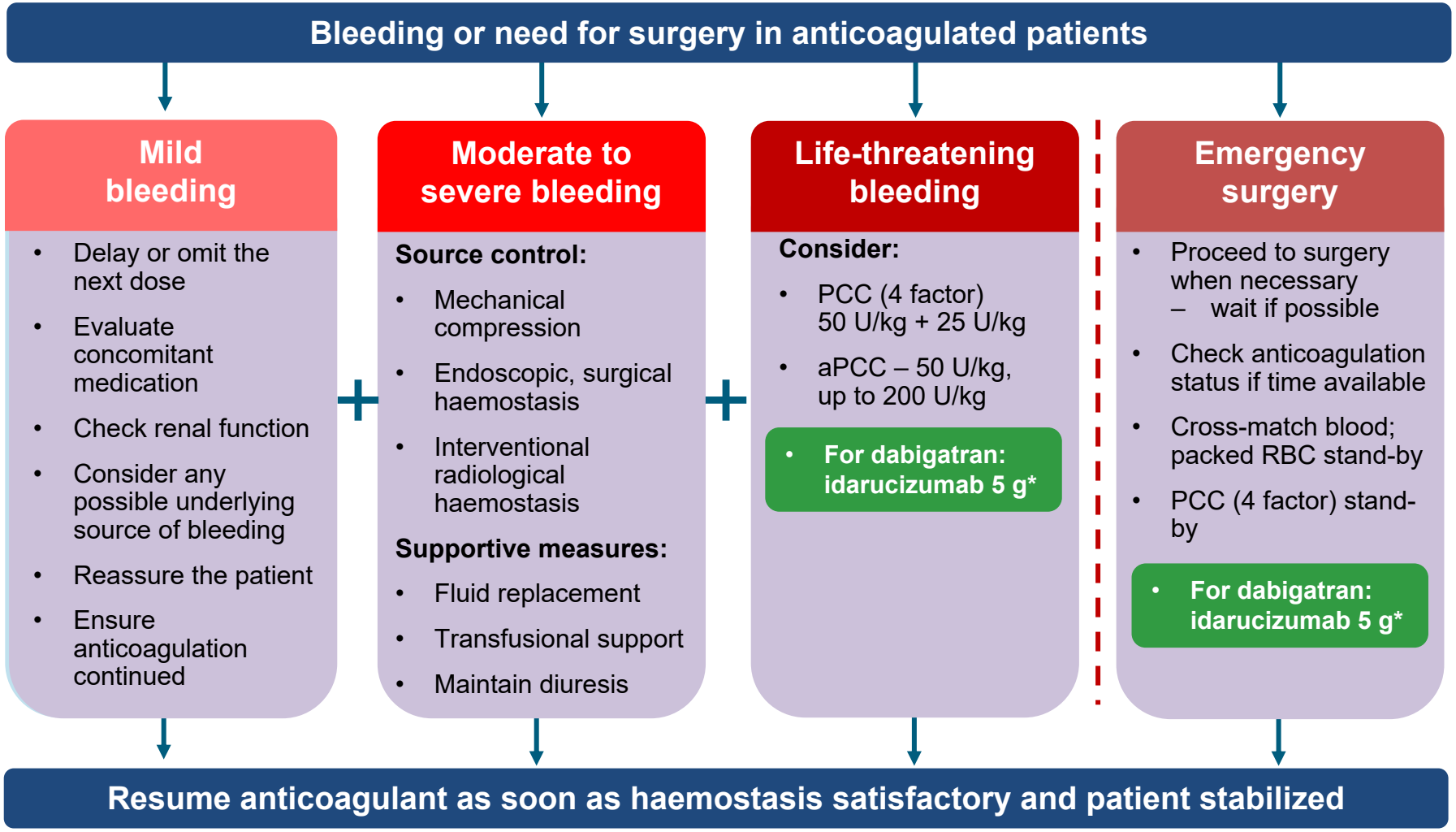
1. **5 g of idarucizumab resulted in immediate, complete, and sustained reversal of dabigatran anticoagulation**
2. **in**
3. **mal' intraoperative haemostasis in 93% of Group B patients**
4. **No safety concerns identified to date**

APPROFONDIMENTO

Pollack C et al. N Engl J Med 2017; Pollack et al. Presented at ISTH 2017

APPROFONDIMENTO

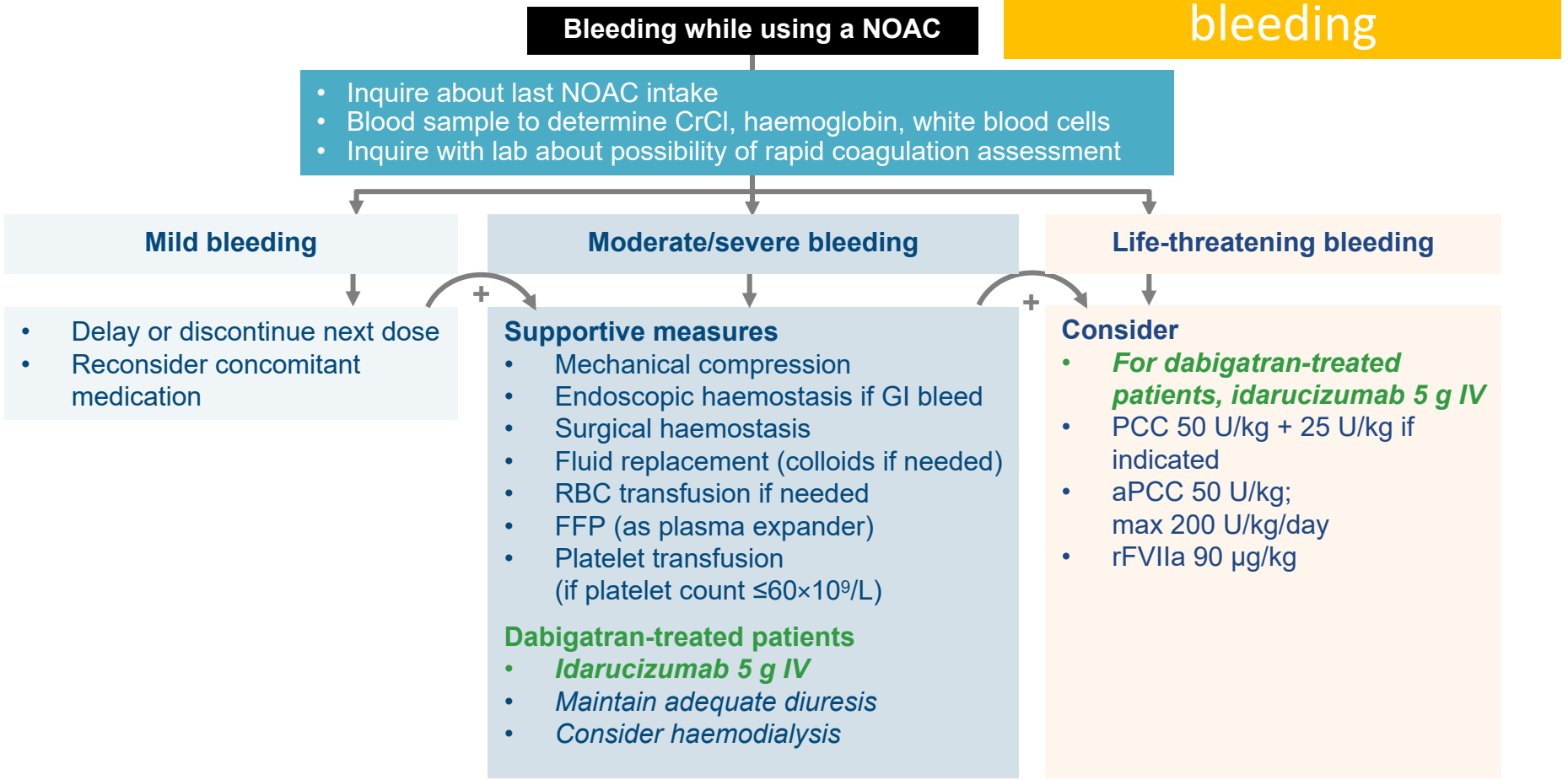
Idarucizumab is recommended to reverse dabigatran anticoagulation in patients requiring emergency surgery or with life-threatening bleeding



*Idarucizumab is the preferred treatment to reverse dabigatran; PCC, prothrombin complex concentrate; RBC, red blood cell; Anticoagulation Education Task Force White Paper: Ageno W et al. Thromb Haemost 2016

