Updated Results of the RE-VERSE AD™ Study

Idarucizumab Reverses the Anticoagulant Effects of Dabigatran in Patients in an Emergency Setting of Major Bleeding, Urgent Surgery, or Interventions

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On behalf of the RE-VERSE AD™ Investigators

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RE-VERSE AD™ Study Update

- Presentation includes data on 494 patients followed for 3 months
- Data cut-off was July 31, 2016
- 369 sites were initiated in 39 countries, 173 sites recruited patients
- Full trial results will be based on data from 503 patients

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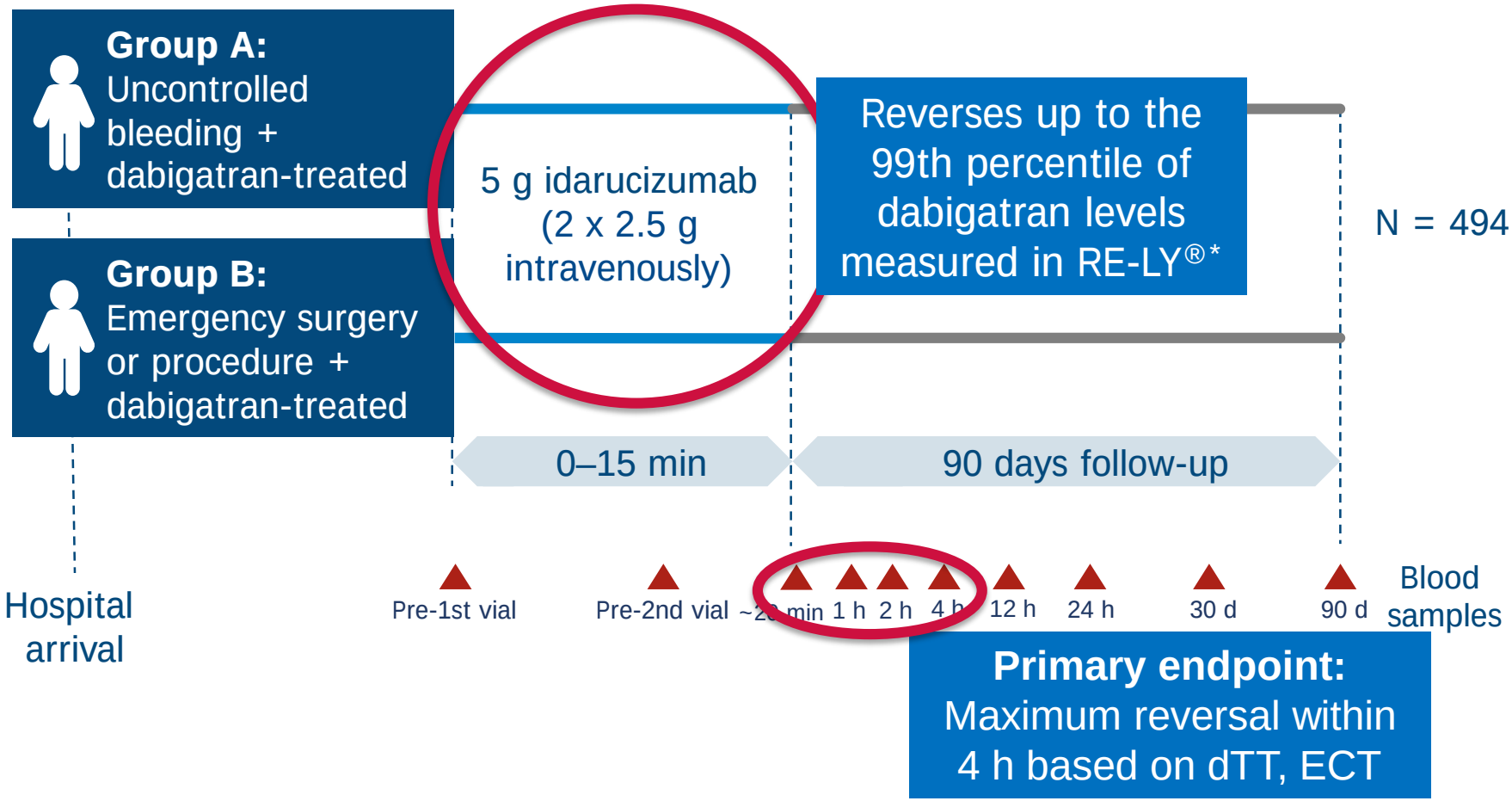
Multicenter, Ongoing, Open-label, Single-arm Phase III study



*Connolly S,et al. *N Engl J Med*. 2009; 361:1139–51.
Pollack C, et al. *Thromb Haemost*. 2015;114:198–205.
dTT, diluted thrombin time; ECT, ecarin clotting time.

