계명대학교 동산의료원
Keimyung University Dongsan Medical Center

"Idarucizumab"
Innovation in Anticoagulation Care

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Arrhythmia Service, Cardiology, Dongsan Medical Center

Treatment Strategies according to Pathophysiology

Atrial Fibrillation

Rapid ventricular resp

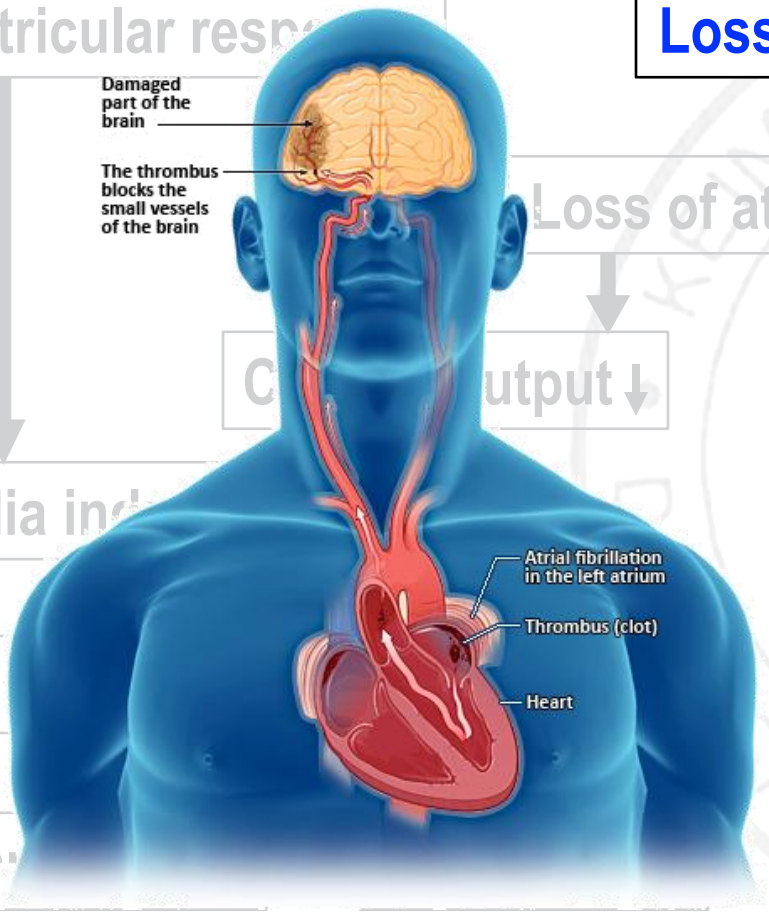
Loss of atrial contraction

Loss of atrial kick

Stasis of blood

C utput ↓

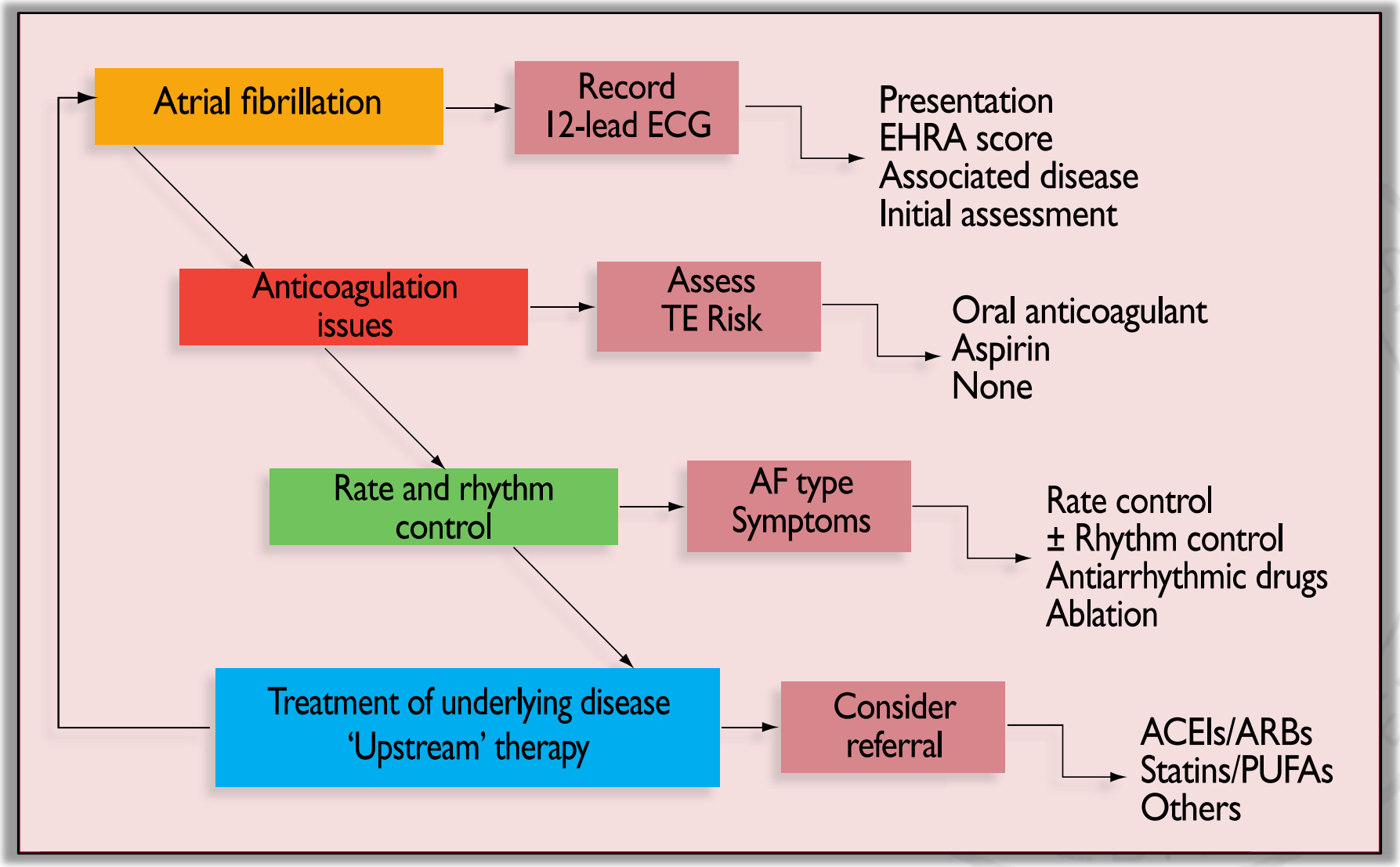