EHRA guidance on the management of bleeding in patients using NOACs

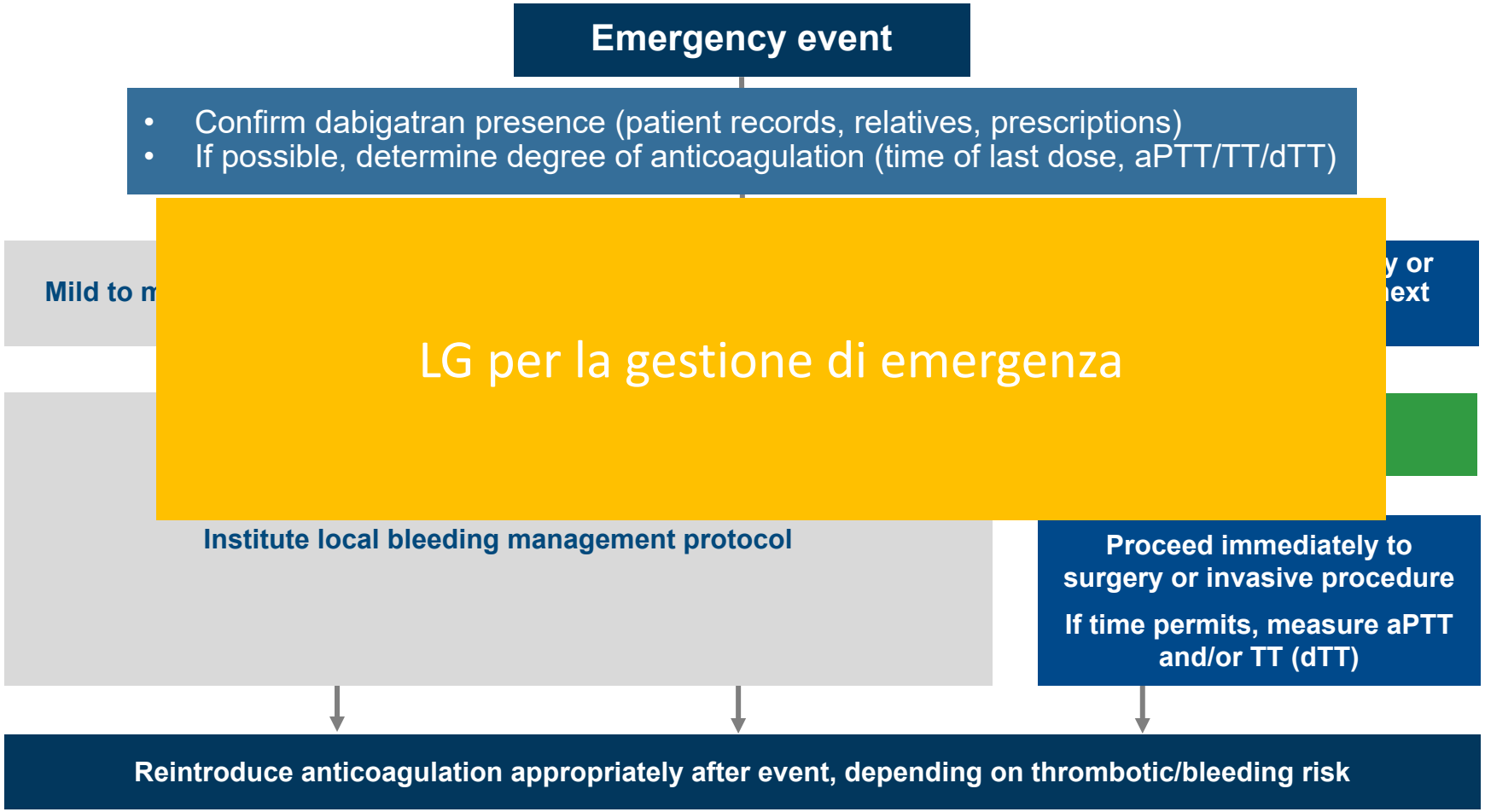
LG per la gestione di bleeding



aPCC, activated prothrombin complex concentrate; FFP, fresh frozen plasma; IV, intravenous; PCC; prothrombin complex concentrate; RBC, red blood cell; rFVIIa, recombinant activated factor VII

Heidbuchel H et al. Europace 2015; Figure adapted from Heidbuchel H et al. Europace 2015

Idarucizumab is part of a multi-modal approach to the management of bleeding or preparation for urgent surgery



aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; TT, thrombin time

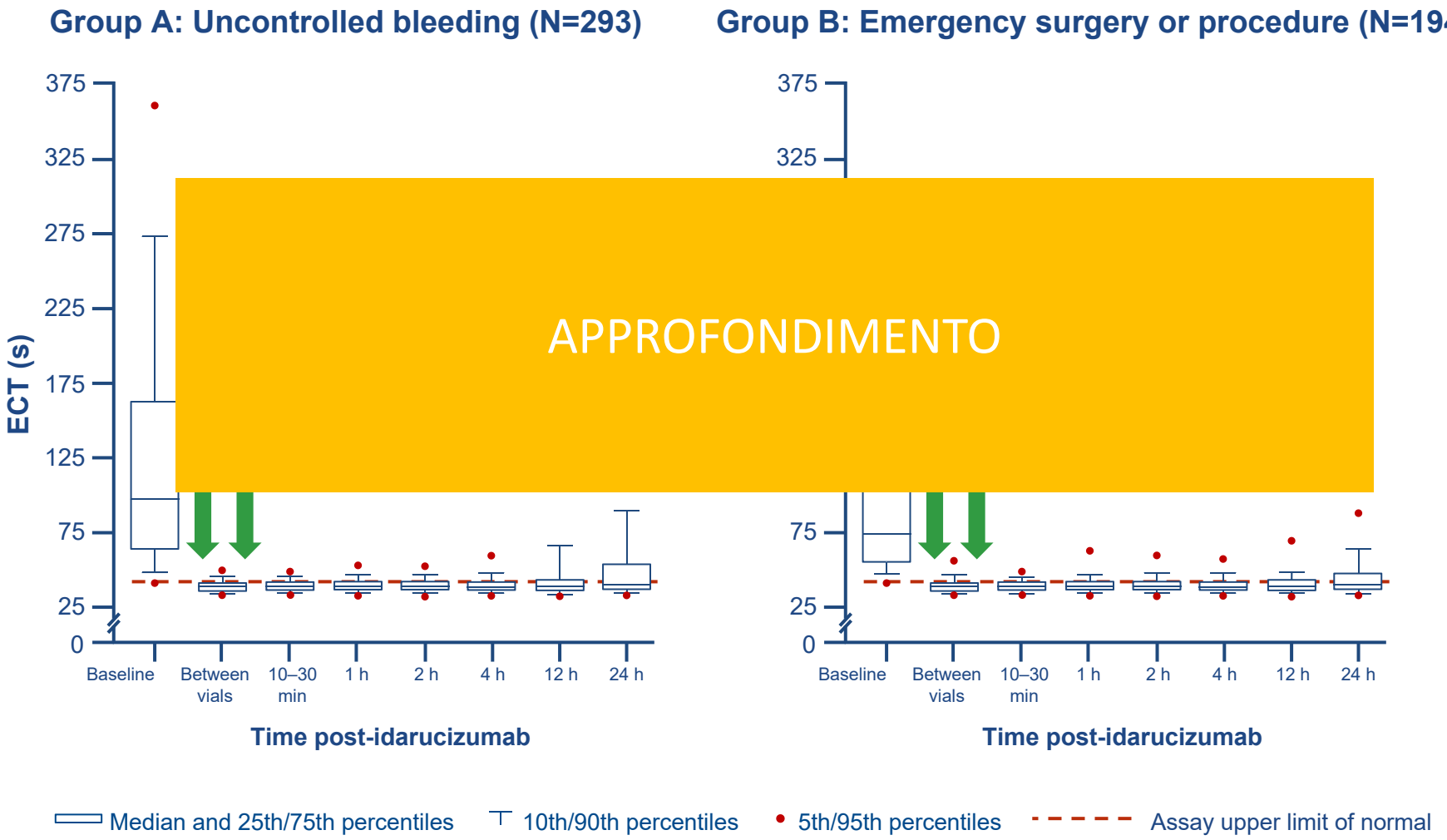
Adapted from Eikelboom J et al. Circulation 2015

Summary

1. Dabigatran has a favourable safety profile shown in clinical trials and confirmed in real-world studies
2. Dabigatran is the only NOAC with a specific reversal agent
3. Idarucizumab provides immediate, complete, and sustained reversal of dabigatran's anticoagulant effect; there are no contraindications
4. Idarucizumab provides an additional option in the emergency management of dabigatran-treated patients taking the NOAC effect out of the equation

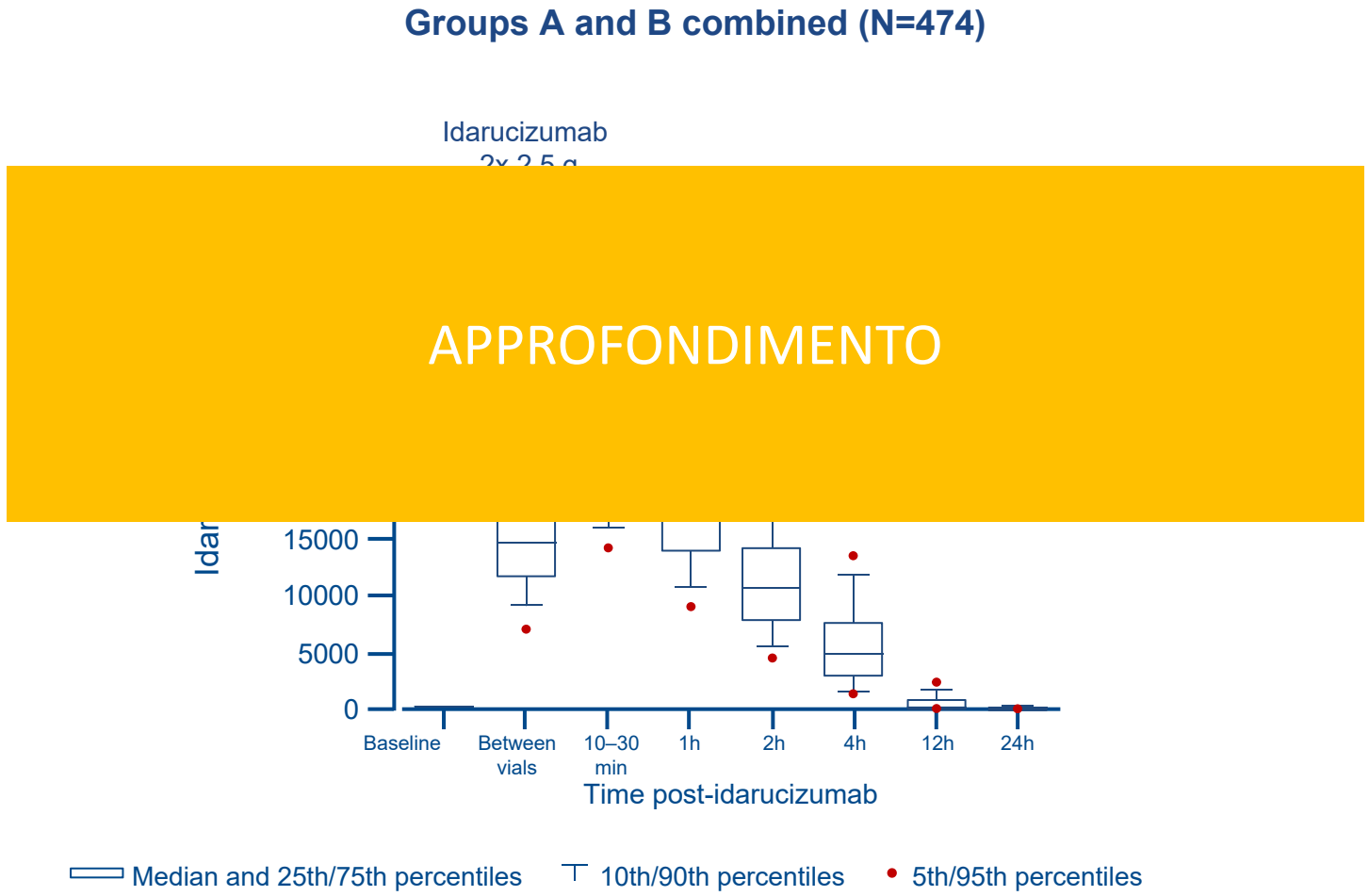
APPROFONDIMENTO

RE-VERSE AD: reversal of dabigatran anticoagulation in Groups A and B, based on ECT