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RE-VERSE AD™: Selected Secondary Endpoints

- Clinical Endpoints
  - Group A: Time to confirmation of hemostasis (bleeding cessation) determined by local investigator
    - CT scans post-treatment for ICH patients were not mandatory
  - Group B: Hemostasis peri-procedural
    - assessed by local investigator as:
      normal or mildly, moderately, or severely abnormal
  - Thrombotic events up to 90 days (adjudicated)
  - Re-initiation of antithrombotic therapy
  - Mortality

- Pharmacodynamic Endpoints
  - Dabigatran levels
  - Local and central laboratory aPTT

aPTT, activated partial thromboplastin time; ICH, intracranial hemorrhage

Patient Demographics

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)

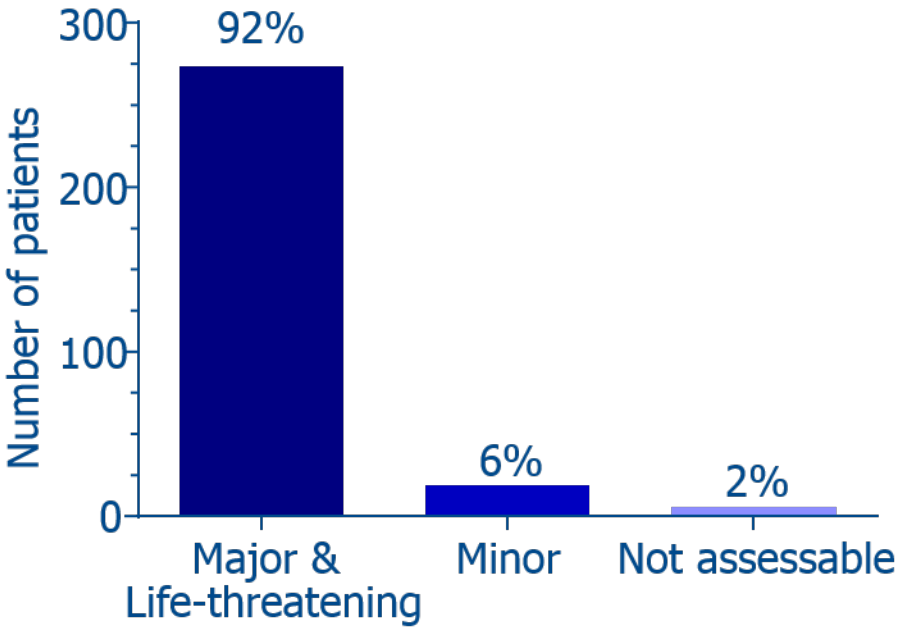
BID, twice daily; dTT, diluted thrombin time; ECT, ecarin clotting time.

Group A: Site of Index Bleed (298 patients)

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

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.

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Primary Results

- Median maximum reversal within 4 hours was 100% for dTT (95% CI, 100–100%)
- dTT normalized within 4 hours in 235/238 patients (98.7%) in Group A and 141/143 patients (98.6%) in Group B*
- Similar results were obtained with ECT and central laboratory aPTT

*Calculated for patients with elevated levels at baseline.
aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; CI, confidence interval; ECT, ecarin clotting time

