Prise en charge d'une hémorragie sous AODs, place d'un antidote spécifique

Caractéristiques de la molécule et des résultats publiés

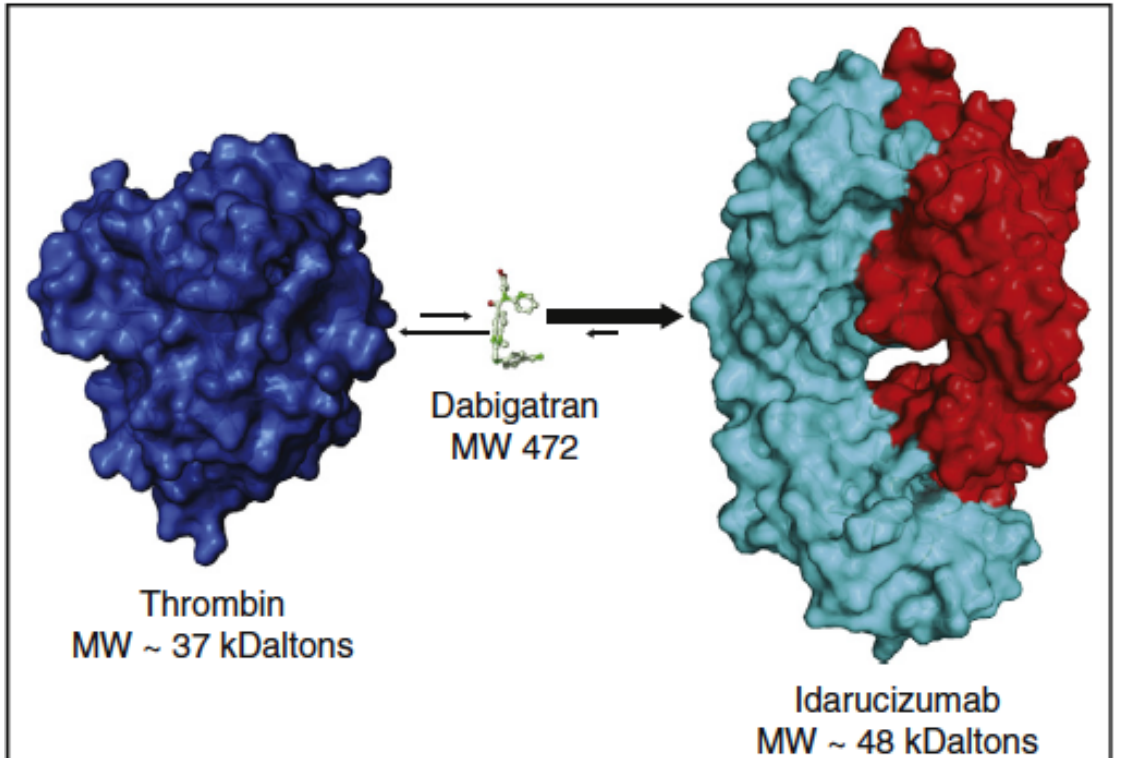
L Camoin
Service d'Hématologie Biologique
CHU TIMONE
APHM

Liens d’Intérêts

- **BMS**
- **Boehringer**
- **Daiichi-Sankyo**
- **Bayer**
- **Sanofi**
- **Leo**