Tachycardia ind



Rhyth

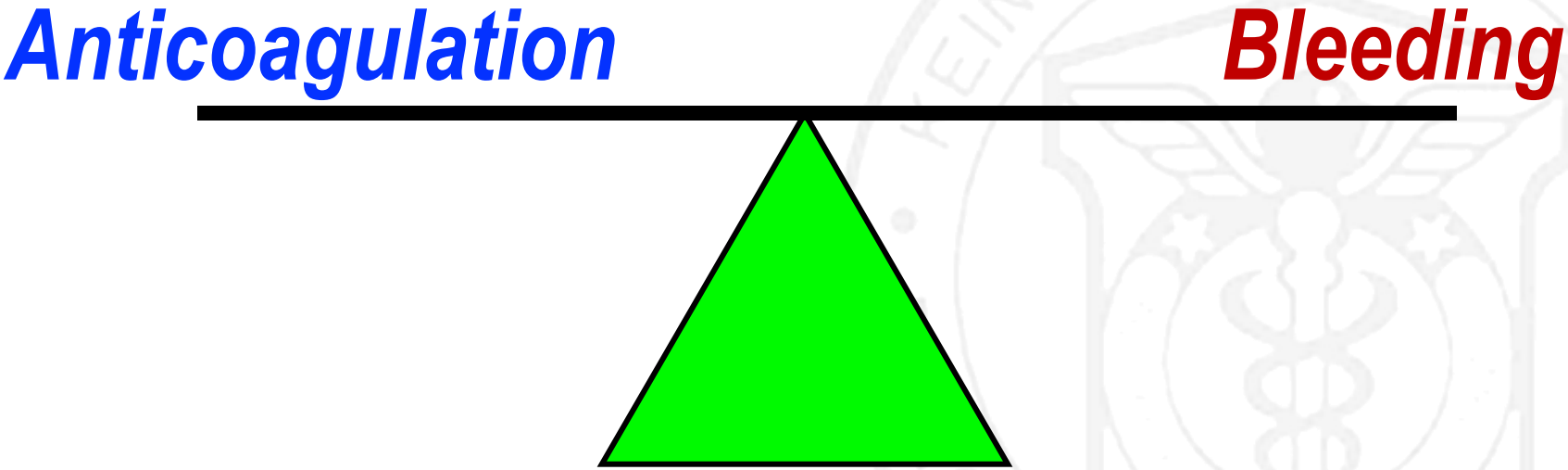
Thromboembolism

Management Cascade of AF

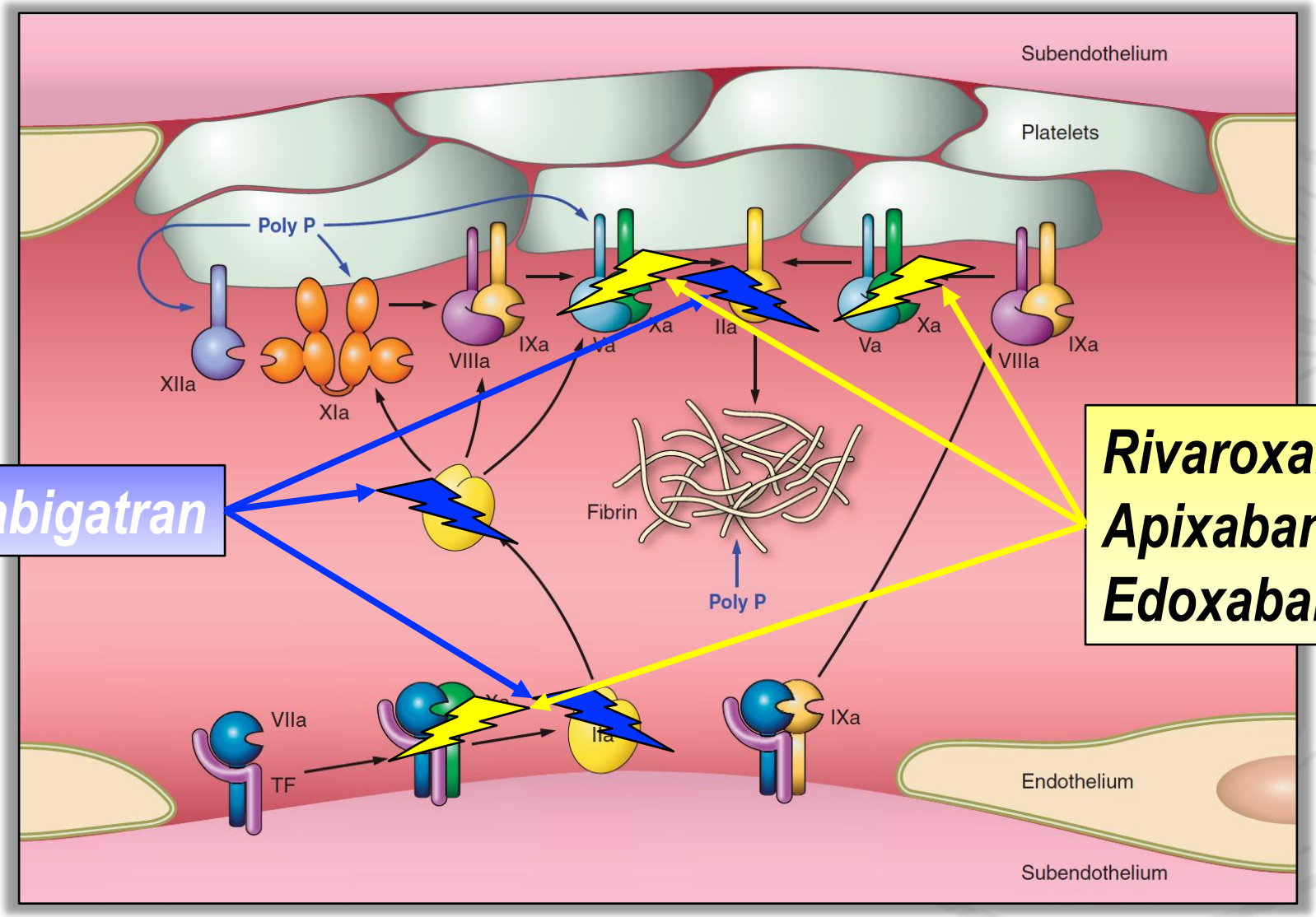


Camm AJ et al. Eur Heart J. 2010;31:2369

Therapeutic Balance in thrombophylaxis

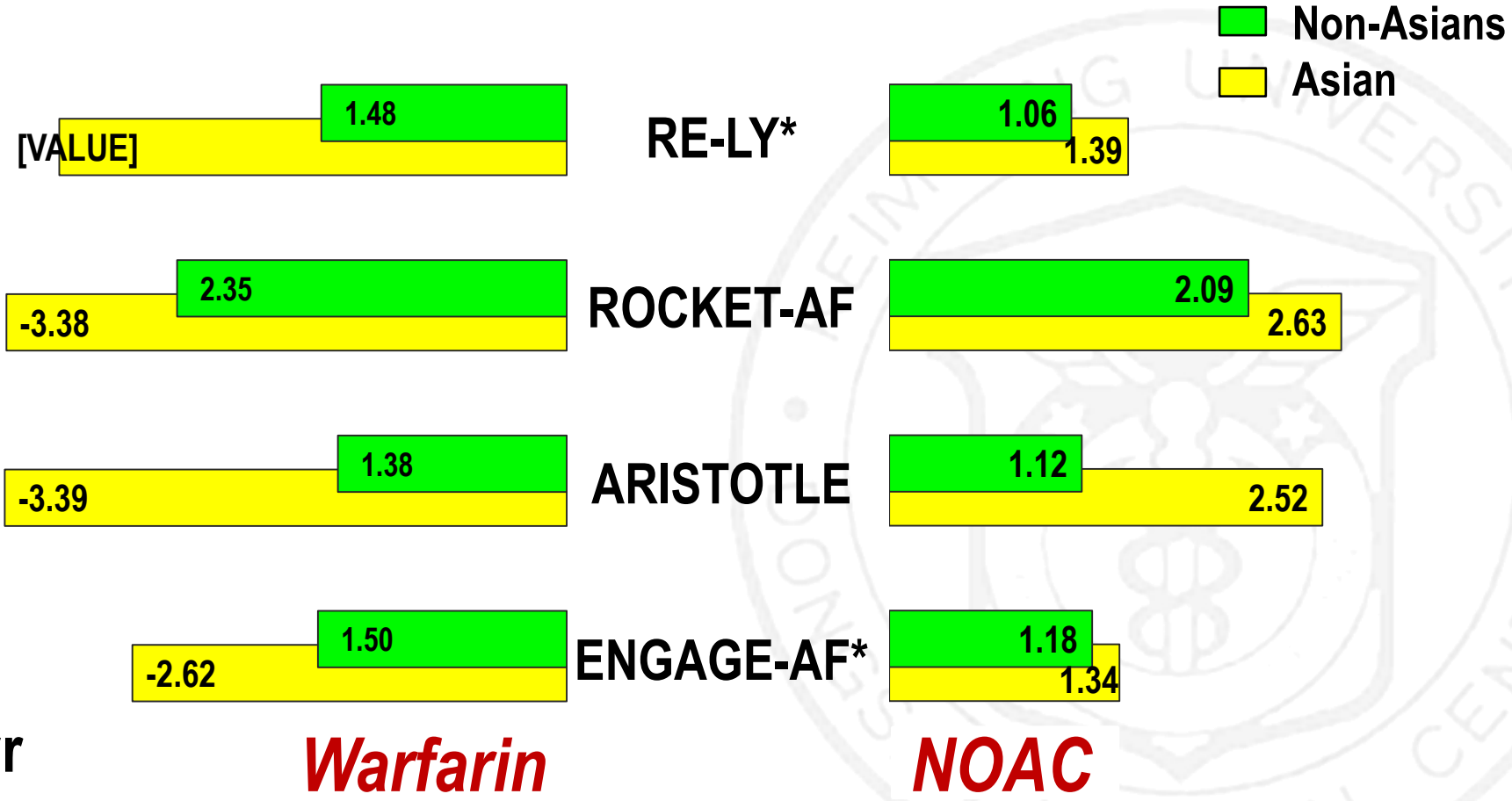


Direct Oral Anticoagulant



Versteeg HH, et al. Physiol Rev 2013;93:327

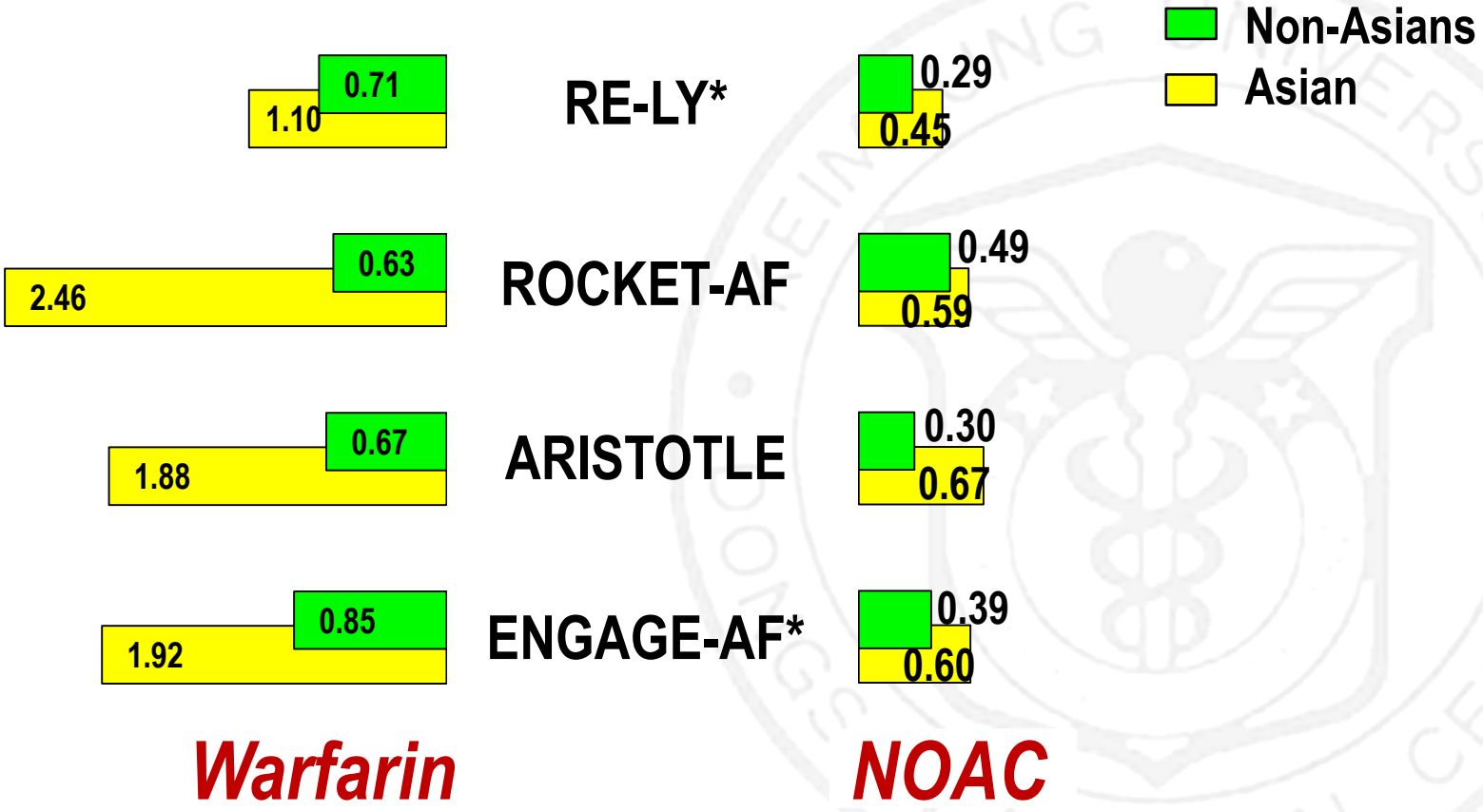
Annual Incidence of Stroke/SE In 4 Phase 3 Trials