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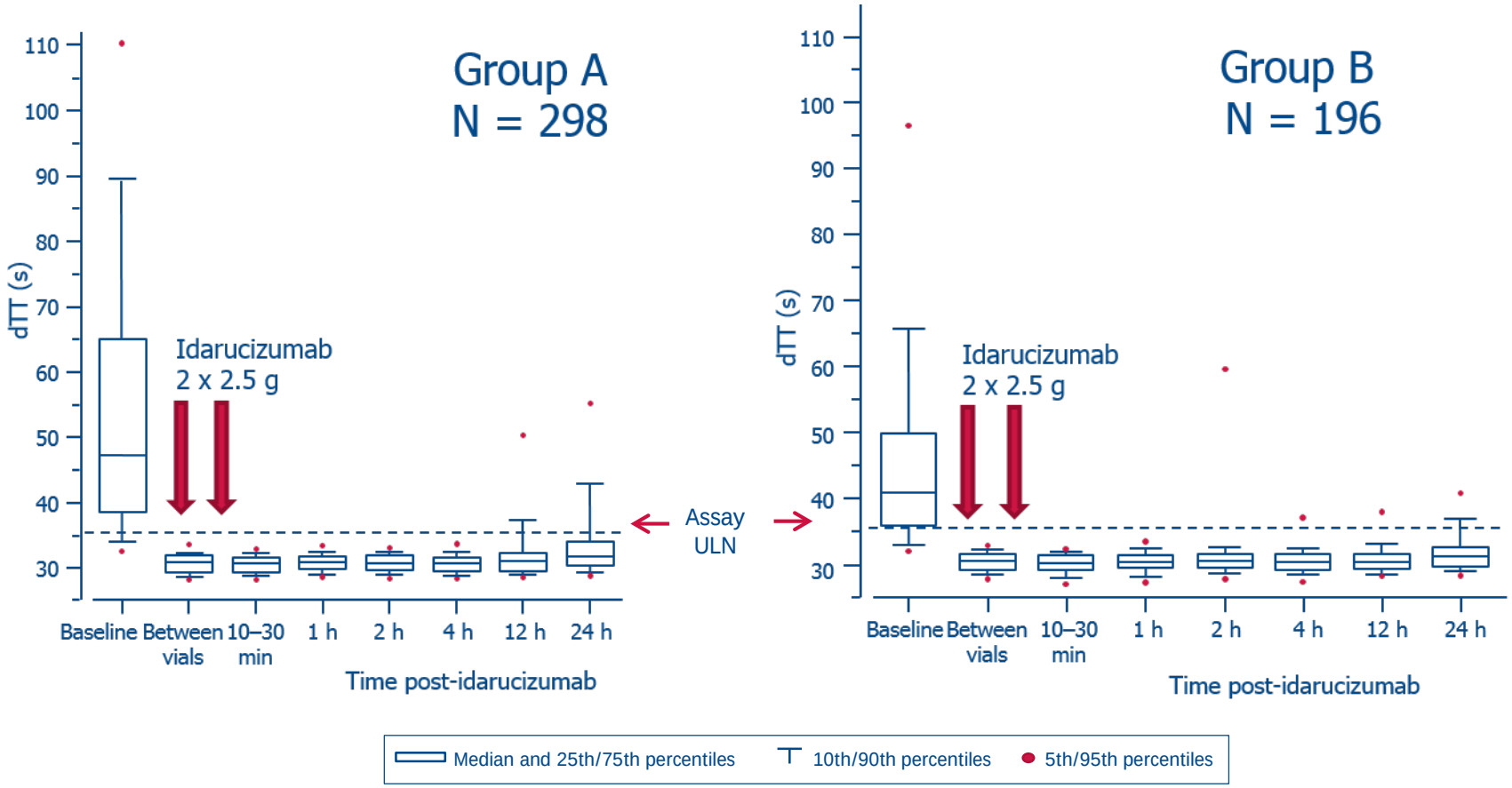
RESULTS: Diluted Thrombin Time (dTT) - Assessment of Reversal of Dabigatran Anticoagulation with Idarucizumab