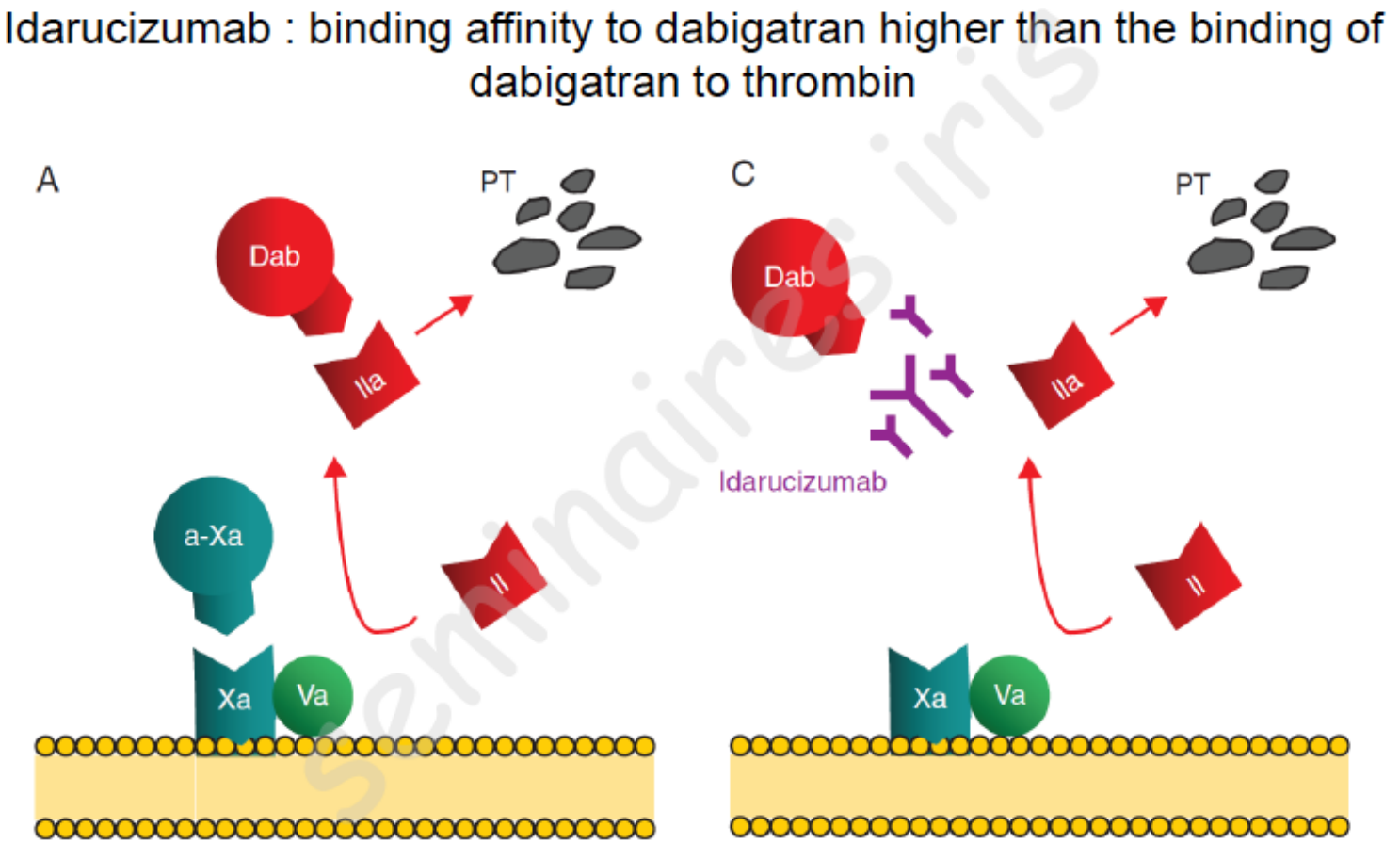
Idarucizumab : Praxbind®

- **Antidote spécifique du dabigatran**
- **Fragment d'anticorps monoclonal murin humanisé**
- **Similarités structurelles avec la thrombine.**
- **Liaison spécifique au dabigatran avec une très forte affinité, ≈300 fois plus grande que l'affinité du dabigatran pour la thrombine**
- **Demi-vie d'élimination ≈ 45 min, principalement sous forme inchangée dans les urines**

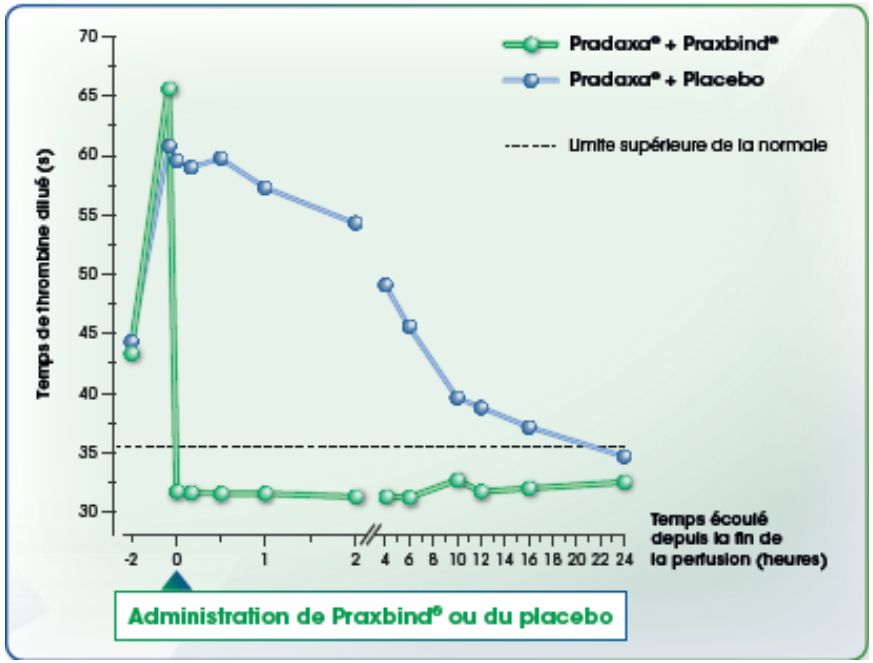


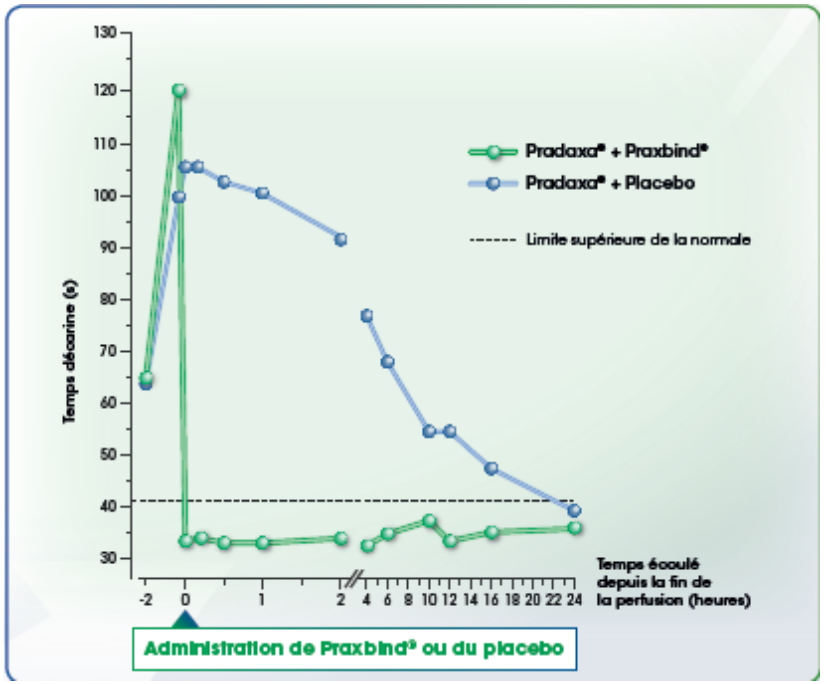
Glund S, et. Thromb and Haemost 2015;113(5):943-51.
Glund S, et al,. Lancet 2015;386(9994):680-90.