Asians refers to all Asians in the RE-LY and East Asians in the others

Toyoda K., et al. Stroke 2015;46:1474

Annual Incidence of ICH In 4 Phase 3 Trials



Asians refers to all Asians in the RE-LY and East Asians in the others

Toyoda K., et al. Stroke 2015;46:1474

Interpretation of coagulation assays in NOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
aPTT	✓	✗	✗	✗
TT, dTT	✓	✗	✗	✗
ECT	✓	✗	✗	✗
Anti-FXa assays	✗	✓	✓	✓
PT	✗	✓	✗	✗
INR	✗	✗	✗	✗

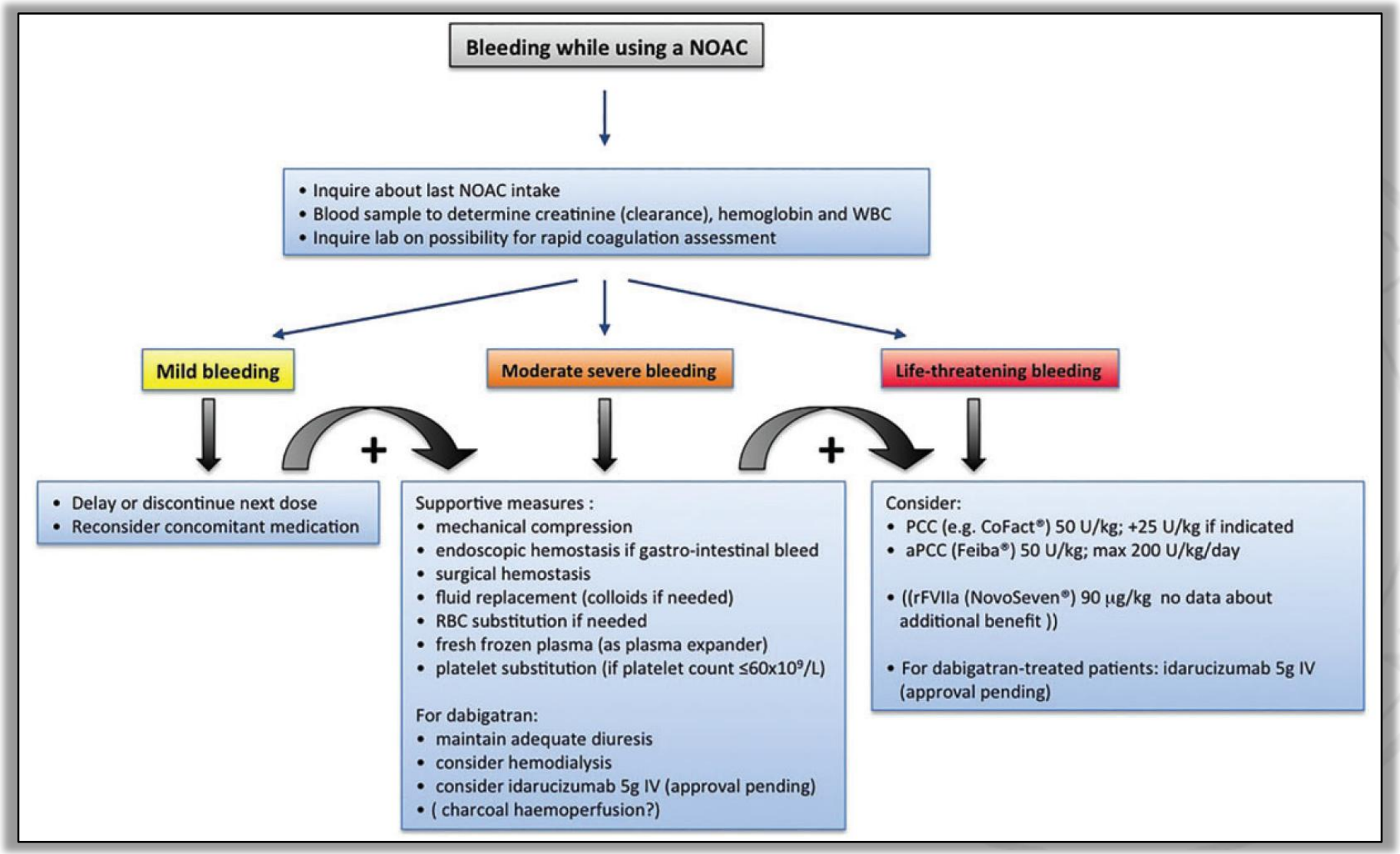
Green = quantitative; Orange = qualitative only; Red = not applicable, PT: neoplastin plus or neoplastin specific

Predictor for high risk of bleeding of Dabigatran

Test	Trough Value
dTT	> 200 ng/ml
ECT	> 3 time of upper limits
aPTT	> 2 time of upper limits

- Important to know when NOAC was administered relative to time of blood sampling
- aPTT may provide useful information for qualitative assessment

Management of bleeding in patients taking NOACs



Heidbuchel H, et al. DOI:10.1093/europace/euv309

" Reversal Agent "

"The word ***antidote*** literally means a drug that ***counteracts a poison***. When used in medical context, the ***word antidote should be reserved*** for those ***agents that inactivate the targeted medication directly***"

Eerenberg ES, et al. Thromb Haemost 2012;108:623

Contra: "Antidotes for novel anticoagulants?" – Do we really need them

Eerenberg ES, et al. Thromb Haemost 2012;108:623

- Size of the problem: ***2~4% of major bleeding*** of NOAC
- ***Available substitutes***: PCC*, rFVIIa

Pro: "Antidotes for new anticoagulants" – Specific target of inhibition requires a specific target for neutralization

Roldan V, Marin F. Thromb Haemost 2012;108:621

- Most studies were performed either in ***animal models*** or in ***healthy subjects*** ***without clinical bleeding endpoint***
- **rFVIIa, activated PCC: thrombotic complications**

**PCC: procoagulant complex concentrates*

Current consensus recommendations for reversal of the target-specific oral anticoagulants

Intervention	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Oral activated Charcoal	***Yes***	***Yes***	***Yes***	***Yes***
Hemodialysis	***Yes***	No	No	No
Hemoperfusion with activated charcoal	***Yes***	Possible	Possible	?
Fresh forozen plasma	No	No	No	No
Activated recombinant FVIIa	Unclear	Unclear	Unclear	Unclear
3 factor PCC (II, IX, X)	Unclear	Unclear	Unclear	Unclear
4 factor PCC (II, IX, X, VII)	***Possible***	***Possible***	***Possible***	***Possible***

Ansell JE. J Thromb Thrombolysis 2016; 41:248

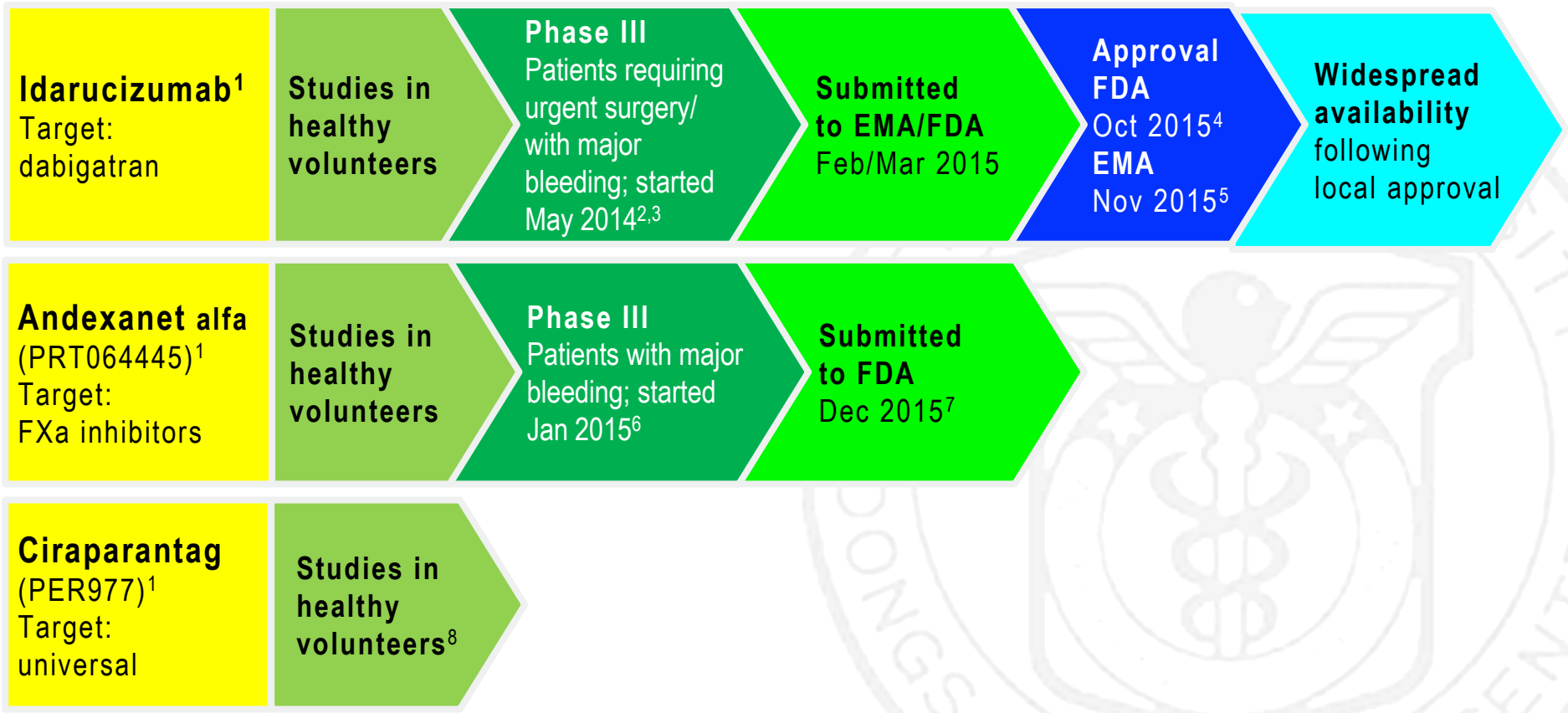
"The ability to turn the anticoagulation effect on and off as required could provide further benefit for patients in need of intervention while on anticoagulation"