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

ULN, upper limit of normal

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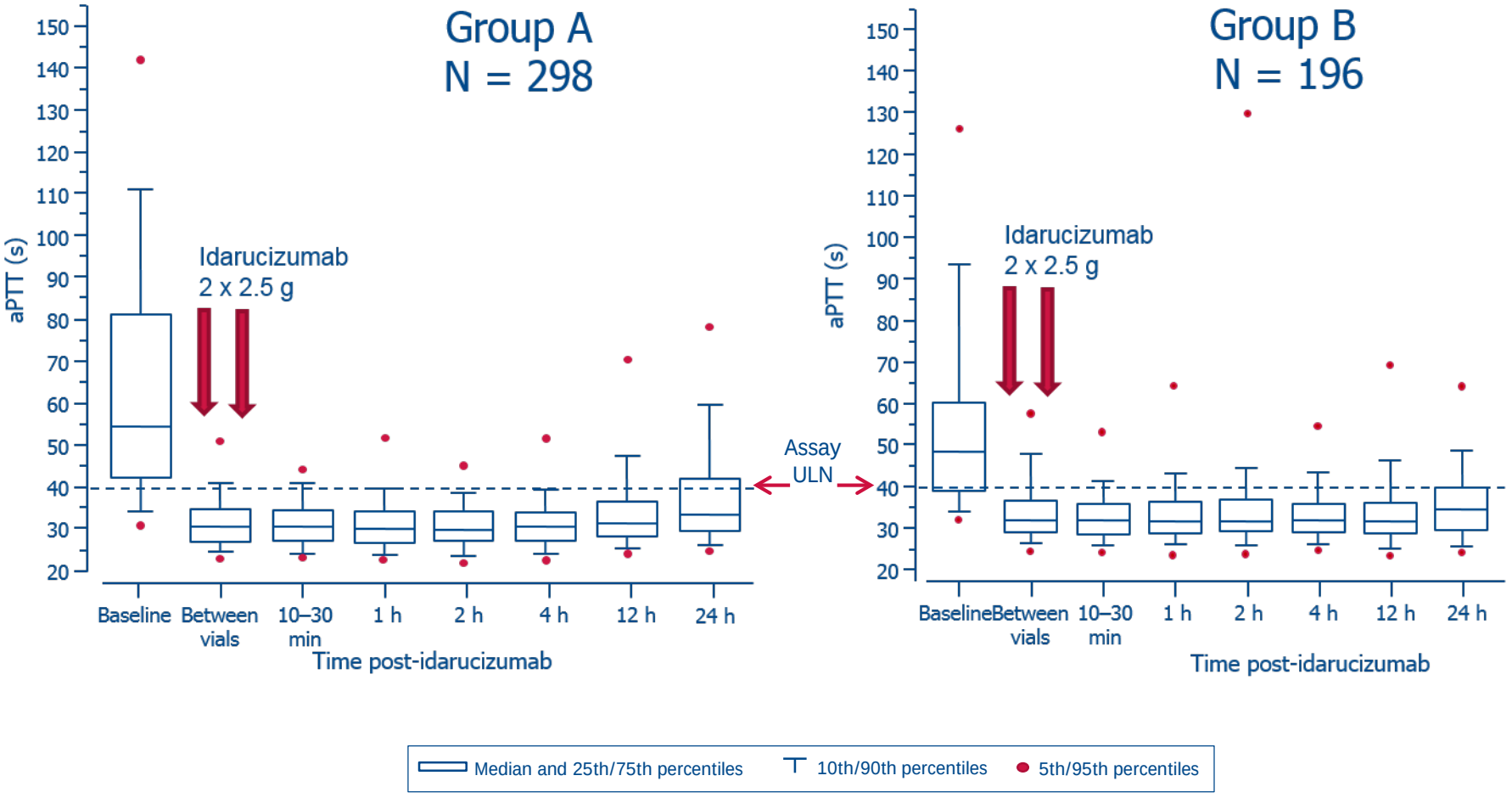
RESULTS: activated Partial Thromboplastin Time (central) Reversal of Dabigatran Anticoagulation with Idarucizumab



aPTT, activated partial thromboplastin time; ULN, upper limit of normal.