Idarucizumab : Praxbind



Données chez le sujet sain





Glund S et al. A randomised study in healthy volunteers to investigate the safety, tolerability and pharmacokinetics of idarucizumab, a specific antidote to dabigatran. Thromb Haemost 2015;113(5):943-51

The NEW ENGLAND JOURNAL of MEDICINE

Idarucizumab for Dabigatran Reversal

… a prospective cohort study was undertaken to examine the efficacy and safety of idarucizumab for the reversal of the anticoagulant effects of dabigatran in patients who presented with serious bleeding or who required urgent surgery or intervention.

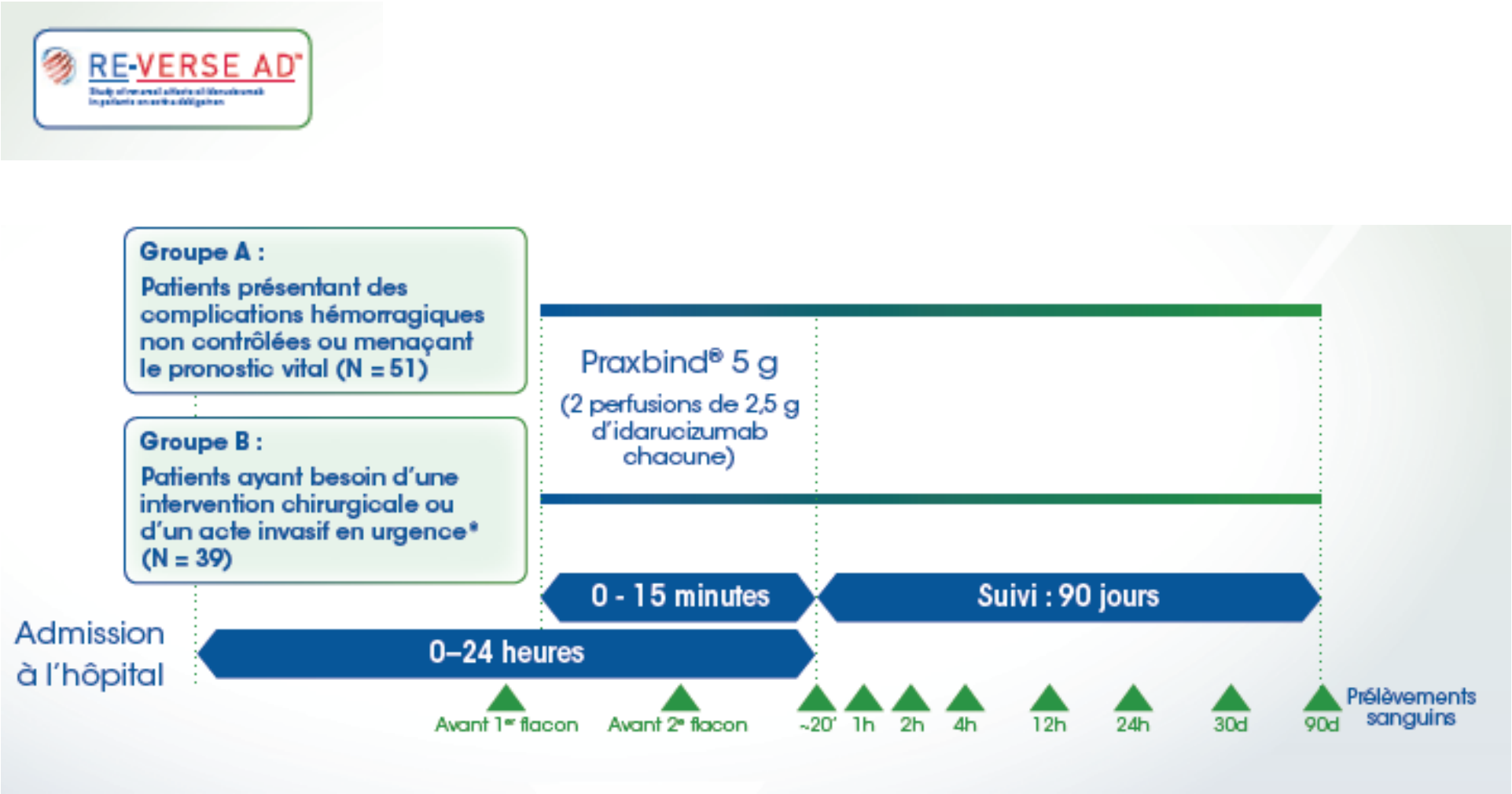
We present the results from the first 90 patients enrolled in the study of

Pollack CV et al. Idarucizumab for Dabigatran Reversal. N Engl J Med 2015;373(6):511-20

The NEW ENGLAND JOURNAL of MEDICINE

Idarucizumab for Dabigatran Reversal

June 22, 2015, at NEJM.org.



The NEW ENGLAND JOURNAL of MEDICINE

Idarucizumab for Dabigatran Reversal

Caractéristiques	Groupe A	Groupe B	Total
Patients inclus dans l'analyse intermédiaire	n = 51	n = 39	N = 90
Indication de Pradaxa® : prévention de l'AVC dans la FA, n (%)	47 (92%)	39 (100%)	86 (96%)
Age médian (min-max), années	77 (48–93)	76 (56–93)	76,5 (48–93)
ClCr médiane (min-max), mL/min*	54 (16–187)	60 (11–171)	58 (11–187)
Temps médian de la dernière prise de Pradaxa® rapporté par le patient, heures	15,2	16,6	15,4
Temps de thrombine diluée élevé à l'inclusion, n (%)	40 (78%)	28 (72%)	68 (76%)
Temps d'écarine élevé à l'inclusion, n (%)	47 (92%)	34 (87%)	81 (90%)
Type d'hémorragie, n (%)**			
- Intracrânienne	18 (35%)	-	18 (20%)
- Post-traumatique	9 (18%)	-	9 (10%)
- Gastro-intestinale	20 (39%)	-	20 (22%)
- Autre	11 (22%)	-	11 (12%)