ECT, ecarin clotting time. Pollack C et al. N Engl J Med 2017

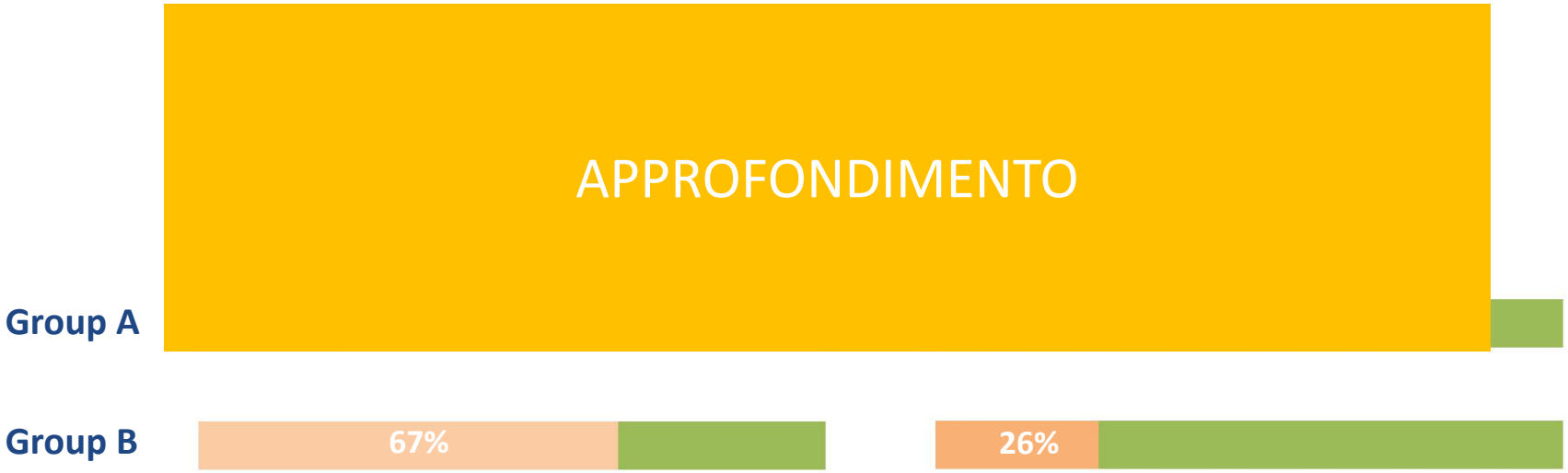
Idarucizumab levels were very low 12 hours after administration



Pollack C et al. N Engl J Med 2017

Re-initiation of antithrombotic treatment within 90 days

Antithrombotic	Group A (N=301)	Group B (N=202)
Any antithrombotic, %	72.8	90.1
Mean time to re-start (days)	13.2	3.5



Pollack C et al. N Engl J Med 2017

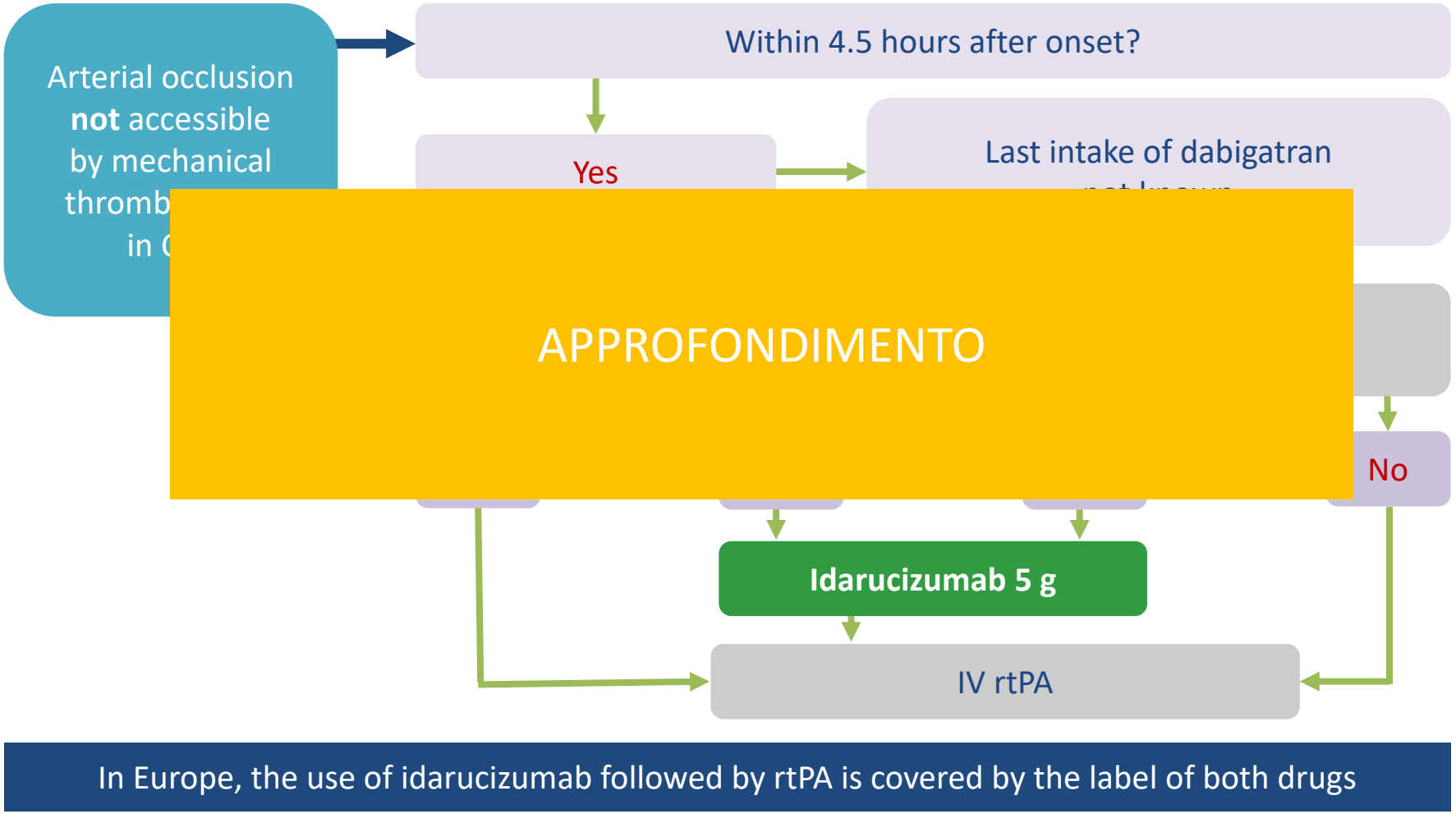
RE-VERSE AD reflects clinical practice as opposed to trials with 4F-PCC

	RE-VERSE AD	4-Factor PCC Major bleeding	4-Factor PCC Urgent surgery
Patient population	Unselected	Highly selected	Highly selected
Reduced causes ot			
Intracrani GCS <7/<			
Confirme			
Expected interventions such as FFP or platelets			
Use of, or expected need for, UFH or LMWH	✓	✗	✗
Acute trauma for which reversal of anticoagulation alone would not be expected to control acute bleeding	✓	✗	✗

APPROFONDIMENTO

GCS, Glasgow coma scale; LMWH, low-molecular-weight heparin; mRS, modified Rankin Score; PCC; prothrombin complex concentrate; UFH, unfractionated heparin; Pollack C et al. Thromb Haemost 2015; Clinicaltrials.gov: NCT02104947; Sarode R et al. Circulation 2013; Clinicaltrials.gov: NCT00708435; Goldstein JN et al. Lancet 2015; Clinicaltrials.gov: NCT00803101

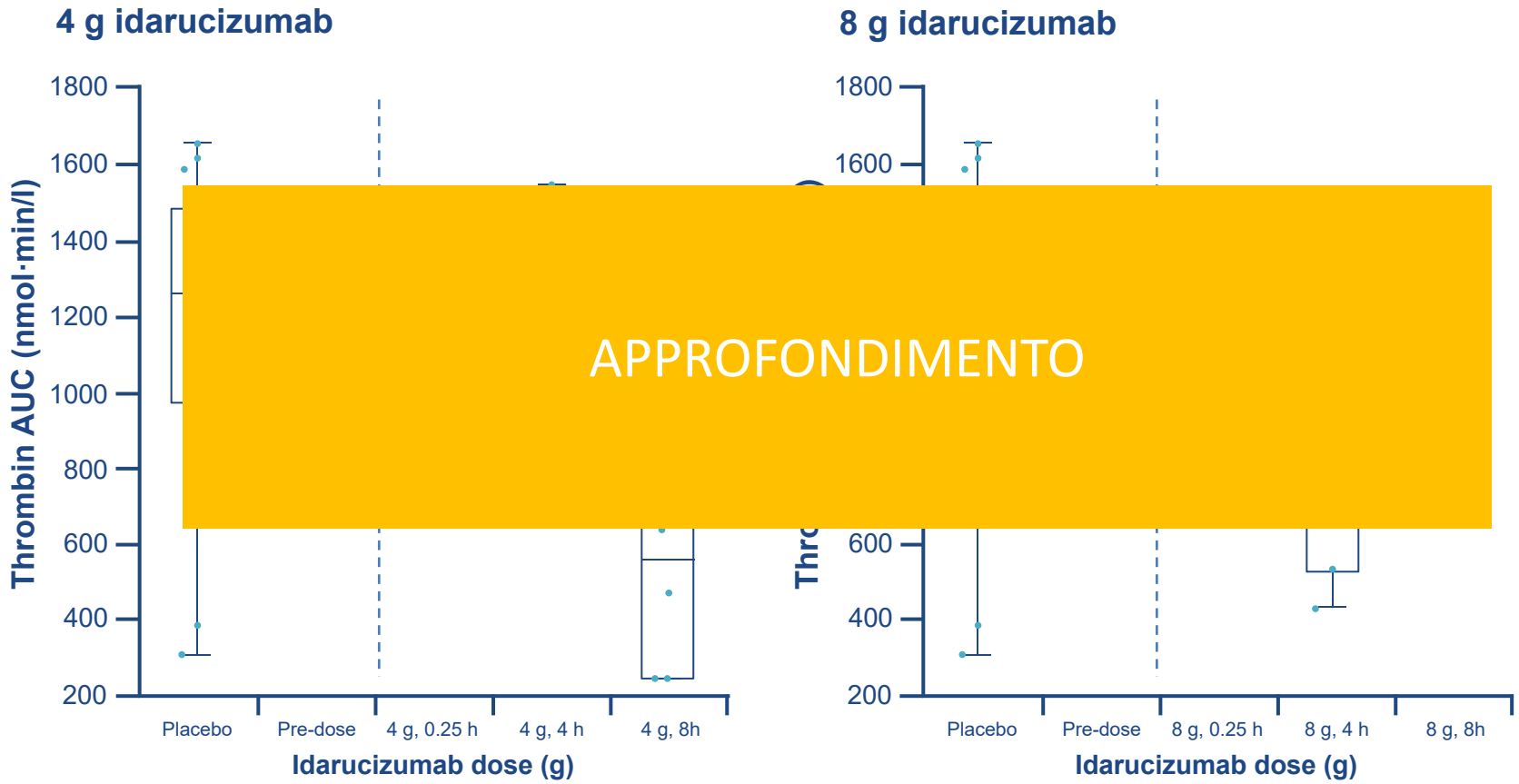
Expert opinion: flow diagram for thrombolysis for acute ischaemic stroke in patients treated with dabigatran