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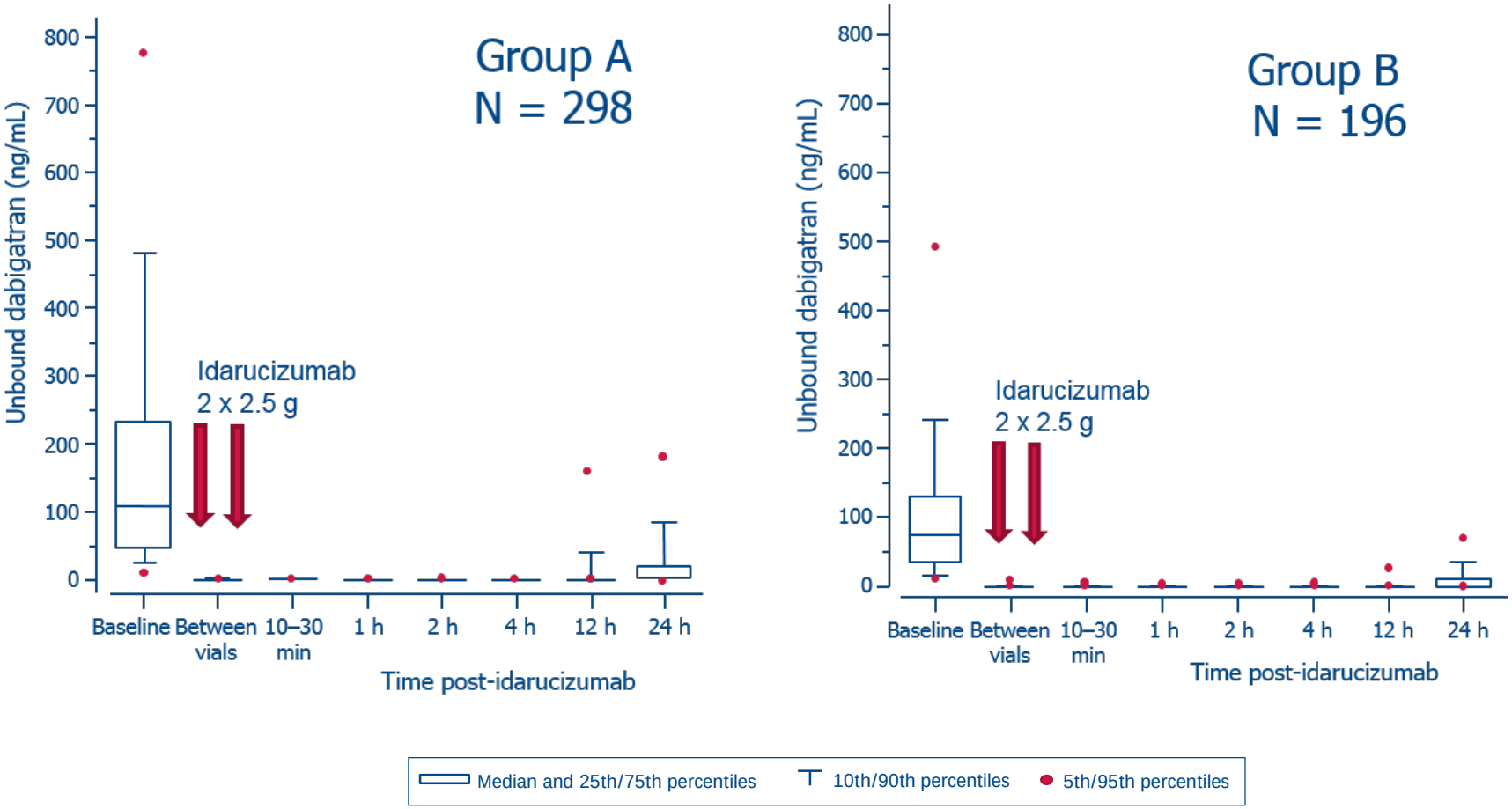
RESULTS: Unbound Dabigatran Levels Showing Reversal of Dabigatran Anticoagulation with Idarucizumab