Pollack CV et al. Idarucizumab for Dabigatran Reversal. N Engl J Med 2015;373(6):511-20

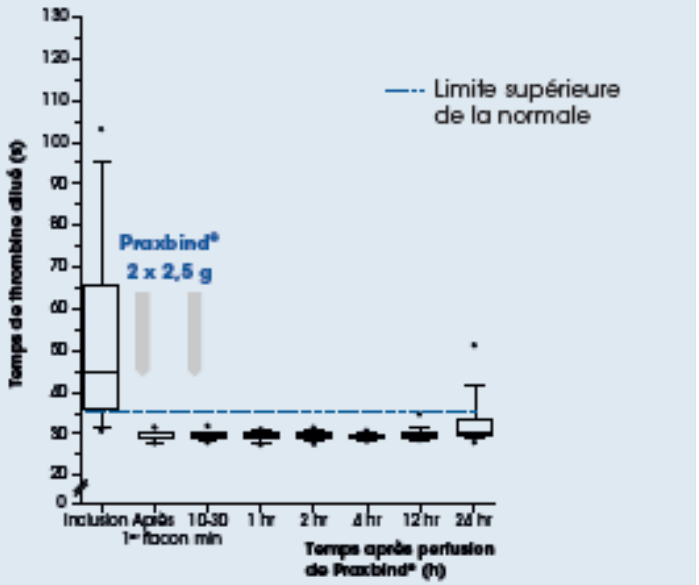
The NEW ENGLAND JOURNAL of MEDICINE

Idarucizumab for Dabigatran Reversal

Critère de jugement :paramètres de laboratoire

Groupe A

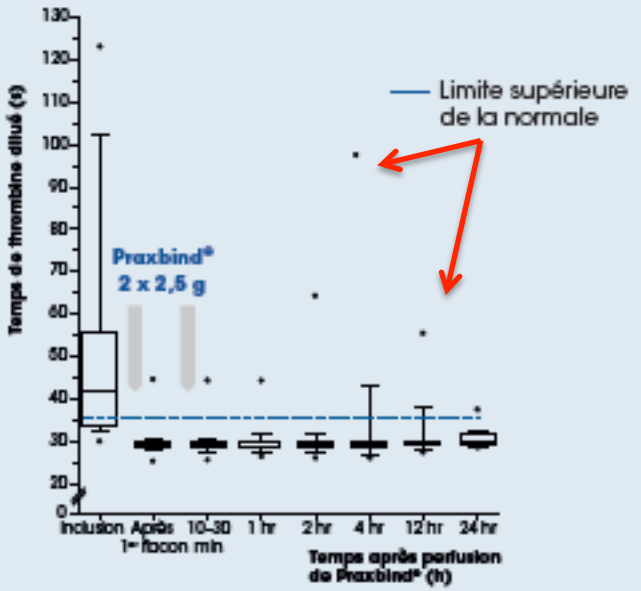
(patients présentant des complications hémorragiques non contrôlées ou menaçant le pronostic vital, N = 51)



Restauration de l'hémostase obtenue chez 91 % des patients évaluables [1]

Groupe B

(Patients ayant besoin d'une intervention chirurgicale ou d'un acte invasif en urgence**, N = 39)



Restauration de l'hémostase obtenue chez 92 % des patients évaluables [1,4]

Pollack CV et al. Idarucizumab for Dabigatran Reversal. N Engl J Med 2015;373(6):511-20

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Idarucizumab for Dabigatran Reversal

Absence de groupe témoin

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

the clinical benefit of this reversal was depending very much on the individual patient clinical situation, disease or bleeding severity or location of the bleeding. It was noted that **bleeding stopped in 44 of 48 evaluable patients** within 72 hours and the median time to cessation of bleeding was 9.8 hours. In the case of emergency surgery, **33 out of 36 evaluable patients had normal hemostasis during surgery**

Pollack CV et al. Idarucizumab for Dabigatran Reversal. N Engl J Med 2015;373(6):511-20

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Idarucizumab for Dabigatran Reversal

5.5 % d'évènements thromboemboliques mais ……

Événements thromboemboliques précoces ou tardifs (N = 90) [4]

Événements thromboemboliques		Nombre de patients (jours après le traitement)
Précoces (≤ 72 h**)	TVP et EP	1 patient (2 jours)
Tardifs (> 72 h**)	TVP seule	1 patient (7 jours)
	TVP, EP et thrombus auriculaire gauche	1 patient (9 jours)
	IDM sans sus-décalage du segment ST	1 patient (13 jours)
	AVC	1 patient (26 jours)

** Après l'administration de Praxbind®.

Pollack CV et al. Idarucizumab for Dabigatran Reversal. N Engl J Med 2015;373(6):511-20

The NEW ENGLAND JOURNAL of MEDICINE

Idarucizumab for Dabigatran Reversal

Table 2. Serious Adverse Events Leading to Death.

Event	Characteristics of the Patients		Study Group*	Time from Treatment to Death
	Age	Sex		
	yr			*days*
Cardiac arrest	82	Female	B	<1
Circulatory collapse	93	Male	B	<1
Hemodynamic collapse	88	Female	B	<1
Septic shock	87	Female	B	1
Sepsis, shock, and gastrointestinal bleeding	60	Male	B	1
Progression of respiratory failure	60	Male	A	1
New intracranial hemorrhage	77	Male	A	1
Progression of intracranial hemorrhage	69	Male	A	2
Multiorgan failure	87	Male	B	2
Progression of intracranial hemorrhage	69	Male	A	4
Pulmonary edema	83	Female	A	11
Cardiac arrest	78	Female	B	21
Ischemic stroke	72	Female	B	26
Congestive heart failure	73	Male	A	30
Parkinson's disease	80	Male	A	43
General health deterioration	83	Male	A	42
Pneumonia	86	Female	A	94
Progression of cancer	80	Male	B	101

20 % de décès
Comorbidité élevée

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Pollack CV et al N Engl J Med 2015;373(6):511-20

There were 26 deaths in the 123 patients included in this analysis, 13 in Group A and 13 in Group B. Thirteen of the deaths occurred in the first 5 days of the study, 6 in Group A and 7 in Group B, while the remaining 13 deaths occurred 6 or more days after treatment, with 7 in Group A and 6 in group B.