In Europe, the use of idarucizumab followed by rtPA is covered by the label of both drugs

aPTT, activated partial thromboplastin time; CTA, computed tomography angiography; dTT, diluted thrombin time; IV, intravenous; rtPA, recombinant tissue plasminogen activator; TT, thrombin time; Adapted from Diener H-C et al. Int J Stroke 2016; Pradaxa® EU SPC, 2017; Praxbind® EU SPC, 2017; Actilyse® EU SPC, 2015

Idarucizumab showed no procoagulant effects in volunteers



No elevation in thrombin generation at any time after idarucizumab administration

AUC, area under the curve; Whiskers extend to the minimum/maximum observations, box starts from the first quartile and ends at the third quartile; median line in box. Adapted from Schmohl M et al. Thromb Haemost 2016

Caso clinico 2

ore 10.00 domenica:
Femmina di 48 anni
Codice di accesso in PS: ROSSO

Motivo: Shock ipovolemico, probabili fratture multiple.

Parametri d'ingresso:
PA 80/60 mmHg, FC 115 bpm, ritmico, Sat.O2 98% in FiO2 21%

Caduta rovinosamente dalla bicicletta da corsa per mancata frenata in discesa, dovuta all'irrigidimento delle mani per freddo intenso.
Urto contro muro in curva, dopo aver saltato il guard-rail.

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Urto contro muro in curva, dopo aver saltato il guard-rail.

Anamnesi: recente trombosi venosa profonda (gemellari), modico sovrappeso, in terapia con **Anticoagulante (X?)**,
Ultima somministrazione di **Anticoagulante** due ore prima, come di regola al mattino. Nessun sanguinamento anamestico.

Esami ed Obiettività

ore 10.05 domenica:
Emogas analisi: ph 7.48 PO2 75 mmHg, pCO2 33 mmHg
K 4.2 mEq Na 139 mEq Hb 12.2 g dL

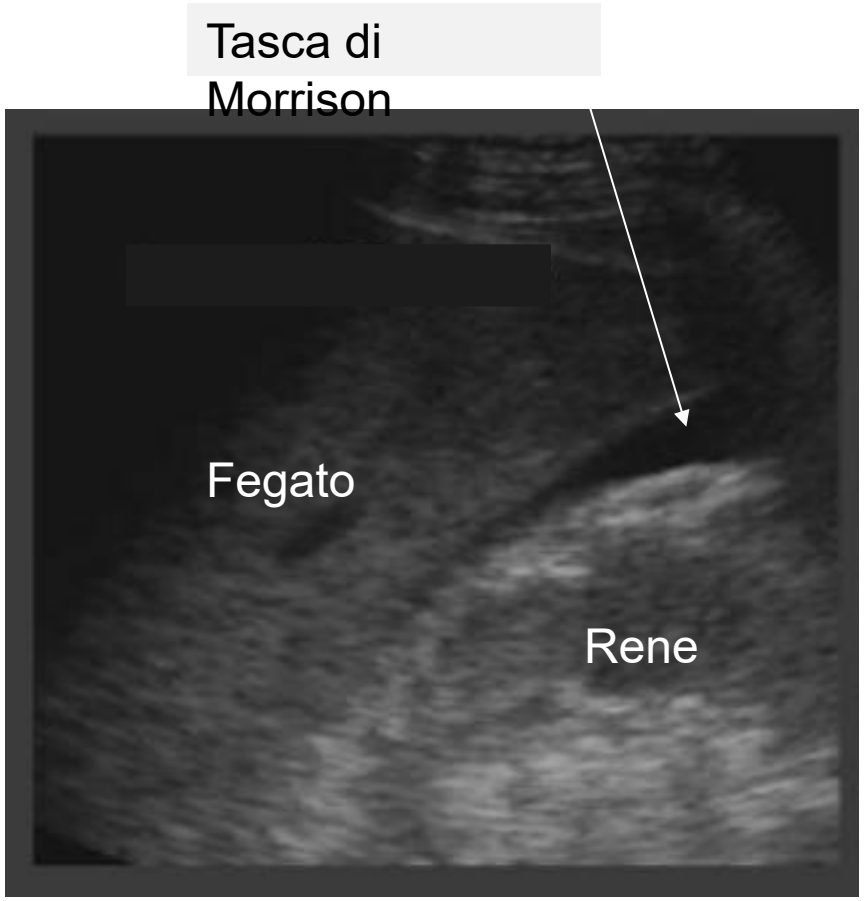
Lamenta poco dolore, soprattutto alla gamba dx che si presenta extraruotata ed accorciata. Addome teso non palpabili gli organi addominali.

Escoriazione frontale sinistra ed modica contusione emitorace inferiore dx con maglietta lacerata.

PA 75/55 mmHg, FC 110 bpm
Egas Hb 12.4 g/dL

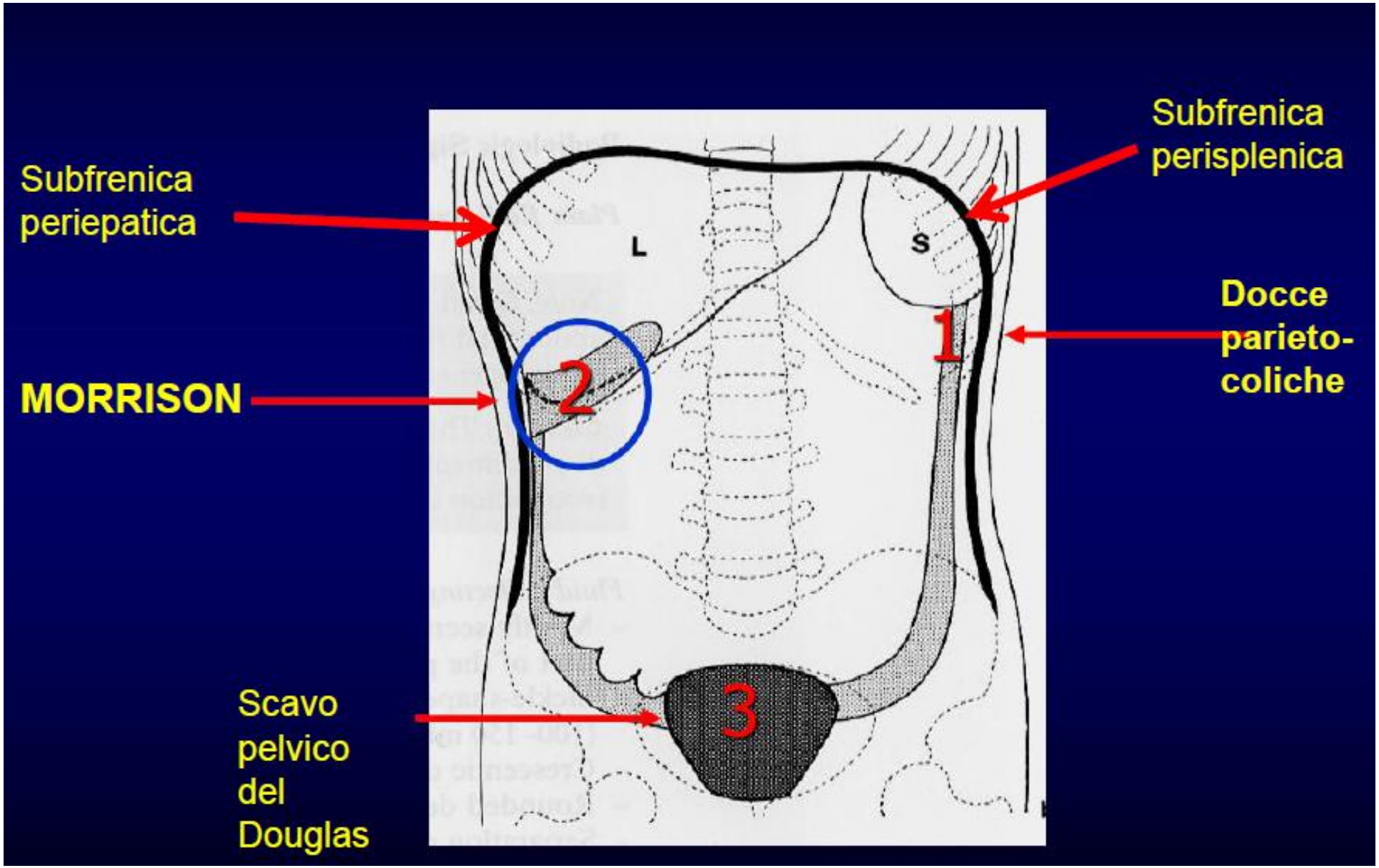
L’incredulità di San Tommaso

Michelangelo Merisi da Caravaggio, 1600-1601
Bildergalerie, Potsdam



…separazione della cavità virtuale di Morrison
è associata a 600 ml circa di fluido endo-addome

Sedi di raccolta fluidi



Esami ed Obiettività

ore 10.20 domenica:
Emogas analisi: ph 7.48 PO2 75 mmHg, pCO2 33 mmHg
K 4.2 mEq Na 139 mEq Hb 12.2 g dL

Lamenta poco dolore, soprattutto alla gamba dx che si presenta extraruotata ed accorciata. Addome teso non palpabili gli organi addominali. Escoriazione frontale sinistra ed modica contusione emitorace inferiore dx con maglietta lacerata.

PA 75/55 mmHg, FC 110 bpm

Ecofast: Douglas 2 cm fluido, Morrison 1 cm, anse intestinali apparentemente fluttuanti.