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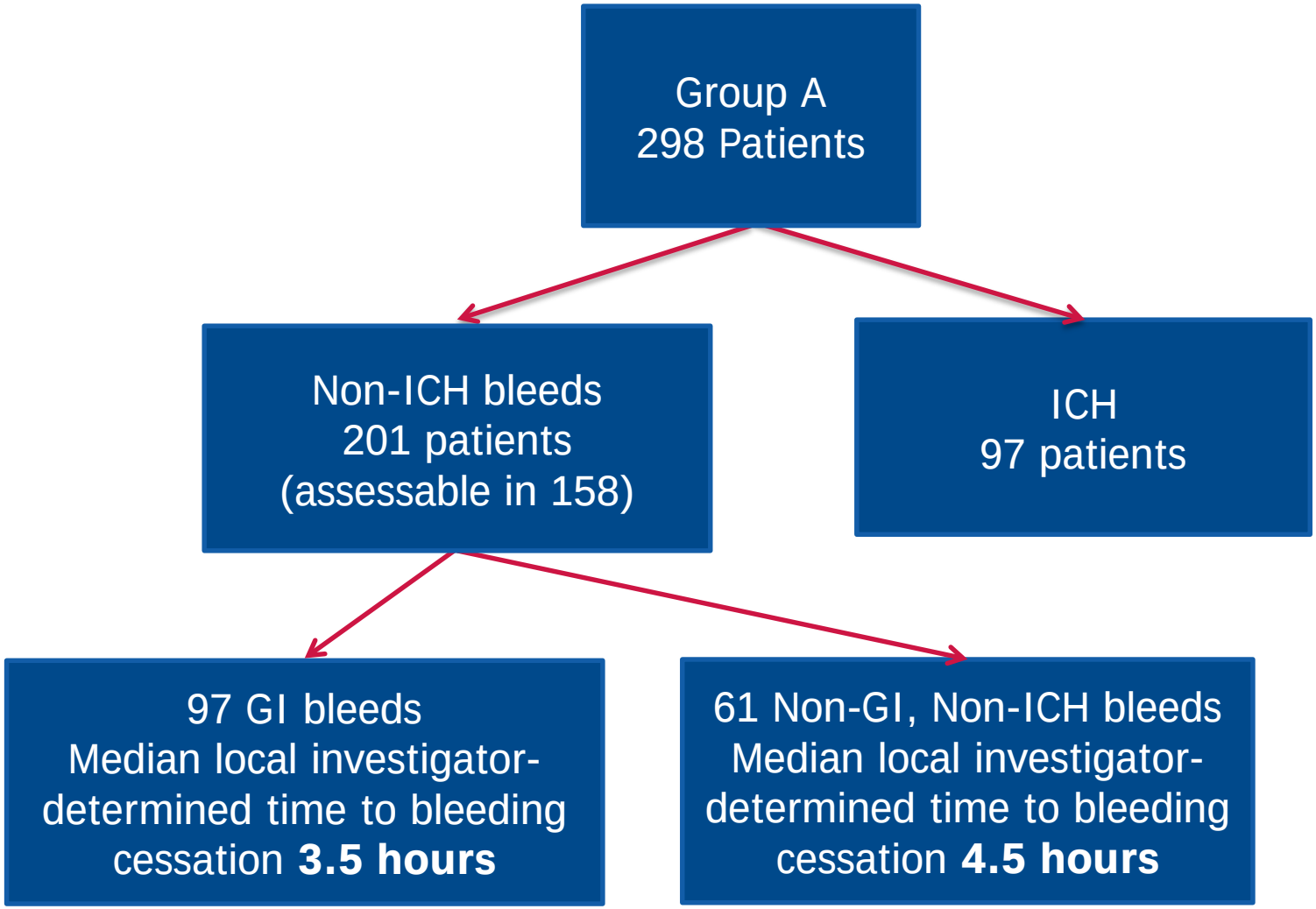
Group A: Local Confirmation of Hemostasis



GI, gastrointestinal; ICH, intracranial hemorrhage.