Reversal Agents for NOAC

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

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

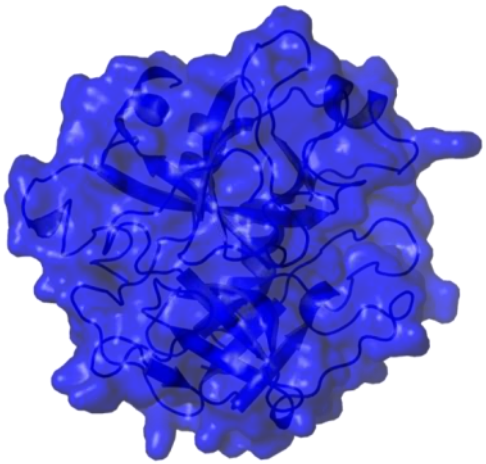
Reversal Agents for NOAC: stages of development



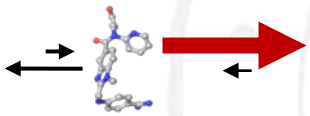
1. Adapted from Greinacher et al. Thromb Haemost 2015; 2. Clinicaltrials.gov: NCT02104947; 3. Pollack et al. Thromb Haemost 2015; 4. US FDA press release 16 Oct 2015; 5. European Commission Community Register of Medicinal Products for Human Use 20 November 2015; 6. ClinicalTrials.gov Identifier: NCT02329327; 7. ClinicalTrials.gov Identifier: NCT02207257

Idarucizumab (Praxbind®)

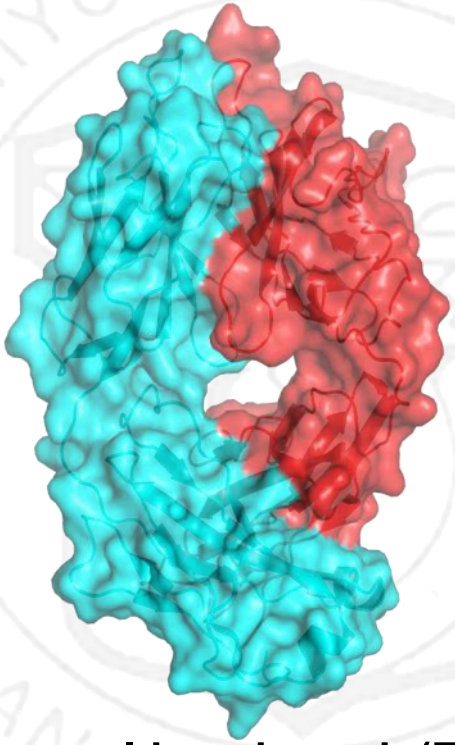
- Humanized Fab Fragment
- Binding affinity for dabigatran: > ***350× higher*** than dabigatran to thrombin



Thrombin
~37000 daltons



Dabigatran
~500 daltons

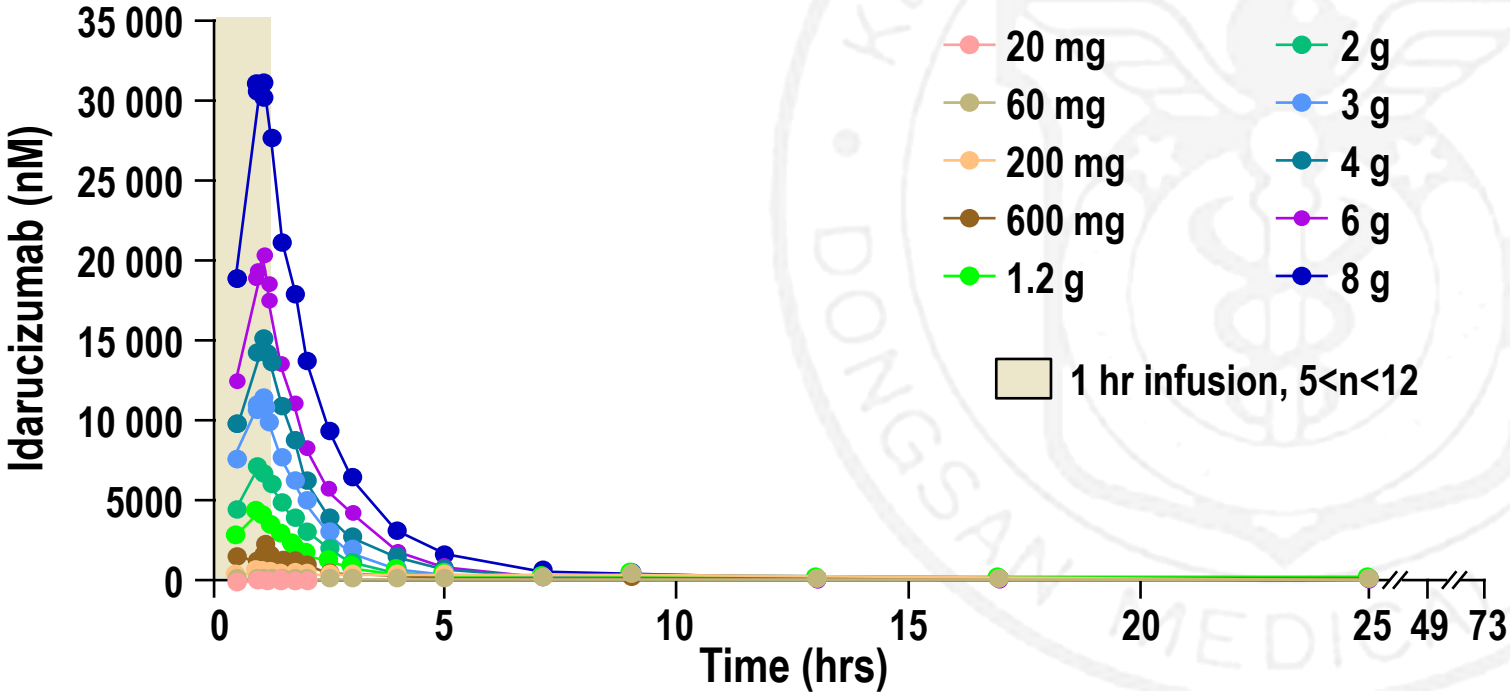


Idarucizumab (Fab)
~47800 daltons

Pollack CV Jr, et al. Thromb Haemost 2015;114:198

Idarucizumab plasma concentration in healthy volunteers

- Low volume of distribution
- Short half-life: ***initial $t_{1/2}$ ~45 min***; terminal $t_{1/2}$ 4.5–9 hours
- ***Within 6 hours 90% of dose had cleared***



Glund S et al. Thromb Haemost 2015;113:943

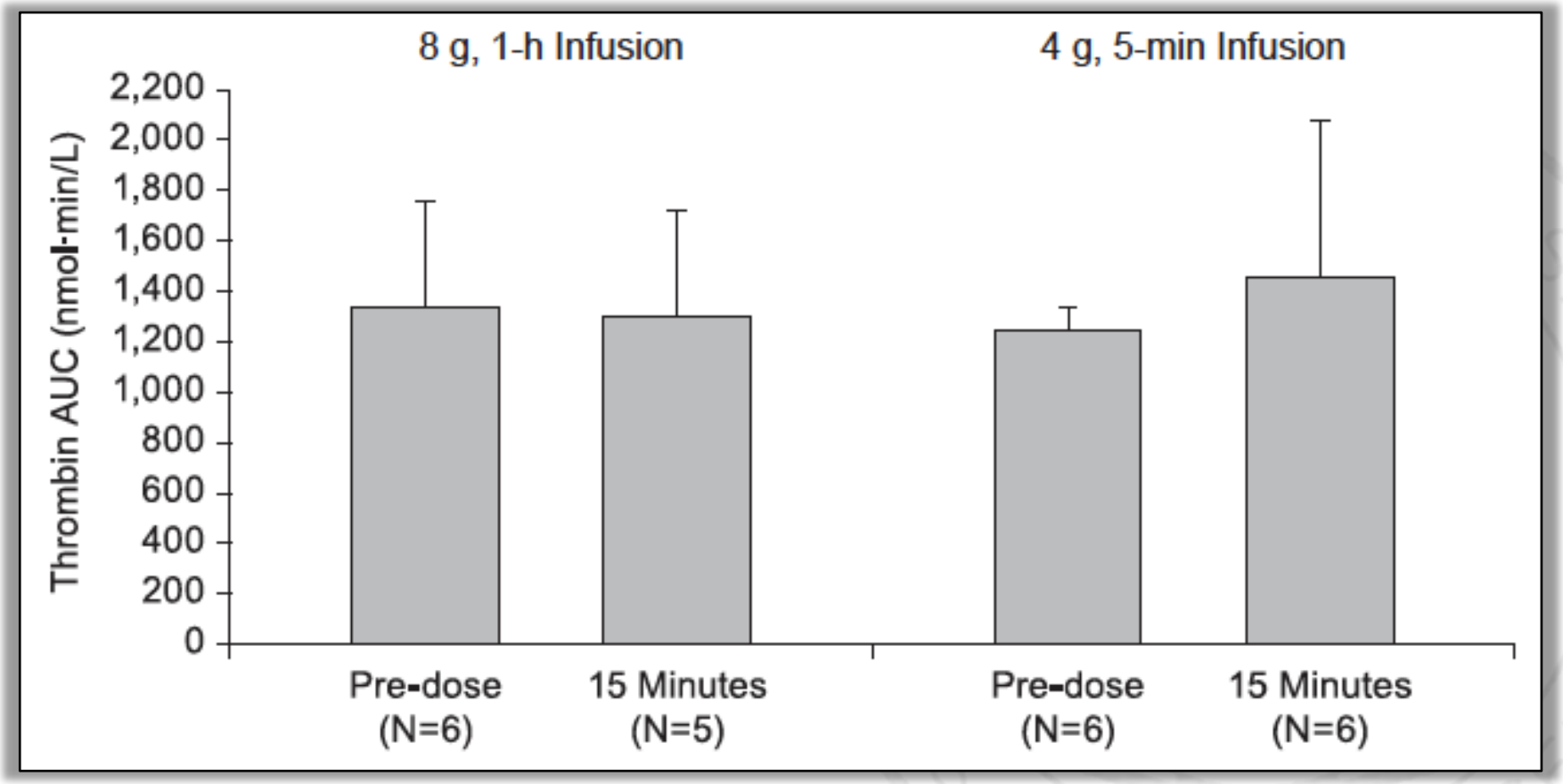
Idarucizumab had no effect on the coagulation markers