The early deaths appeared to be progressions of the index events or underlying pre-treatment conditions

Patient Demographics

AHA 2016

Characteristic	Group A (n = 298)	Group B (n = 196)	Total (N = 494)
Dabigatran indication, atrial fibrillation (n,%)	285 (96)	183 (93)	468 (95)
Dabigatran daily dose (n, %)			
110 mg BID	183 (61)	122 (62)	305 (62)
150 mg BID	93 (31)	56 (29)	149 (30)
75 mg BID	16 (5)	7 (4)	23 (5)
Age (y) median, range	79 (24–96)	77 (21–96)	78 (21–96)
Male sex, (n, %)	170 (57)	101 (52)	271 (55)
Creatinine clearance (mL/min), median, range	51.0 (6.1–216.9)	56 (7.9–198.7)	52.7 (6.1–216.9)
Time since last dose (h) median, range	14.2 (1.5, 90.4)	18 (2.6, 106)	15.3 (1.5, 106)
Elevated dTT or ECT at baseline (n, %)	266/298 (89)	177/196 (90)	443/494 (89.6)
Patients receiving >1 dose of 5g	5/298 (1.7)	2/196 (1.0)	7/494 (1.4)

BID, twice daily; dTT, diluted thrombin time; ECT, ecarin clotting time.

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

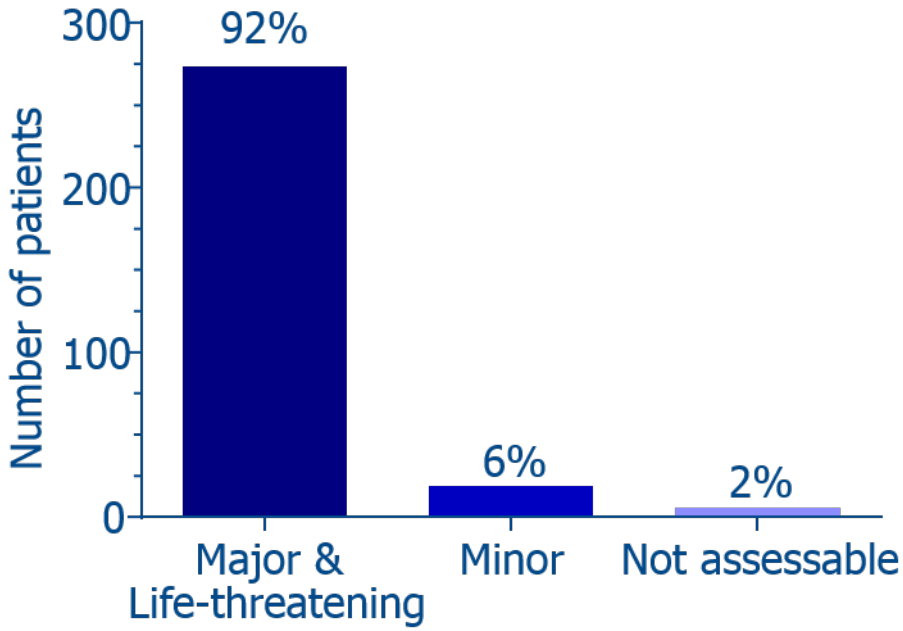
Group A: Site of Index Bleed (298 patients)

AHA 2016

Type of Bleeding*	N
Intracranial	**97**
Intracerebral	53
Subdural	38
Subarachnoid	25
Gastrointestinal	**135**
Upper	52
Lower	45
Unknown	42
Non-GI, Non ICH	**87**
Pericardial	7
Intramuscular	9
Retroperitoneal	10
Intra-articular	5
Other	56
Total	**319**

*Bleeding may occur at more than one site.
GI, gastrointestinal; ICH, intracranial hemorrhage;
ISTH, International Society on Thrombosis and Haemostasis.

ISTH Bleeding Severity (n = 298)
(determined locally upon patient entry)



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Group B: Indications for Surgery/Procedures