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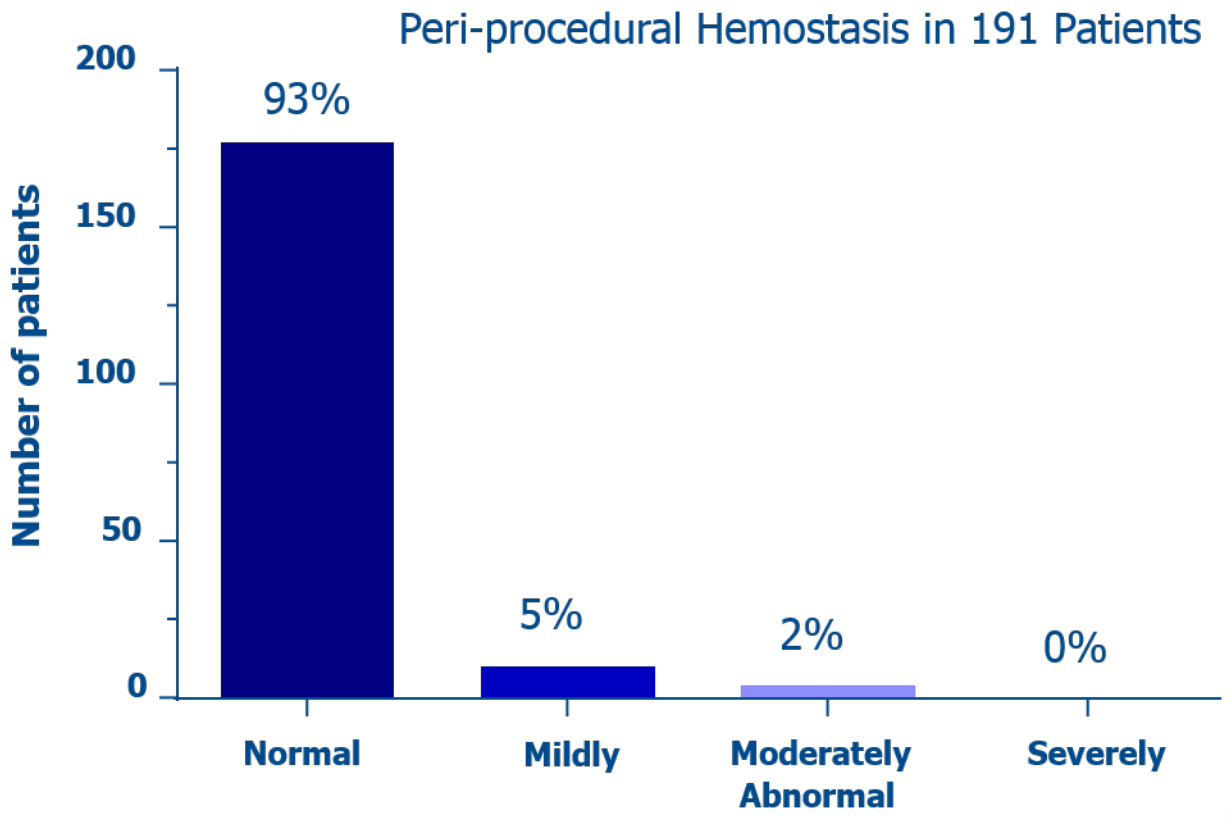
Group B: Peri-procedural Hemostasis

- 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

- 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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Re-initiation of Antithrombotic Treatment within 90 days

Antithrombotic (n, %)*	Group A (n = 298)	Group B (n = 196)
Frequency:		
None	82 (28)	19 (10)
Any antithrombotic	216 (72)	177 (90)
Median time to re-start (days)	5.3	1.2

- Parenteral anticoagulation was re-initiated in 44% of patients in Group A and 71% of patients in Group B
- 29% of patients in Group A and 61% in Group B were re-initiated on dabigatran anticoagulation, usually at hospital discharge
- ~16% in each group were switched to other oral anticoagulants
- ~18% in each group were given antiplatelet agents

†Patients may be counted in more than one category.

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Mortality (Kaplan-Meier Survival)

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

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RE-VERSE AD™: Discussion

- Open label cohort study
  - Currently no approved treatment for comparison
- Inclusive “real-world” study
  - Condition and bedside evaluation drive treatment decision
  - Provides a broad and heterogeneous emergency patient population including patients requiring urgent surgery and interventions
- Fixed dose based on anticipated dabigatran loads
  - Massive overdose or acute renal failure could result in higher dabigatran levels
  - Some patients show re-appearance of low levels of dabigatran at 24 hours, without apparent clinical consequences

RE-VERSE AD™: Conclusions

In a cohort of multi-morbid, elderly patients taking dabigatran who presented with life-threatening emergencies:

- 5 g of idarucizumab resulted in immediate, complete, and sustained reversal of dabigatran anticoagulation
- Median time to cessation of extracranial bleeding in Group A was between 3.5–4.5 hours after reversal, depending on anatomical location of the bleed
- Median time to surgery after reversal was 1.6 hours, with intraoperative hemostasis “normal” in 93% of Group B patients, and prompt re-initiation of antithrombotic therapy post-procedure
- No safety concerns identified to date

Back-Up slides

Patients Treated with More Than One 5 g Dose of Idarucizumab

- Seven patients (1.4%) experienced re-bleeding and had re-elevation of clotting tests 12–24 hours later and received a second dose
  - Five (Group A) due to re-bleeding up to 72 hours later
  - Two (Group B) due to post-operative bleeding
- After second dose: 5 stopped bleeding, 1 fatal bleed, 1 fatal sepsis

GI, gastrointestinal.