Esami ed Obiettività

ore 10.40 domenica:

Ecofast: Douglas 2 cm fluido, Morrison 1 cm, anse intestinali apparentemente fluttuanti.

Trattamento:
Inizia colloidi 1000 ml e Cristalloidi 2000 ml
Linea arteriosa per monitoraggio continuo
Ventimask 50% O2 12 litri min
Infusione 2 Unità GRC 0 negativo
Richieste 3 Unità GRC

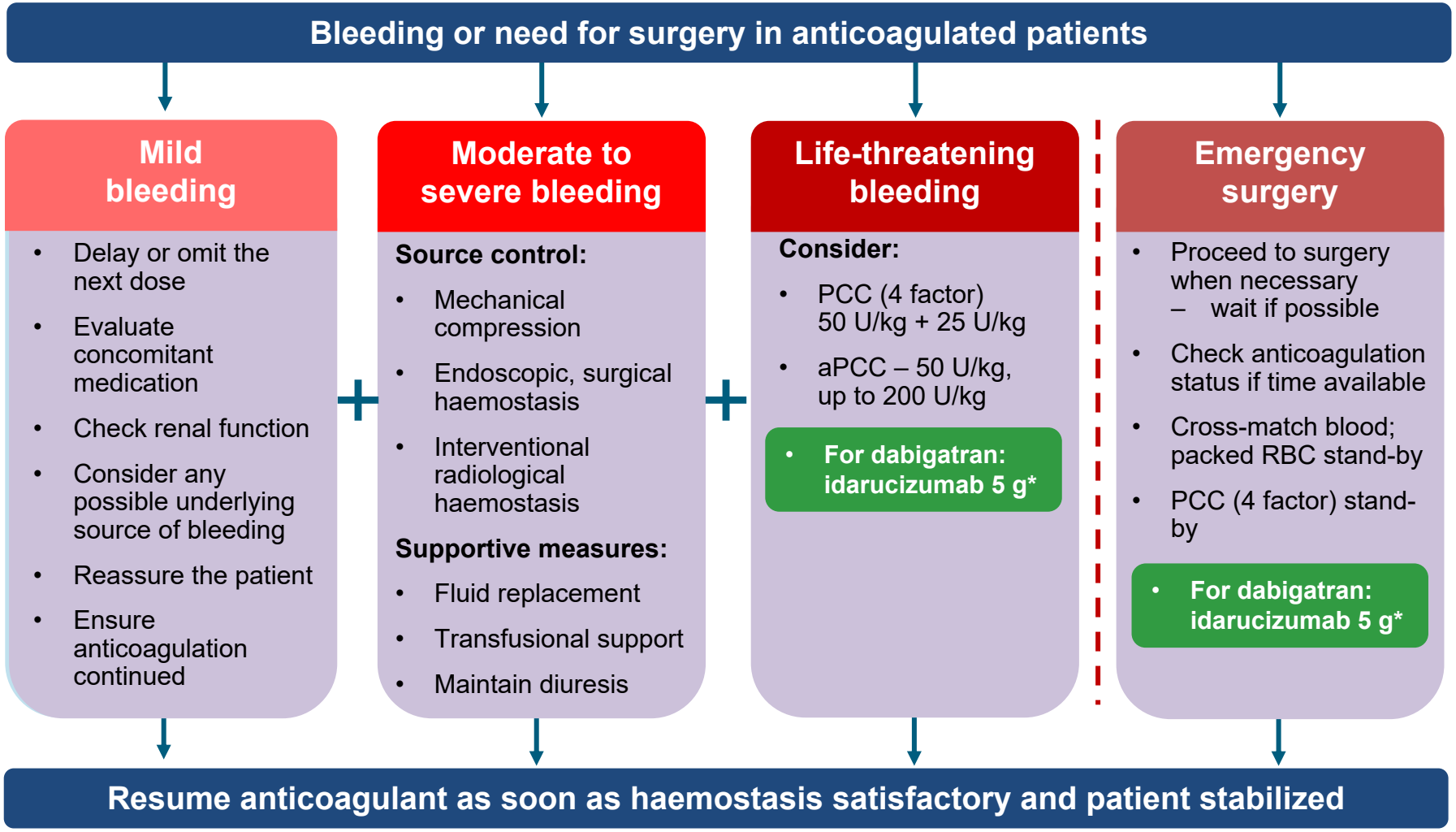
Esami di laboratorio

ora	Hb	GR	GB	Creat	INR	PT	aPTT	aPTT Ratio
10.00	12,8	4,450,000	21,000	1,01	1,39	54	49 sec	1,54
10.40	**8,6**	3,060,000	12,030	1.10	**1.8**	**35**	**66 sec**	**2,1**

Caso clinico 2

Raccordo anamnestico con il familiare; TERAPIA:
Dabigatran 110 mg *bis in die*, Patoprazolo 20 mg die.
Conferma assunzione di **Dabigatran** due ore prima.

Idarucizumab is recommended to reverse dabigatran anticoagulation in patients requiring emergency surgery or with life-threatening bleeding



*Idarucizumab is the preferred treatment to reverse dabigatran; PCC, prothrombin complex concentrate; RBC, red blood cell; Anticoagulation Education Task Force White Paper: Ageno W et al. Thromb Haemost 2016

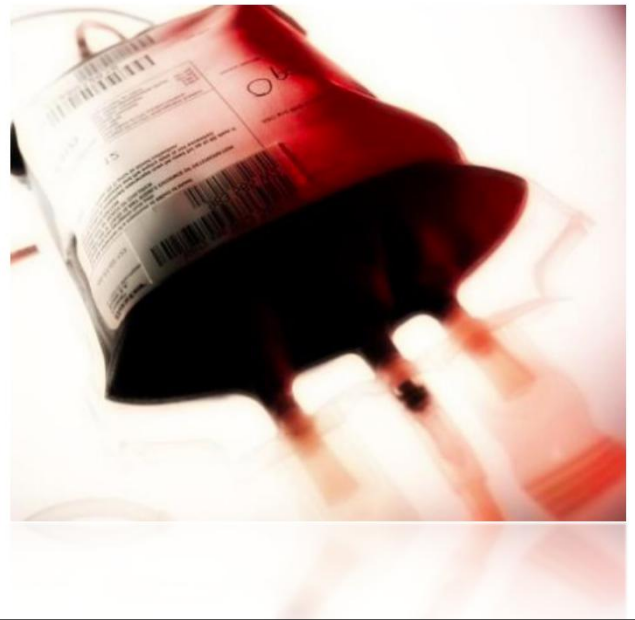
Esami ed Obiettività

ore 10.40:

TC addome diretta: abbondante fluido in cavità libera. Possibile rima di soluzione parenchima splenico polo inferiore. Parenchima epatico e reni senza alterazioni da segnalare. Frattura IX costa dx

Frattura pertrocanterica femore dx

FC 105 b min
PA 90/60 mmHg



Obiettività

ore 11.20:
Consulenza chirurgica ed anestesiologica: indicato intervento in emergenza

Inizia infusione di Praxbind secondo protocollo
(2 flaconi via e.v.: 2.5 mg ciascuno a distanza di 15 min)

Ore 11.20:
Quadro clinico sostanzialmente invariato
PA 100/60 mmHg
Egas Hb 9,1 g/dL
La paziente viene affidata
all'equipe chirurgica di sala

Rescue?

Warfarin
Heparin
Fondaparinux
Dabigratan
Rivaroxaban
Apixaban
Edoxaban

Guidelines for reversal of anticoagulants

NAMES	ELIMINATION HALF-LIFE	REMOVED BY HD	STRATEGIES TO REVERSE OR MINIMIZE DRUG EFFECT
apixaban *(Eliquis)*	8-15 hours (longer in renal impairment)	NO	• Drug activity can be assessed with anti-factor Xa activity assay (UWMedicine: apixaban assay [APIXN1]) • If ingested within 2 hours, administer activated charcoal • *Consider 4-factor PCC (KCentra) 50 units/kg (maximum 5000 units)* *(25 unit/kg, maximum 2500 units for intraparenchymal hemorrhage)* **NOTE:** PCC may partially correct PT/aPTT but will not affect anti-factor Xa activity and will not increase drug clearance; correlation of shortening PT/aPTT with reduction in bleeding risk is unknown
dabigatran *(Pradaxa)*	14-17 hours (up to 34 hrs in severe renal impairment)	~ 65%	• Drug activity can be assessed with aPTT and/or plasma-diluted thrombin time (UWMedicine: dabigatran assay [DABIG]) • If ingested within 2 hours, administer activated charcoal • *For life-threatening bleeding or emergency surgery, consider idarucizumab (Praxbind) 5gm IV* **NOTE:** idarucizumab will likely correct aPTT and plasma-diluted thrombin time but the correlation of lab results with improved outcomes is not established **NOTE**: Plasma dabigatran concentrations can increase more than 12-24 hours after idarucizumab, likely due to re-distribution from the extravascular compartment. **NOTE**: The risks and benefits of repeat idarucizumab administration are not known.
Edoxaban (Savaysa)	10-14 hours (longer in renal impairment)	~ 25%	• There is no assay for edoxaban at this time. • If ingested within 2 hours, administer activated charcoal • *Consider 4-factor PCC (KCentra) 50 units/kg (maximum 5000 units)* *(25 unit/kg, maximum 2500 units for intraparenchymal hemorrhage)* **NOTE:** PCC may partially correct PT/aPTT but will not affect anti-factor Xa activity and will not increase drug clearance; correlation of shortening PT/aPTT with reduction in bleeding risk is unknown
Rivaroxaban *(Xarelto)*	Healthy: 5-9 hrs Elderly: 11-13 hrs (longer in renal impairment)	NO	• Drug activity can be assessed with anti-factor Xa activity (UWMedicine: rivaroxaban assay [RIVAR1]) • If ingested within 2 hours, administer activated charcoal • *Consider 4-factor PCC (KCentra) 50 units/kg (maximum 5000 units)* *(25 unit/kg, maximum 2500 units for intraparenchymal hemorrhage)* **NOTE:** PCC may partially correct PT/aPTT but will not affect anti-factor Xa activity and will not increase drug clearance; correlation of shortening PT/aPTT with reduction in bleeding risk is unknown

Algorithm for management of dabigatran-treated patients with bleeding or requiring urgent surgery