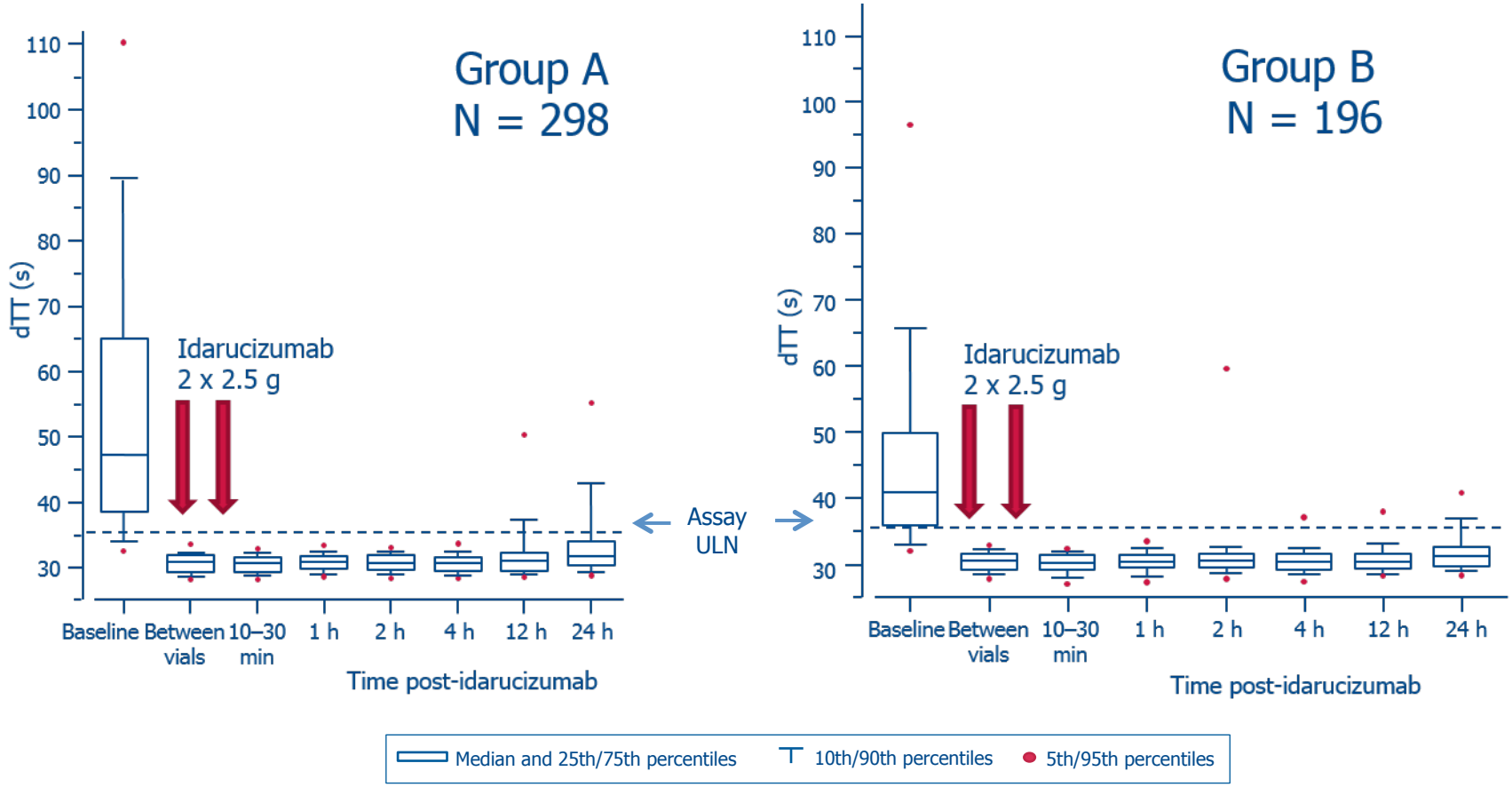
AHA 2016

Indication / Procedure	Frequency
Acute abdomen (gall bladder, appendix, bowel obstruction)	45
Bone fracture (hip, femur, open extremity, other)	30
Infection (joint, abscess, sepsis)	20
Incarcerated hernia	16
Acute renal failure, obstruction	11
Pacemaker implant	10
Pneumothorax for tube thoracostomy	9
ICH (surgical intervention)	7
Reperfusion for MI	5
Aortic aneurysm repair	5
Pericardiocentesis	4
Emergent spinal surgery	4
Heart transplant	3
Lumbar puncture	2
Other	25
Total	**196**

ICH, intracranial hemorrhage; MI, myocardial infarction.

AHA 2016

Diluted Thrombin Time (dTT) - Assessment of Reversal of Dabigatran Anticoagulation with Idarucizumab



Similar results were also obtained with Ecarin Clotting Time (ECT)

ULN, upper limit of normal

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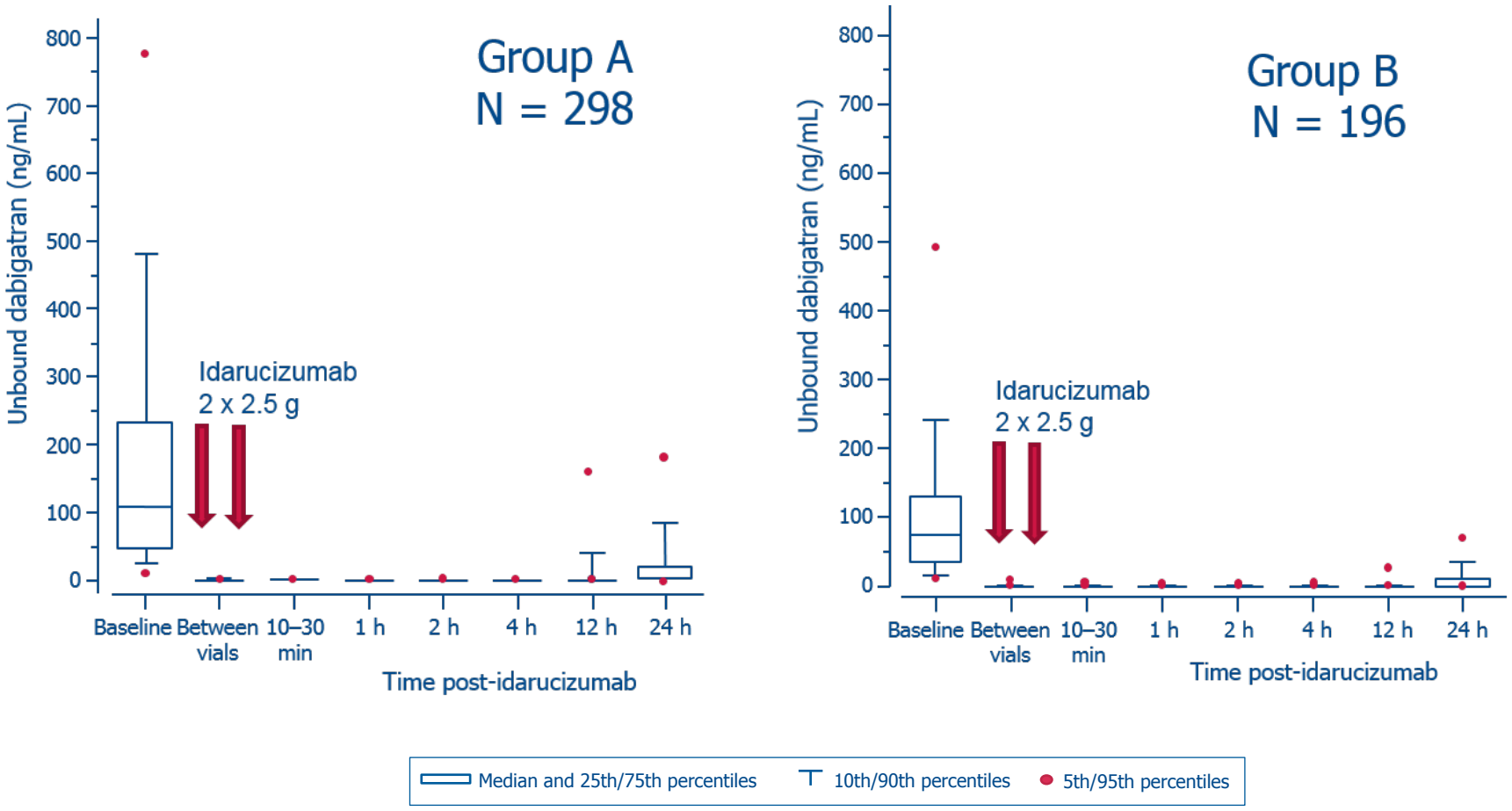
Unbound Dabigatran Levels Showing Reversal of Dabigatran Anticoagulation with Idarucizumab