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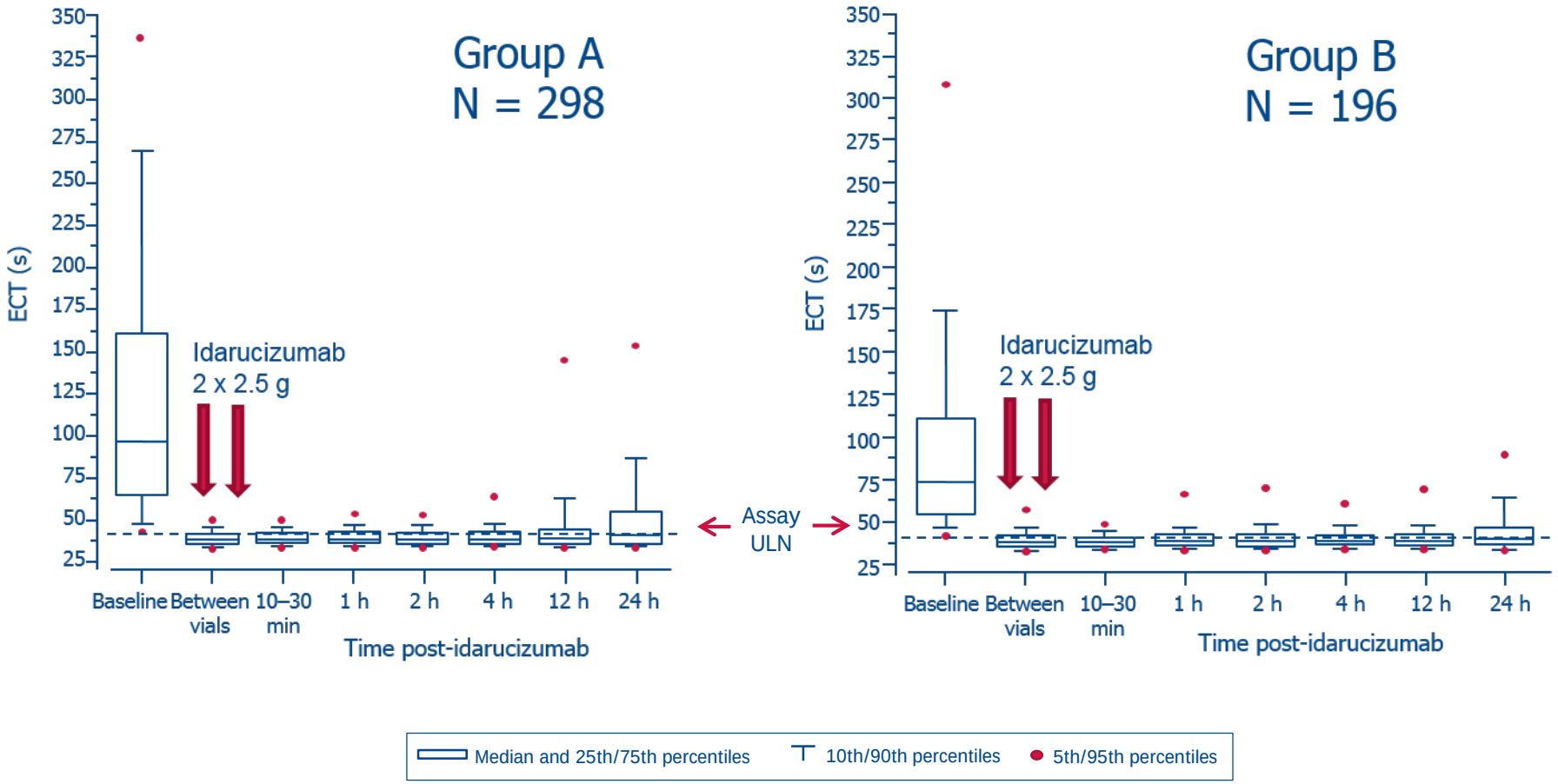
RESULTS: Primary Endpoint: Ecarin Clotting Time (ECT) Reversal of Dabigatran Anticoagulation with Idarucizumab



ULN, upper limit of normal.

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