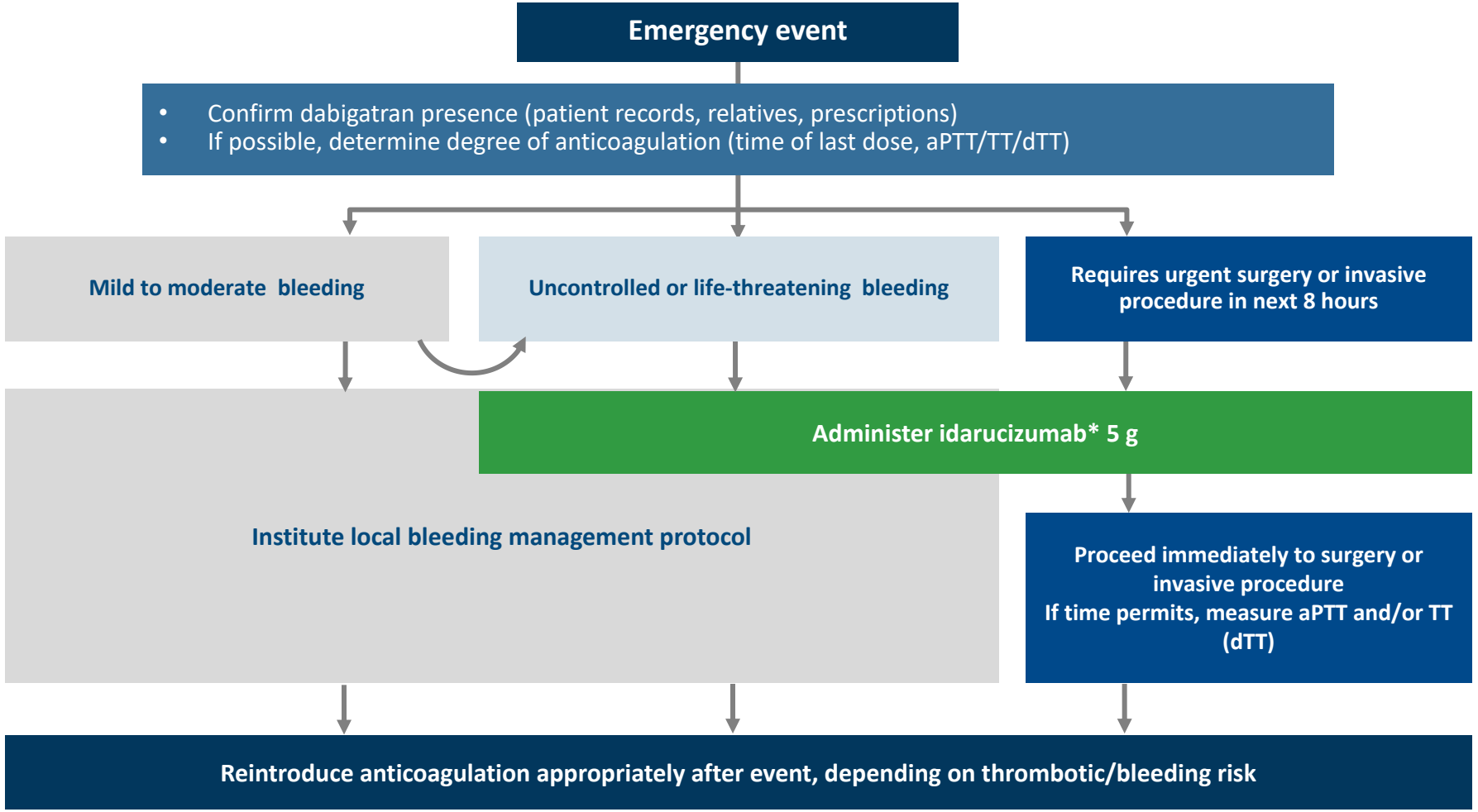


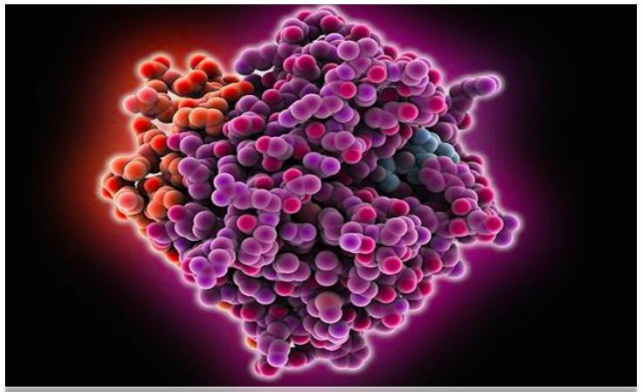
Figure ad m. Et al. *Circulation*. 2015;132:2412-2422

Somministrazione dell’antidoto

Ore 10.40:
inizia, previo consenso informato:
PROTOCOLLO IDARUCIZUMAB

Ore 11.00 PA 80/60 mmHg, eseguita prima fiala **Idarucizumab 2,5 gr**
Ore 11.15 PA 90/55 mmHg, eseguita seconda fiala **Idarucizumab 2,5 gr**

Ore 12.00 PA **105/65 mmHg**. Paziente sostanzialmente stabile per clinica



Esami di laboratorio

ora	Hb	GR	GB	INR	PT	aPTT	aPTT Ratio
12.00	9,1*	3,140,000	11,190	**1,2**	**68**	**33**	**1,06**