AHA 2016



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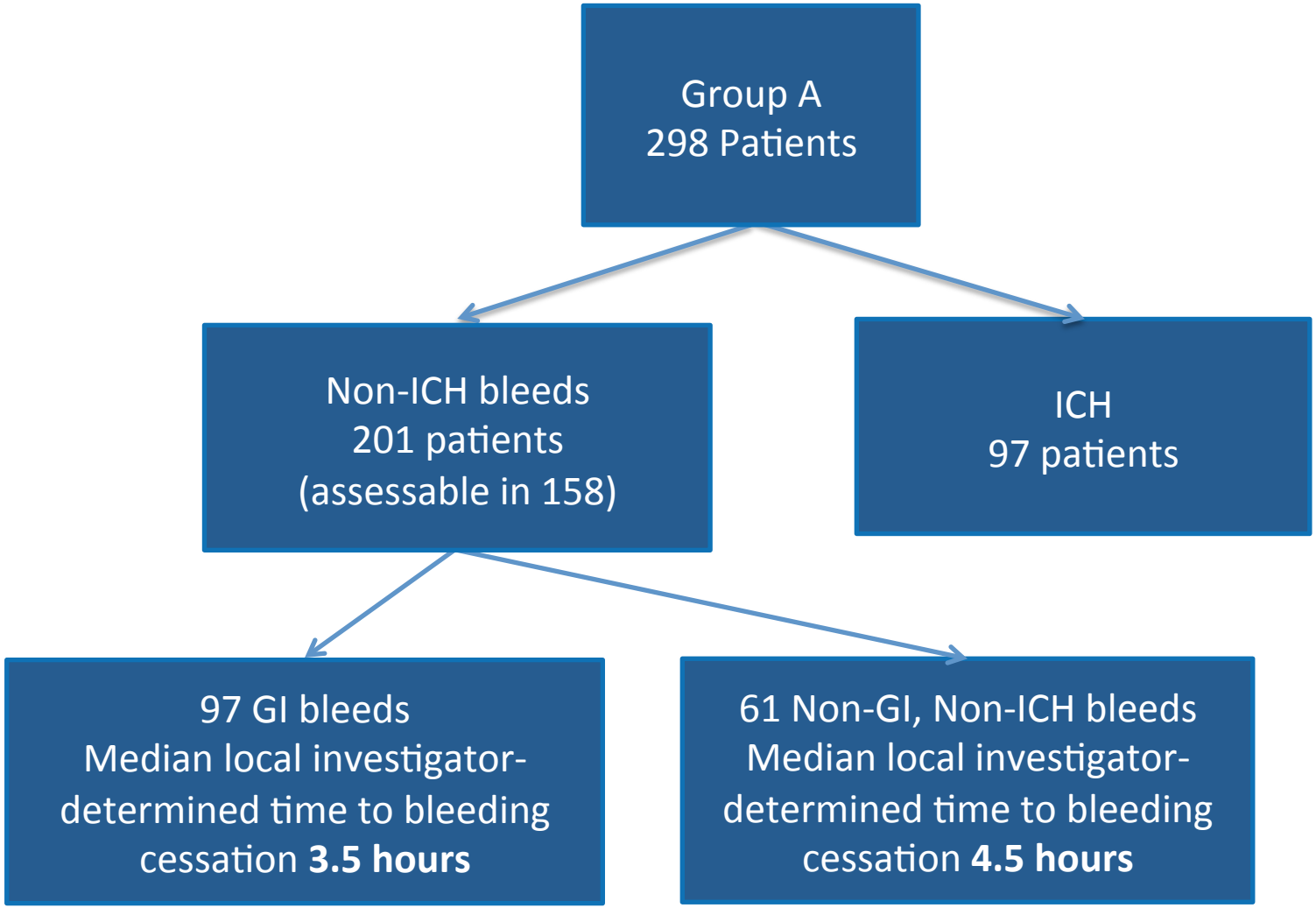
AHA 2016

Group A: Local Confirmation of Hemostasis



GI, gastrointestinal; ICH, intracranial hemorrhage.