	8 g idarucizumab, 1-h infusion				4 g idarucizumab, 5-min infusion			
	Baseline (N=6)		15 min post infusion (N=5)		Baseline (N=6)		15 min post infusion (N=6)	
	Mean ± SD, s	CV, %	Mean ± SD, s	CV, %	Mean ± SD, s	CV, %	Mean ± SD, s	CV, %
dTT	32.0 ± 0.3	0.871	31.5 ± 0.4	1.16	31.9 ± 0.3	0.986	31.4 ± 0.6	1.80
ECT	37.3 ± 3.8	10.2	39.2 ± 5.3	13.4	36.6 ± 1.3	3.58	37.8 ± 1.9	4.93
TT	11.9 ± 0.5	4.29	12.3 ± 0.8	6.42	11.7 ± 1.0	8.36	11.7 ± 1.0	8.46
aPTT	31.4 ± 4.9	15.5	33.4 ± 4.8	14.3	32.8 ± 3.1	9.37	31.9 ± 2.4	7.60
ACT	114 ± 19.3	16.9	110 ± 13.5	12.3	112 ± 9.0	8.00	104 ± 12.8	12.4

ACT, activated clotting time; aPTT, activated partial thromboplastin time; CV, coefficient of variation; dTT, diluted thrombin time; ECT, ecarin clotting time; s, seconds; SD, standard deviation; TT, thrombin time.

Glund S et al. Thromb Haemost 2015;113:943

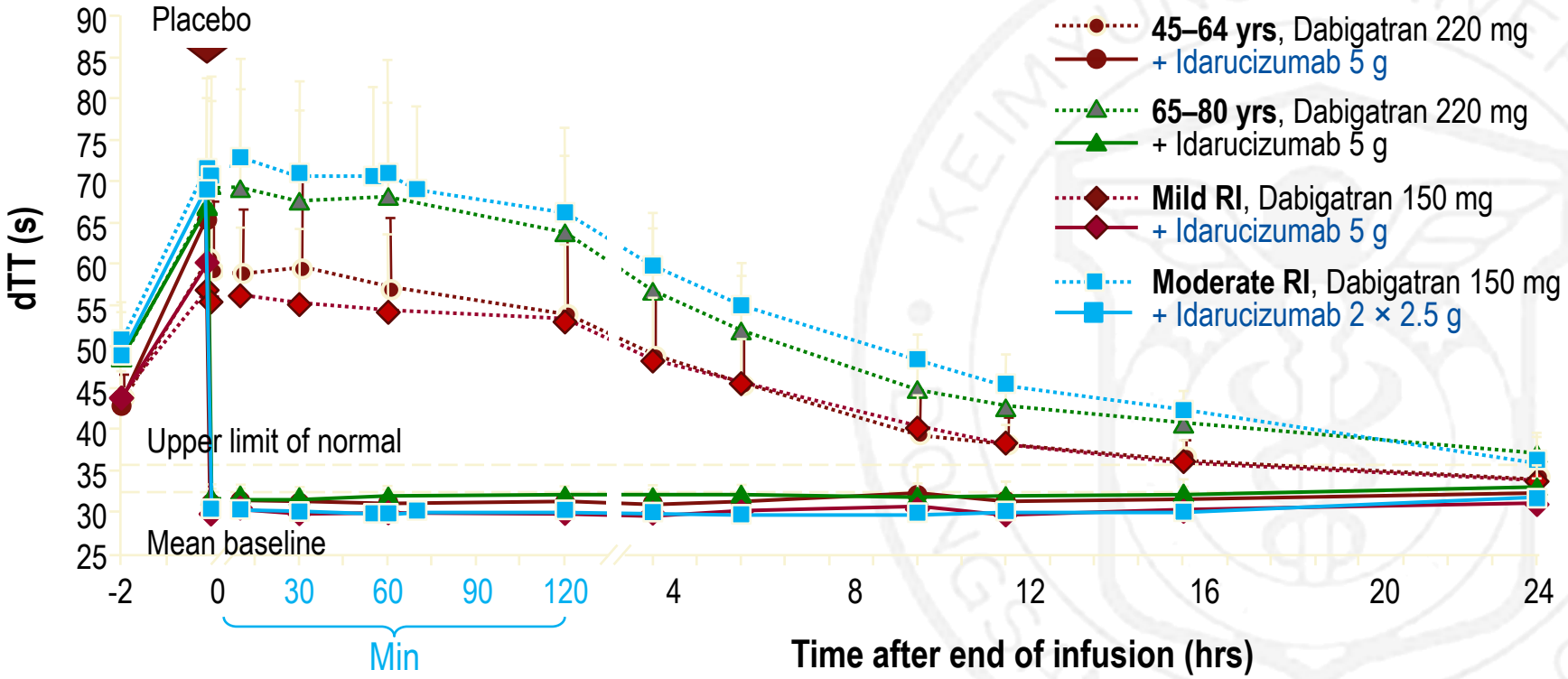
Absence of Prothrombotic Properties of Idarucizumab



- Effect of idarucizumab on endogenous thrombin generation potential

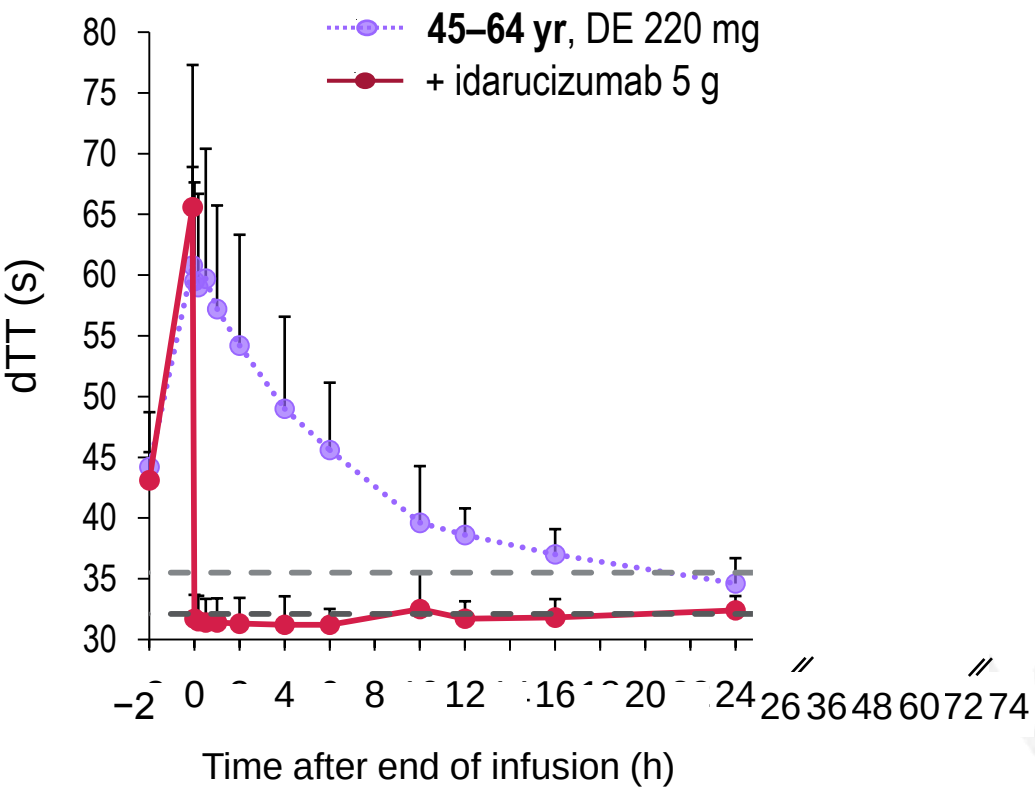
Glund S et al. Thromb Haemost 2015;113:943