*Hb dopo due sacche di emazie concentrate

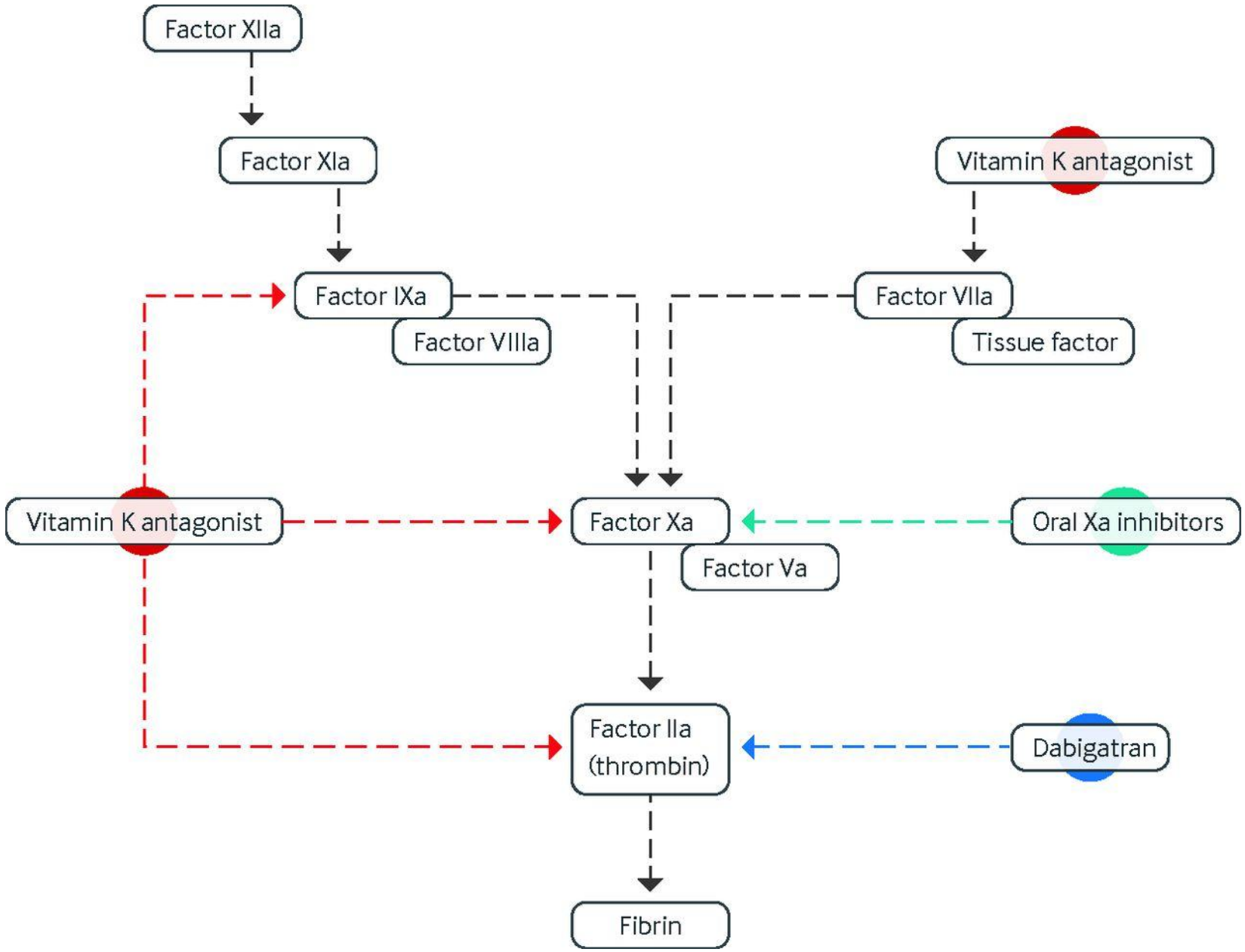
NOAC reversal agents are in development

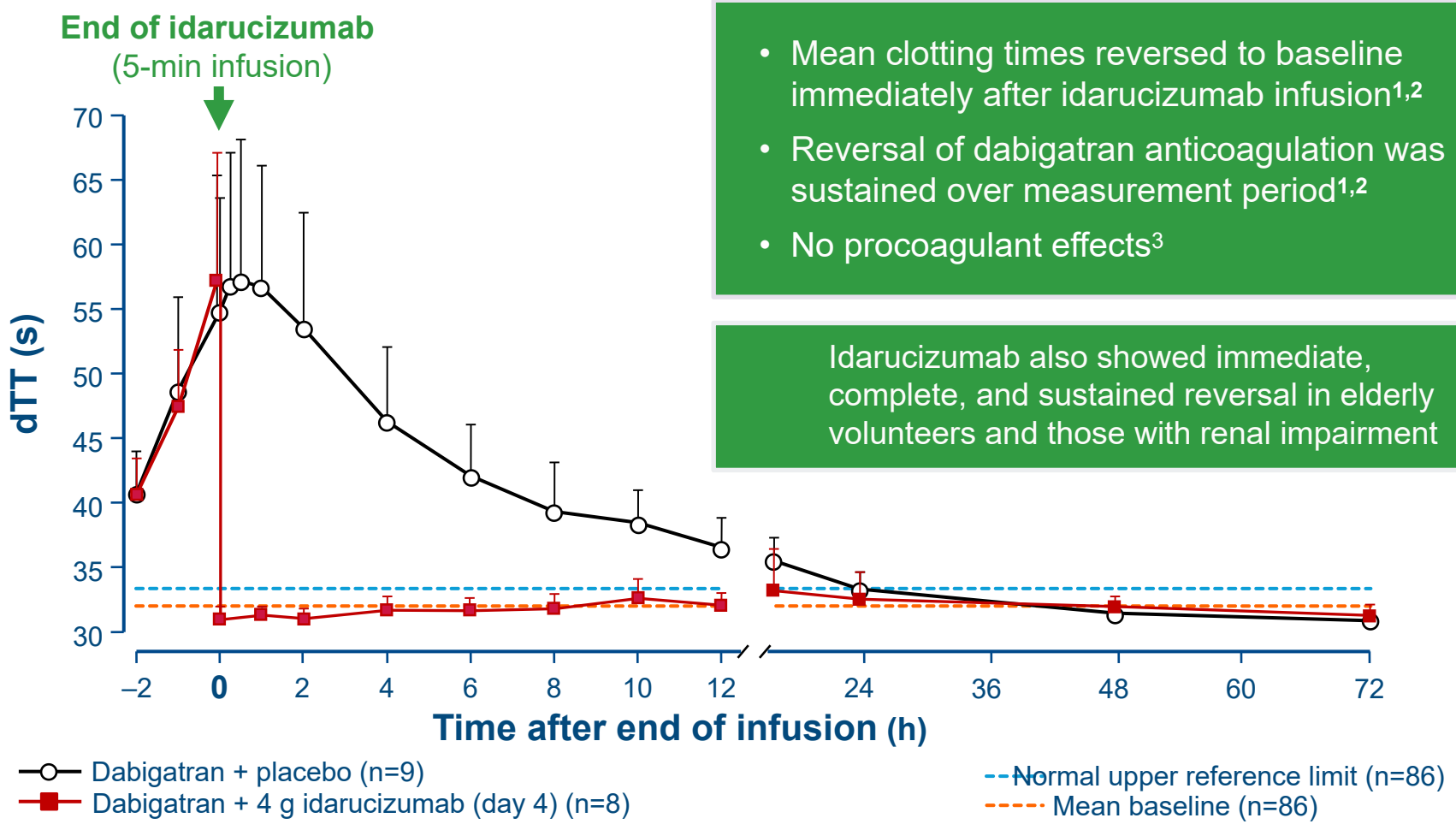
NOAC reversal agent	Target	Mechanism of action
Idarucizumab[1]	Dabigatran	Humanized Fab: specifically binds dabigatran with high affinity[2]
Andexanet alfa (PRT064445)[1]	FXa inhibitors	Recombinant modified FXa: competitive affinity for direct FXa inhibitors[3]
Ciraparantag (PER977)[1]	Universal	Synthetic small molecule: hydrogen bonds (NOACs); charge–charge interactions (heparin)[4]

FXa, activated Factor X

1. Greinacher et al. Thromb Haemost 2015; 2. Schiele et al. Blood 2013; 3. Lu et al. Nat Med 2013;
4. Ansell et al. N Engl J Med 2014

Coaugulation cascade





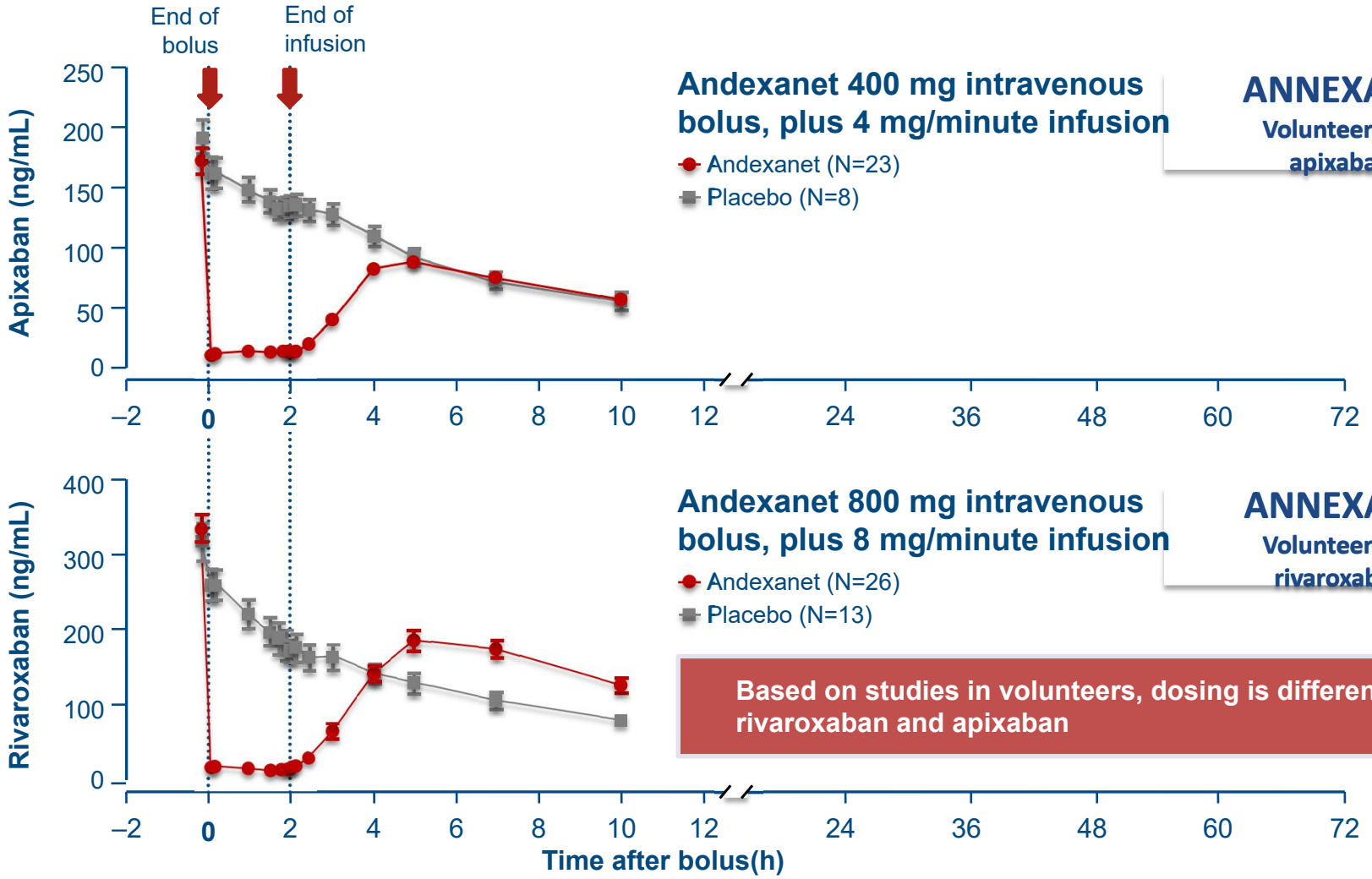
- Mean clotting times reversed to baseline immediately after idarucizumab infusion[1,2]
- Reversal of dabigatran anticoagulation was sustained over measurement period[1,2]
- No procoagulant effects[3]

Idarucizumab also showed immediate, complete, and sustained reversal in elderly volunteers and those with renal impairment

dTT, diluted thrombin time. 1. Glund S et al. Lancet 2015; 2. Glund S et al. Thromb Haemost 2015; 3. Glund S et al. ASH 2014

Andexanet alfa

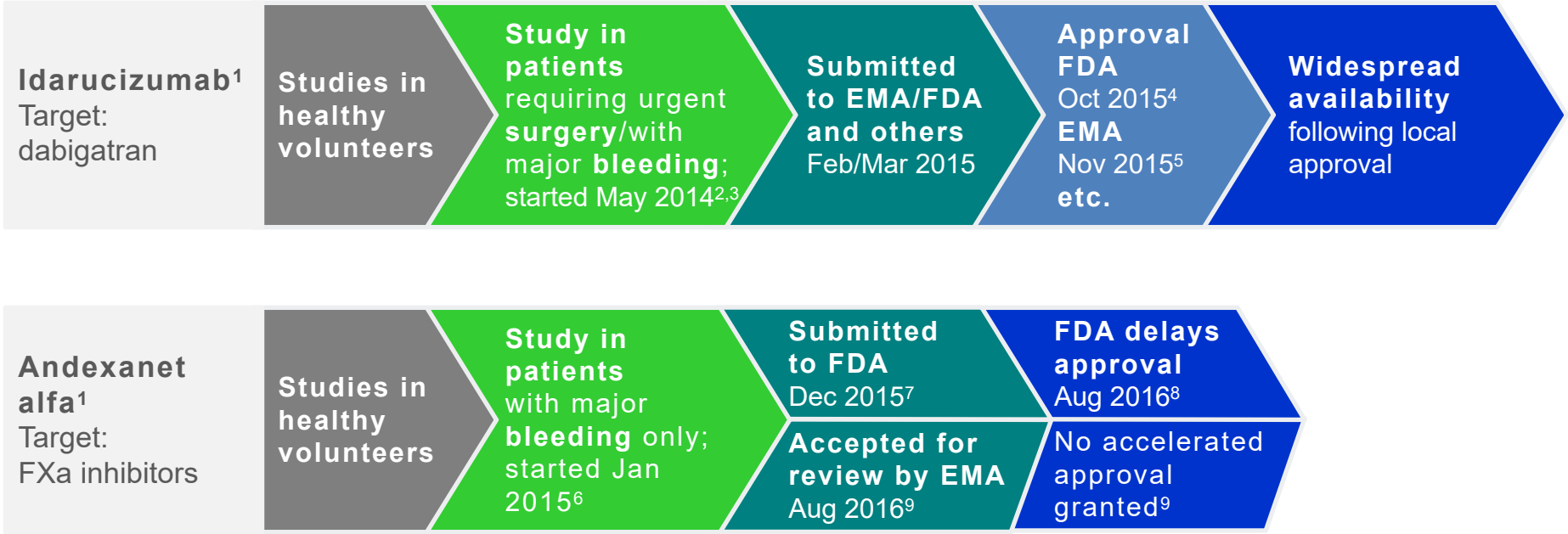
In healthy volunteers, the reversal effects of andexanet alfa were not sustained beyond the 2-hour infusion



Based on studies in volunteers, dosing is different for rivaroxaban and apixaban

1. Siegal DM et al. N Engl J Med 2015

What specific reversal agents for NOACs are available?