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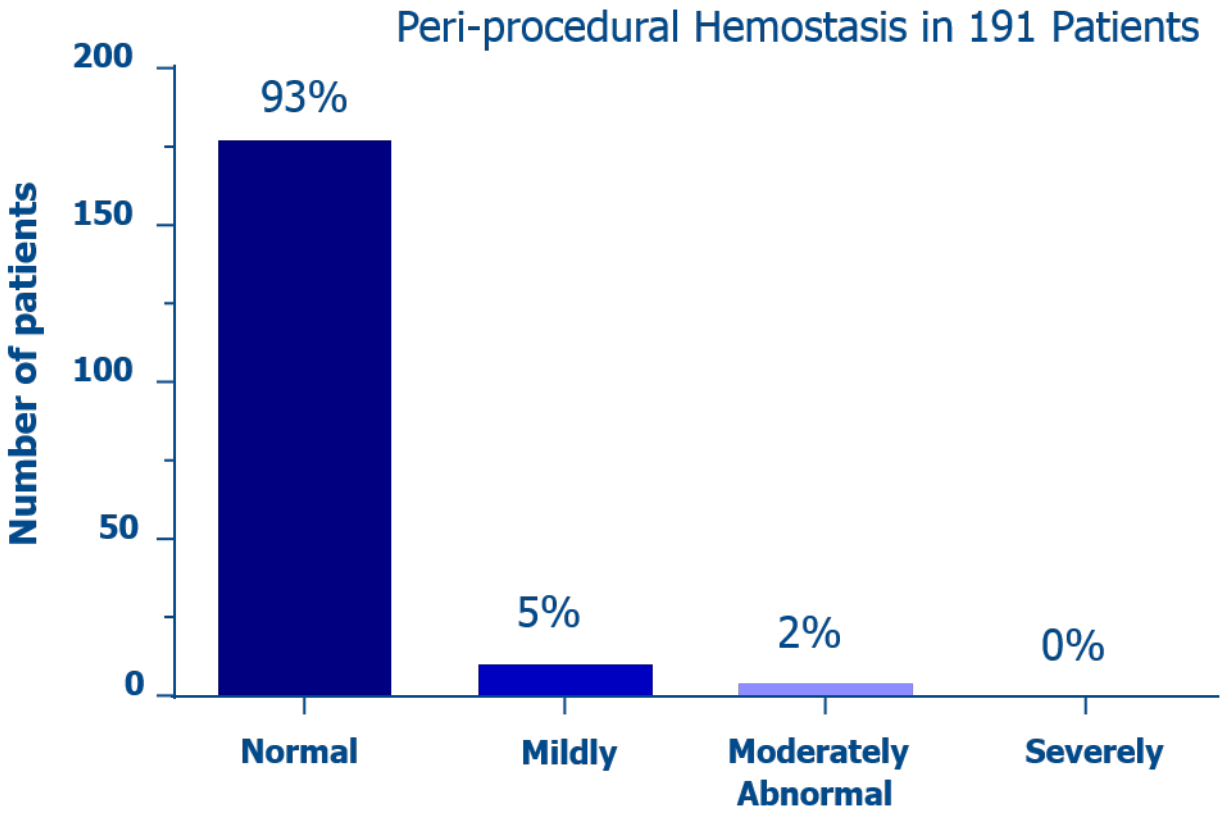
AHA 2016

Group B: Peri-procedural Hemostasis

- 191 of 196 (97.4%) patients underwent surgery/procedures
- **Median time from administration of first vial to procedure was 1.6 hours**
- Adequacy of hemostasis during surgery determined locally



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Adjudicated Post-Reversal Thromboembolic Events through 90 Days

AHA 2016

- In total, 35 thrombotic events occurred in 31 of 494 patients (6.3%) at 90 days
  - At 30 days thrombotic events occurred in 4.4% of patients in group A and 4.6% of patients in group B
- ~2/3 of these received no antithrombotic therapy prior to the event

Events	No. of Patients
VTE	15
Ischemic stroke	8
MI	7
Systemic embolism	1

VTE, venous thromboembolism; MI, myocardial infarction

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Mortality (Kaplan-Meier Survival)

AHA 2016

Follow-up	Group A (N = 298)	Group B (N = 196)
30 days		
Patients at risk, n	250	164
Mortality, %	12.3	12.4
90 days		
Patients at risk, n	149	105
Mortality, %	18.7	18.5

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

Praxbind®
idarucizumab
2,5 g/50 mL – Solution injectable / pour perfusion

Dose recommandée de Praxbind®*

5 g

Soit **2 flacons** de 2,5 g / 50 mL
de **solution prête à l'emploi**
en administration par **voie IV**

- **Aucune adaptation de dose nécessaire**
  chez les patients insuffisants rénaux, les patients insuffisants hépatiques et les patients âgés ≥ 65 ans[1]

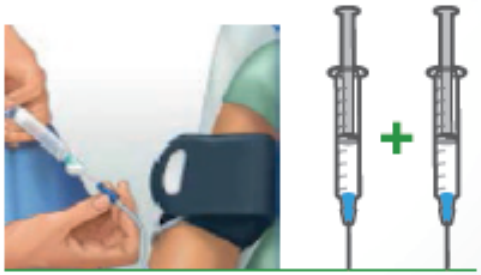
Praxbind®
idarucizumab
2,5 g/50 mL – Solution injectable / pour perfusion

Administration de la dose en perfusion IV ou en injection IV en bolus [1]

2 perfusions IV consécutives

ou

2 injections IV consécutives en bolus



- Perfusion avec un débit de 5 à 10 mL/min
- en 5 à 10 min pour chaque flacon

Synthèse

Réactualisation des propositions du Groupe d'Intérêt en Hémostase Périopératoire (GIHP) - septembre 2016

- Les premières données disponibles suggèrent que l'idarucizumab corrige immédiatement les paramètres de la coagulation des patients traités par dabigatran.
- Il est indiqué chez les patients adultes traités par dabigatran quand une correction rapide de l'effet anticoagulant est requise pour une procédure invasive urgente ou en cas de saignement incontrôlé ou menaçant le pronostic vital