Effect of Idarucizumab in Elderly and renally Impaired Volunteers



Glund S et al. Blood 2014;124:Abstr 344

Re-administration of dabigatran 24 h after idarucizumab

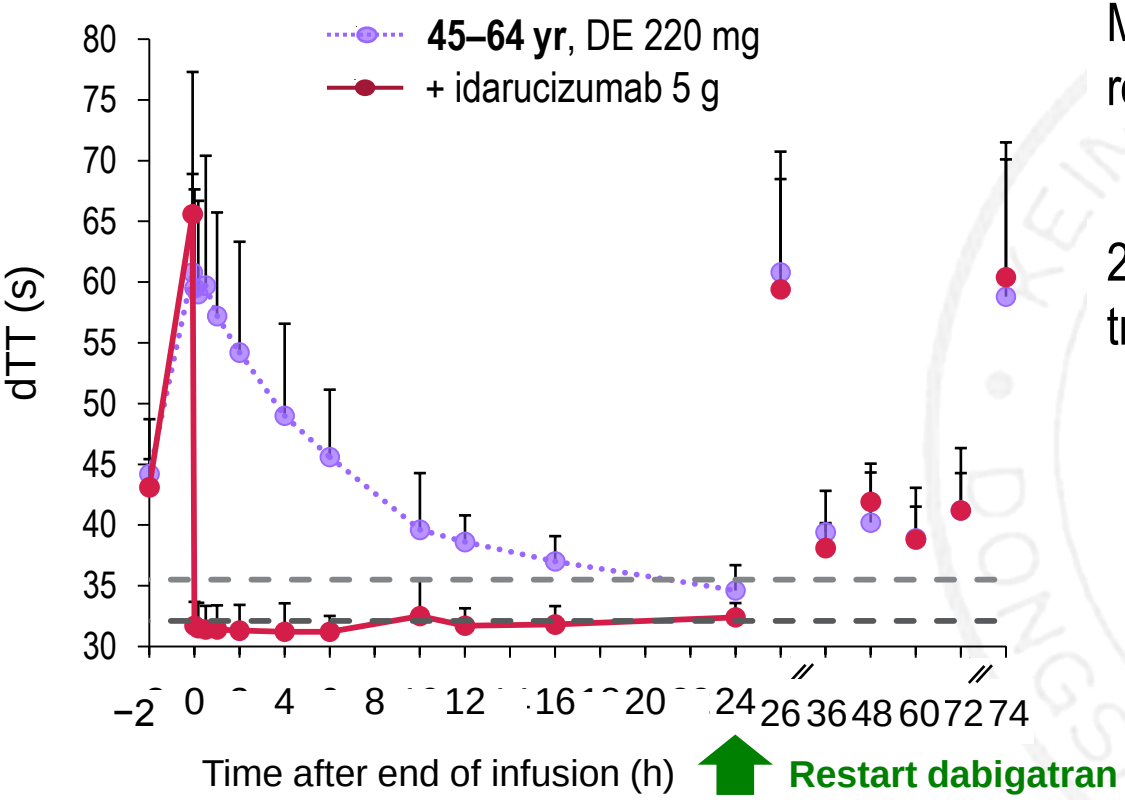


Middle-aged subjects (45–64 yrs) received 5 g idarucizumab or placebo

N=6–8/group, mean ± SE

Glund S et al. Blood 2014;124:Abstr 344

Re-administration of dabigatran 24 h after idarucizumab



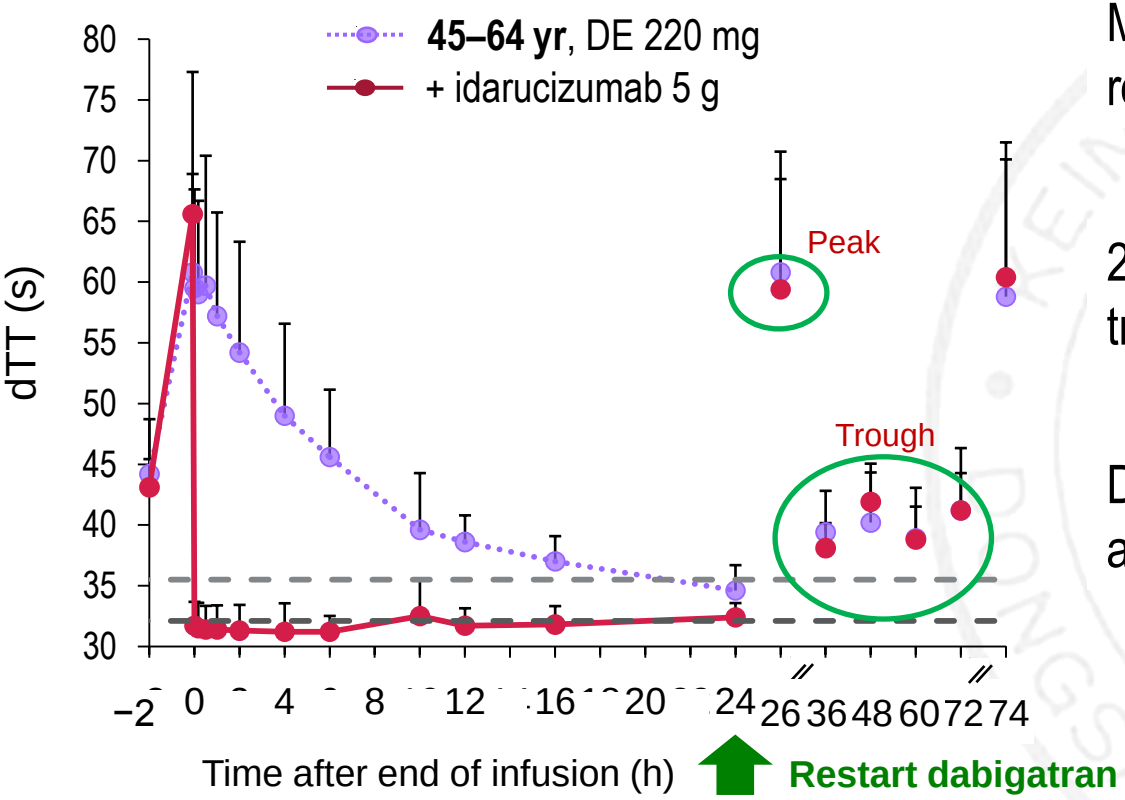
Middle-aged subjects (45–64 yrs) received 5 g idarucizumab or placebo

24 hours later, dabigatran treatment was restarted

N=6–8/group, mean ± SE

Glund S et al. Blood 2014;124:Abstr 344

Re-administration of dabigatran 24 h after idarucizumab



Middle-aged subjects (45–64 yrs) received 5 g idarucizumab or placebo

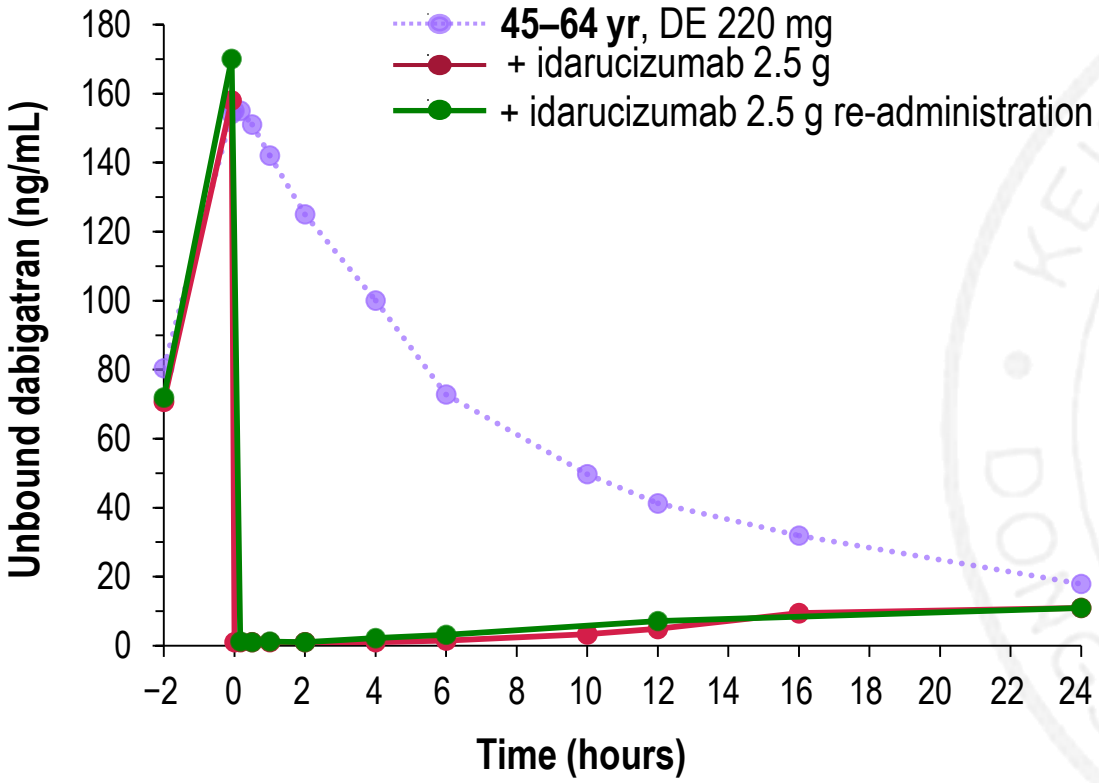
24 hours later, dabigatran treatment was restarted

Dabigatran-mediated anticoagulation was restored

N=6–8/group, mean ± SE

Glund S et al. Blood 2014;124:Abstr 344

Re-dosing of idarucizumab ~2 months after first dose: unbound dagibatran



- Idarucizumab (2.5 g) was re-administered 2 months after first administration
- Re-administration was safe and well tolerated
- Re-administration resulted in similar efficacy vs first dose
- ***No hypersensitivity***