1. Adapted from Greinacher A et al. Thromb Haemost 2015;
2. Pollack C et al. N Engl J Med 2015;
3. Pollack C et al. Thromb Haemost 2015;
4. US FDA 2015 press release, 16 October 2015;
5. European Commission Community Register of Medicinal Products for Human Use 2015;
6. ClinicalTrials.gov Identifier: NCT02329327;
7. Portola Pharmaceuticals press release, 18 Dec 2015;
8. Portola Pharmaceuticals press release 17 August 2016;
9. Portola Pharmaceuticals press release 19 August 2016

Overview of key differentiators

	Idarucizumab	Andexanet alfa
Approval and availability	Approved in many countries and widely available	If approved, initial availability will be limited by supply
Type of agent	Humanized Fab fragment	Recombinant modified FXa
Specificity	Specific to dabigatran	Targets direct and indirect FXa inhibitors
Reversal in volunteers and patients	Immediate, complete, sustained reversal	Immediate but sustained only with continuous infusion
Safety in volunteers	No safety concerns, and no procoagulant or prothrombotic effects	Transient procoagulant signal observed
Patient study design	Representative of clinical practice in urgent surgery and life-threatening bleeding	Highly selected to exclude patients requiring urgent surgery and those with reduced life expectancy
Ease of use	Fixed dose; ready-to-use solution; single injection	Variable dose; lyophilized; bolus plus infusion
Use with other bleeding management strategies	Tested in RE-VERSE AD™	Unknown
Restarting anticoagulation	Dabigatran after 24 hrs, others (including heparin) at any time	Rapidly cleared; FXa inhibitors can likely be restarted soon after reversal, however this has not been tested under controlled conditions in any study to date

Riflessioni

Aver avuto a disposizione l'antidoto specifico
ha permesso

-stabilizzazione clinica
-riduzione del sanguinamento
- l'invio in sala chirurgica

.....in sicurezza

Real-Life Evidence

SIMEU Toscana

Bleeding at the Emergency Department

Survey ASL NordOvest SSN Toscana
Apuane Community Hospital, Massa
Catchment area: 250.000 inhabitants
4.430 patients enrolled,
3-year Survey 2015-2017

Contents lists available at ScienceDirect

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Short and long-term mortality of patients presenting with bleeding events to the Emergency Department

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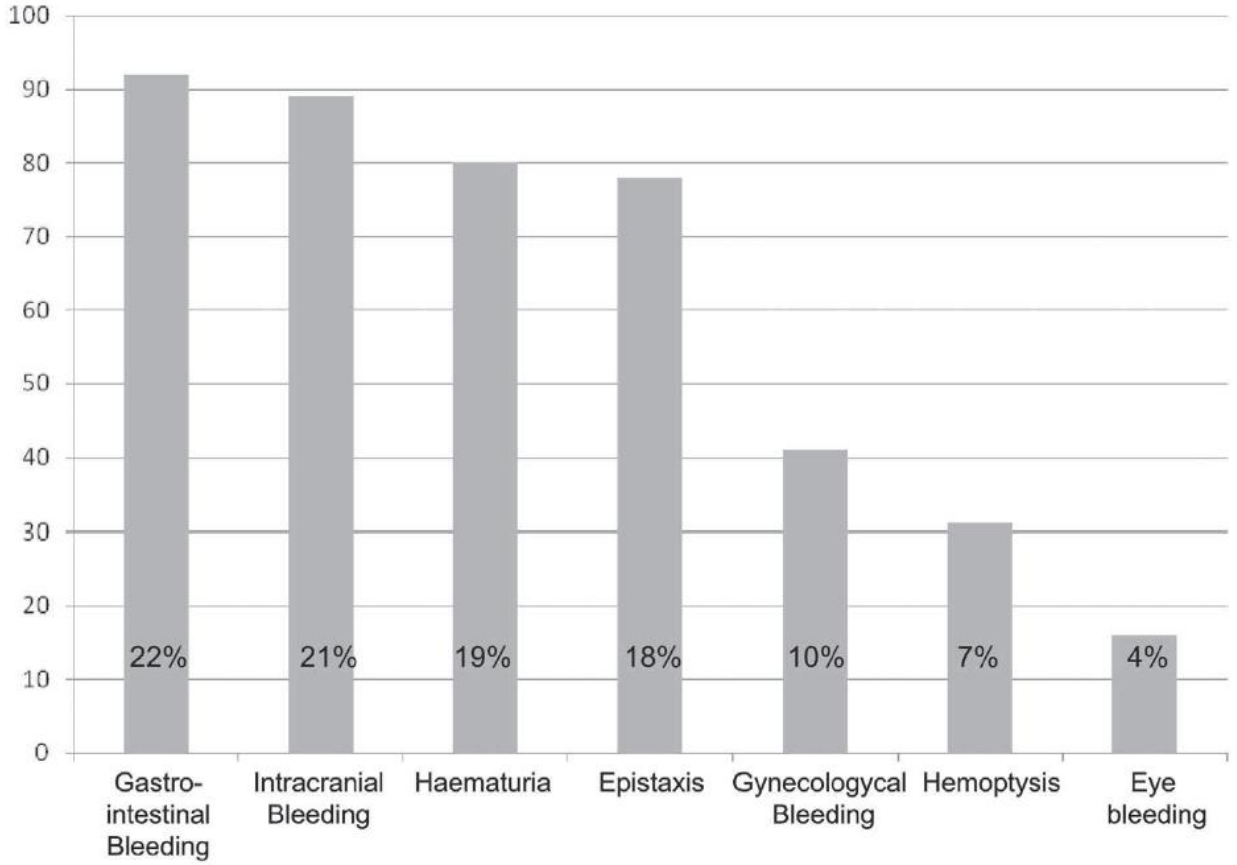

. Patients enrolled in the study and stratified according to the different site of bleeding (n = 429).

Conti A. Am J Emerg Med 2017

ORIGINAL ARTICLE

e of Hypertension and Other Clinical Variables in ognostication of Patients Presenting to the Emergency Department With Major Bleeding Events

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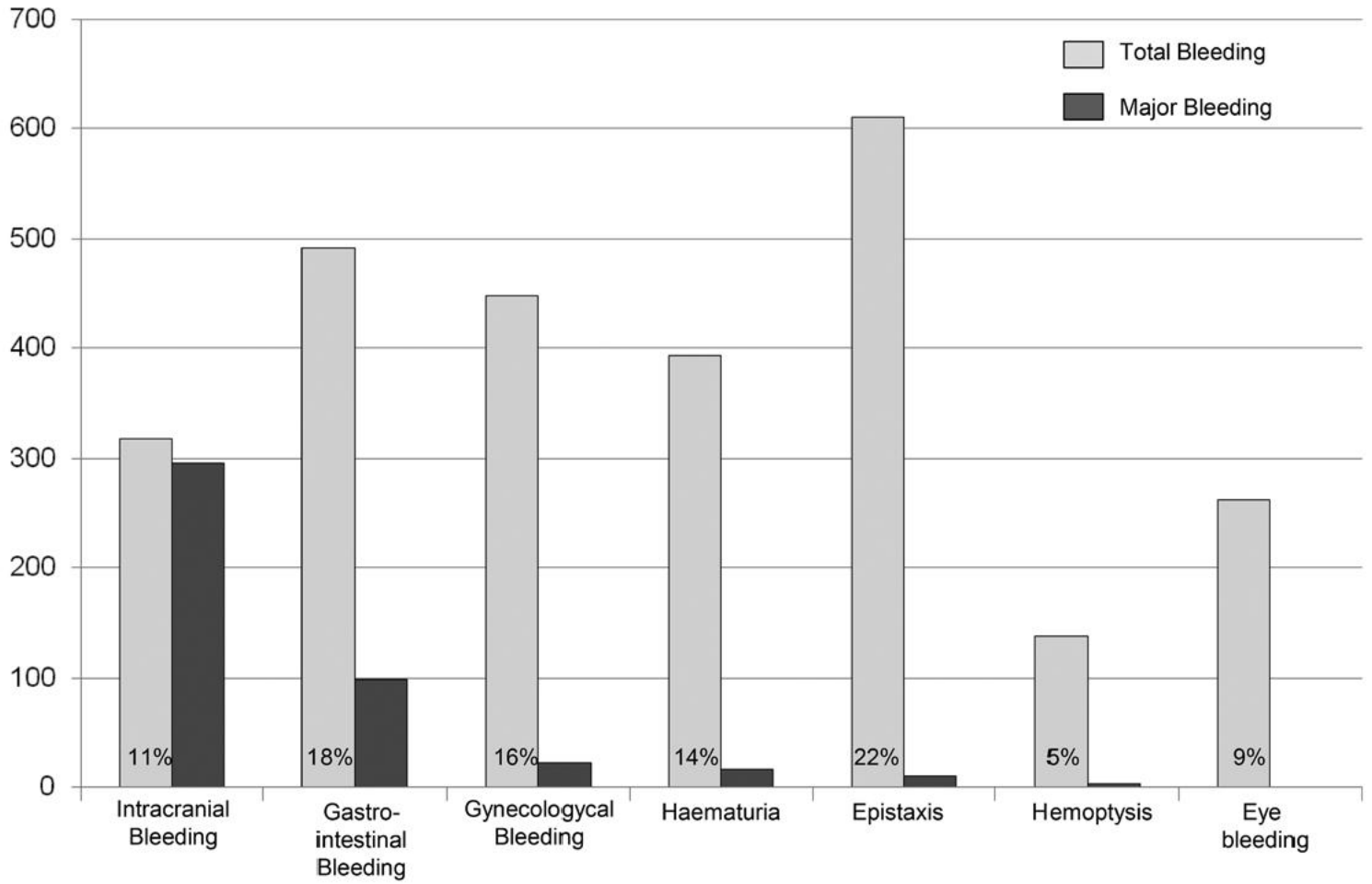
Conti A et al Crit Path Cardiol 2018 (in press)



Patients enrolled in the study and stratified according to the different site of any bleeding (n = 2.792) and major bleeding events (n = 474).

Major bleeding events in the subsets of patients with different anticoagulants treatment strategy (n=577).

Anticoagulation treatment strategy	Patients with ongoing anticoagulation in the catchment area 200,000 inhabitants (n=16.551)	Major Bleeding events according to anticoagulation (n= 577)	Chi square Yates' correction p value
Dabigratan	1.887 (11.4%)	58 (10.1%)	0.374
Rivaroxaban	2.156 (13.0%)	55 (9.5%)	
Apixaban	1.143 (6.91%)	24 (4.2%)	
Edoxaban	319 (1.93%)	7 (1.2%)	
Total DOACs	5.505 (33.3)	144 (25.0%)	<0.0001
Total Warfarin	11.046 (66.7%)	433 (75.0%)	

…via ringrazio per l’attenzione

Regione Toscana