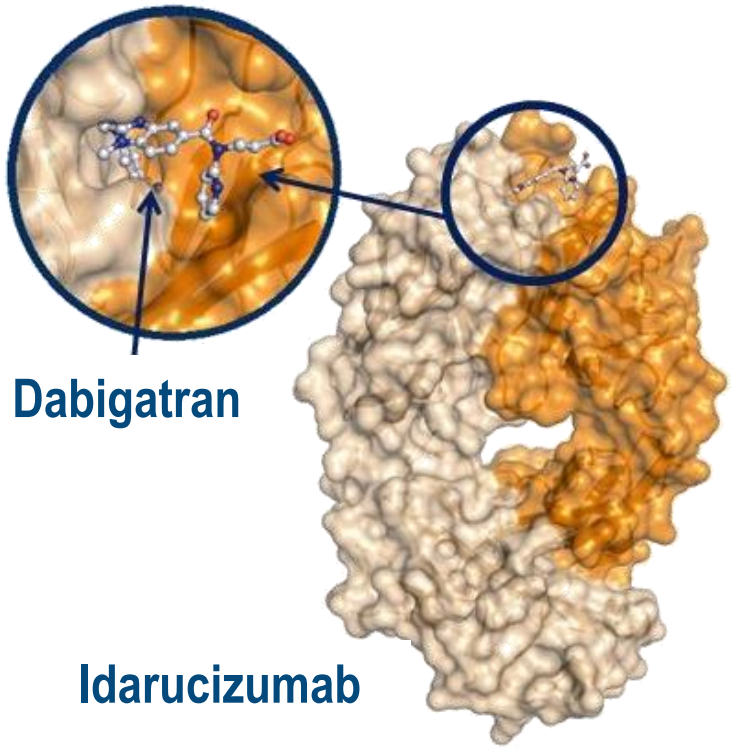
N=6/group, mean ± SE

Glund S et al. Blood 2014;124:Abstr 344

Safety of Idarucizumab: Summary of Phase I studies

- No clinically relevant drug-related adverse events
- No dose-related adverse events
- No adverse events indicative of immunogenic reactions
- A dose-dependent, transient increase in urine protein and low-weight proteins was observed
  - Values returned to normal range within 4–24 h

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



- Humanized Fab fragment
- Binding affinity for dabigatran ~350× higher than dabigatran to thrombin
- IV administration, immediate onset of action
- Short half-life
- No intrinsic procoagulant or anticoagulant activity expected

Schiele F, et al. Blood. 2013;121:3554

Idarucizumab for Dabigatran Reversal

- To determine the ***safety of 5 g of IV idarucizumab*** and its capacity to ***reverse the anticoagulant effects of dabigatran***
- 5g dose: calculated to reverse the total body load of dabigatran that was associated with the 99th percentile of the dabigatran levels measured in RE-LY trial
- ***interim results from the first 90 patients***

Group A:
Uncontrolled bleeding

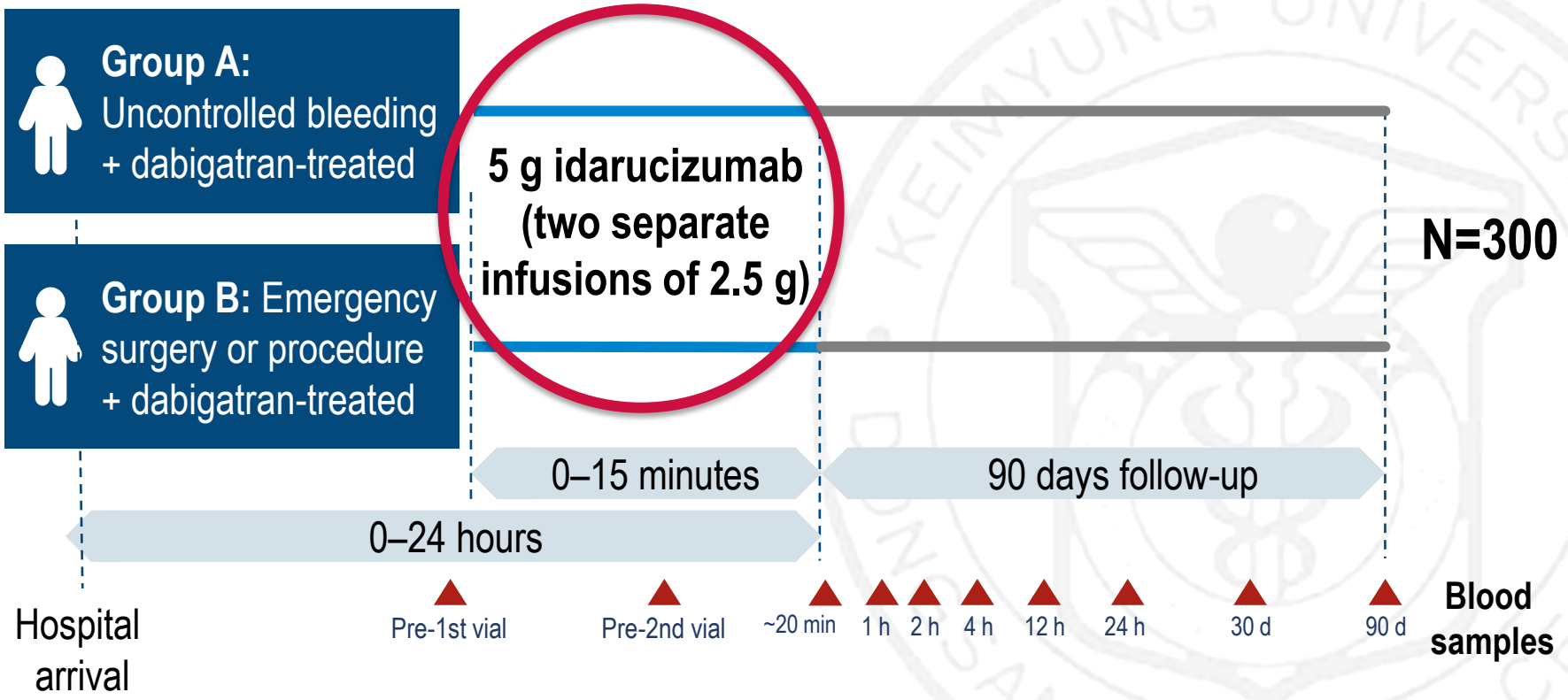
51 patients

Group B:
Emergency surgery or procedure

39 patients

Pollack CV Jr, et al. N Engl J Med 2015;373:511

Idarucizumab for Dabigatran Reversal

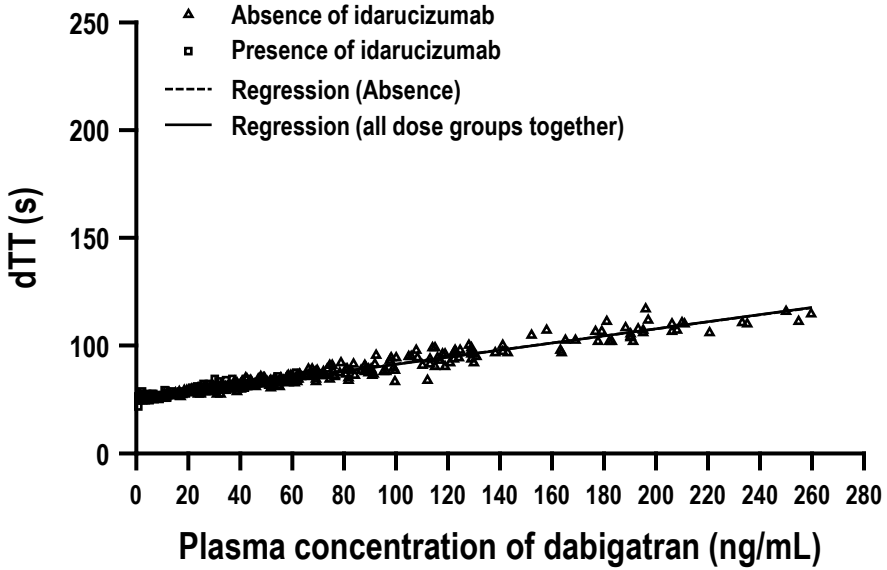


Pollack CV Jr, et al. N Engl J Med 2015;373:511

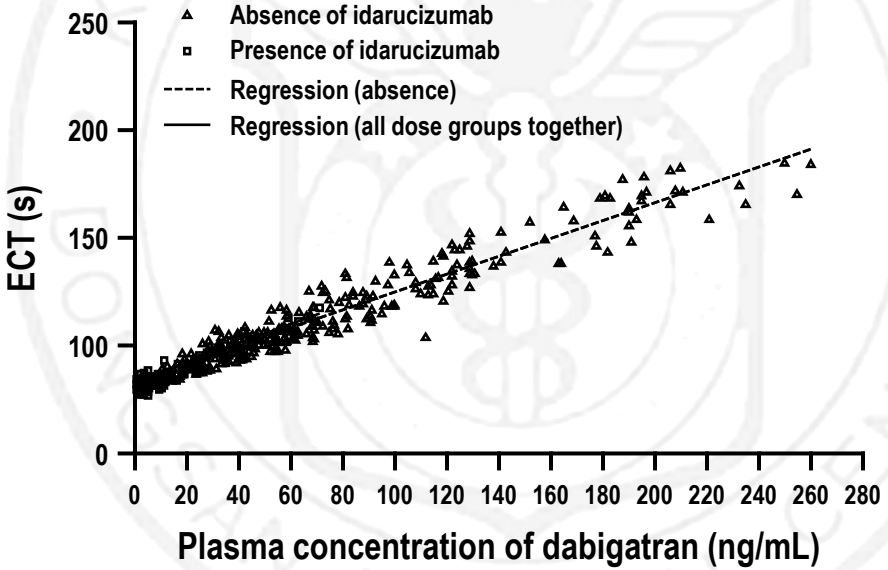
Idarucizumab for Dabigatran Reversal

Primary endpoints: Maximum % reversal of the anticoagulation effect of dabigatran within 4 hours after idarucizumab administration, on the basis of the determination at a central laboratory of the dTT or ECT

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



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

Pollack CV Jr, et al. Thromb Haemost 2015;114:198

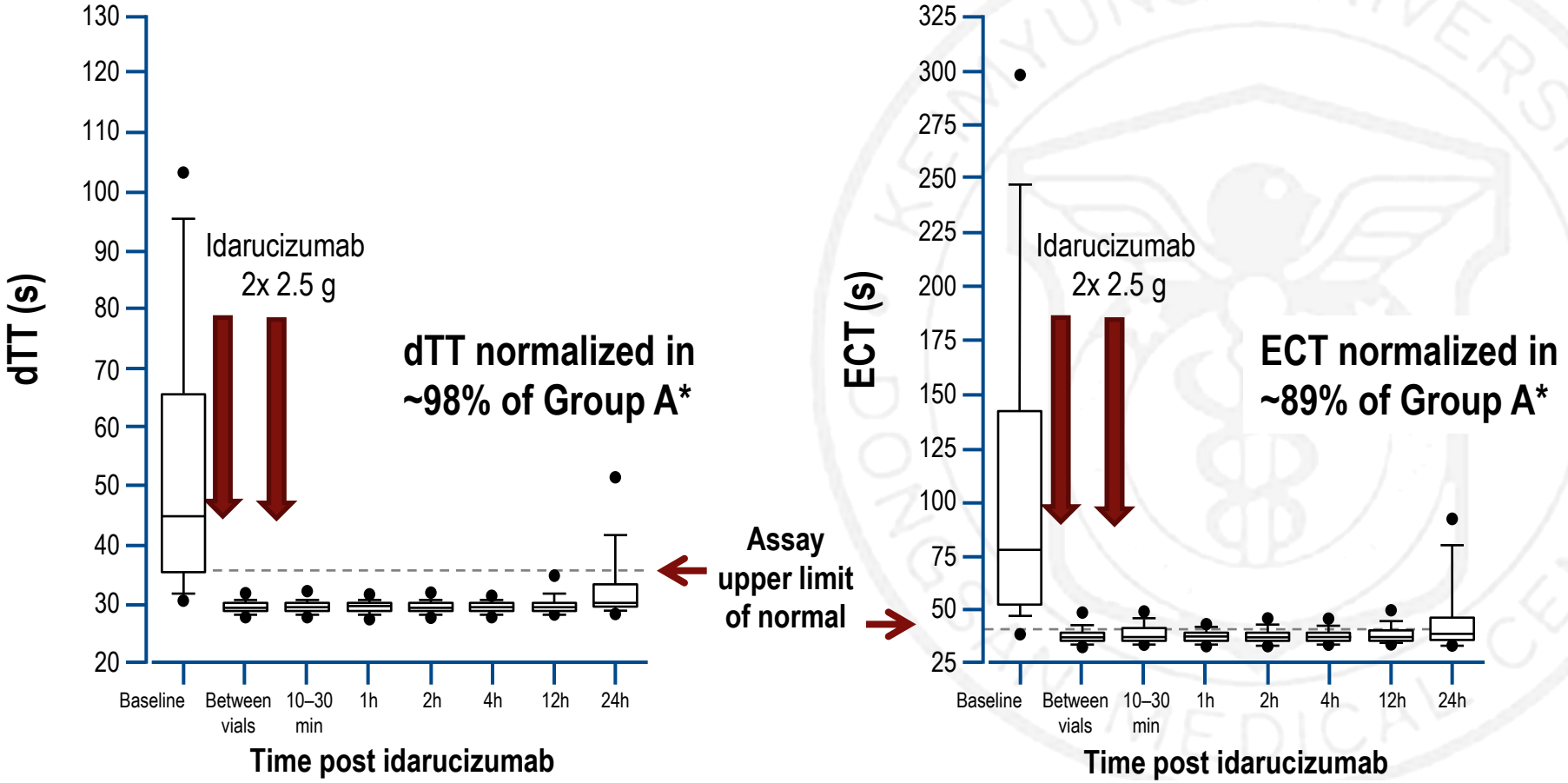
RE-VERSE AD™: enrolled patients were elderly with mild-moderate renal impairment

	Group A (n=51)	Group B (n=39)	Total (N=90)
Male, n (%)	32 (63)	18 (46)	50 (56)
Age (yrs), median (min, max)	77.0 (48, 93)	76.0 (56, 93)	**76.5** (48, 93)
CrCl (Cockcroft-Gault), mL/min			
Median (min, max)	54 (16, 187)	60 (11, 171)	**58** (11, 187)
<30	5	7	12
≥30–<50	**14**	**6**	**20**
≥50–<80	**16**	**11**	**27**
≥80	6	9	15
Missing	10	6	16
Elevated dTT at baseline	40	28	68
Elevated ECT at baseline	47	34	81

Pollack CV Jr, et al. N Engl J Med 2015;373:511

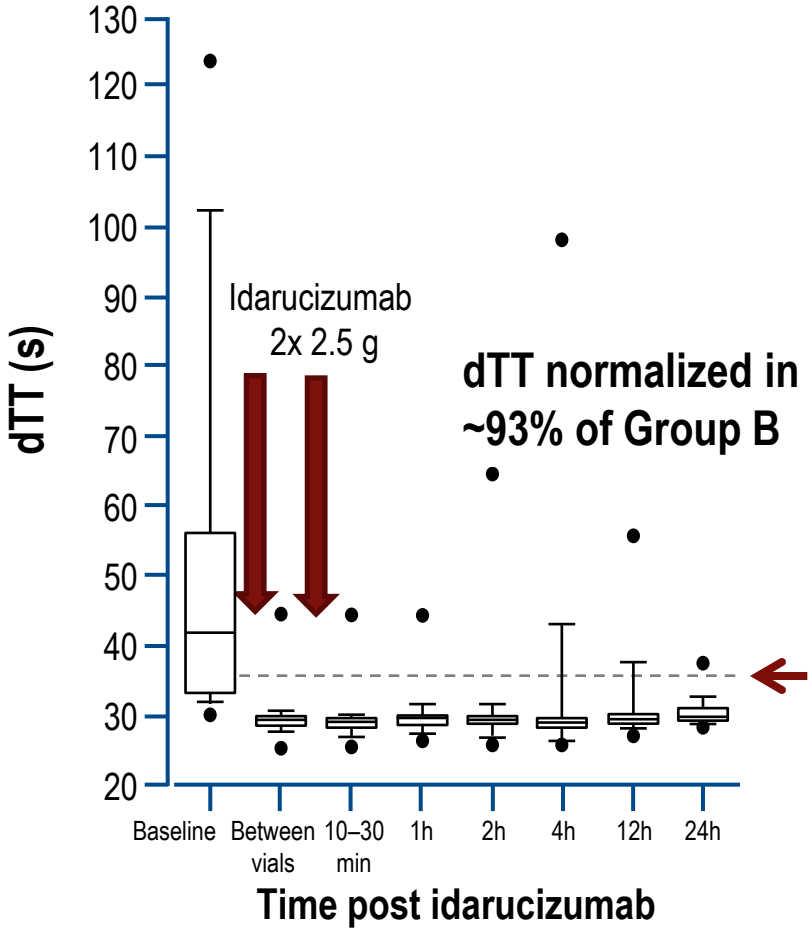
Primary Endpoint in Group A (uncontrolled bleeding)

Median maximum reversal within 4 hours was 100% for both dTT and ECT (95% CI, 100–100), evident after first vial of idarucizumab

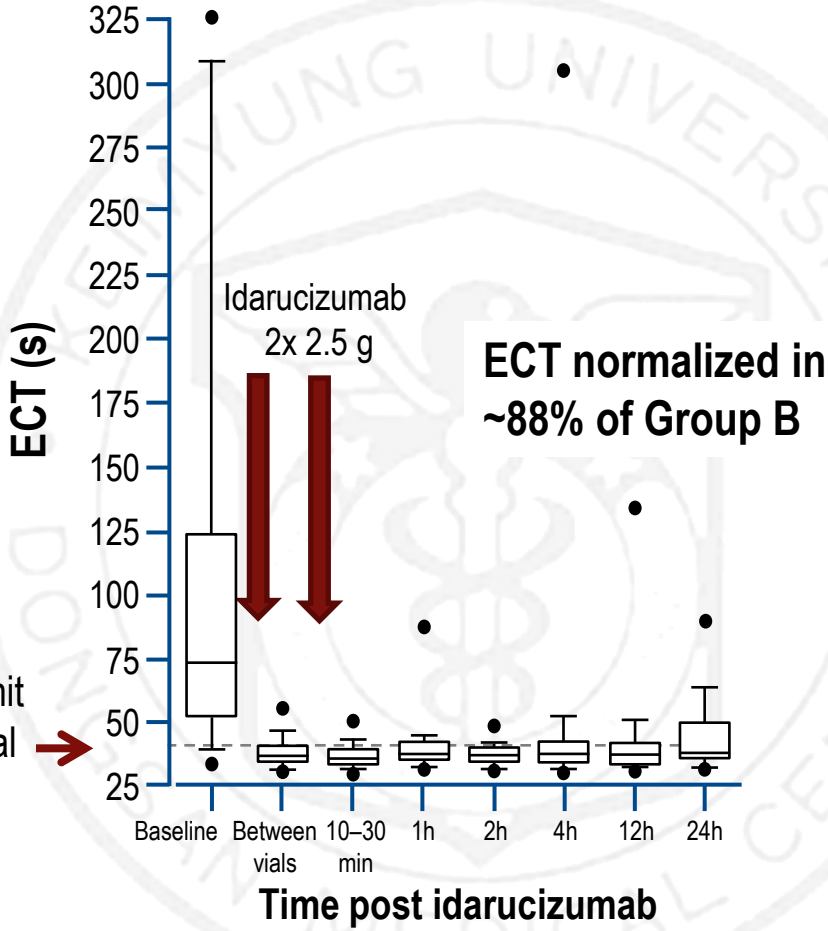


Pollack CV Jr, et al. N Engl J Med 2015;373:511

Primary Endpoint in Group B (emergent surgery)



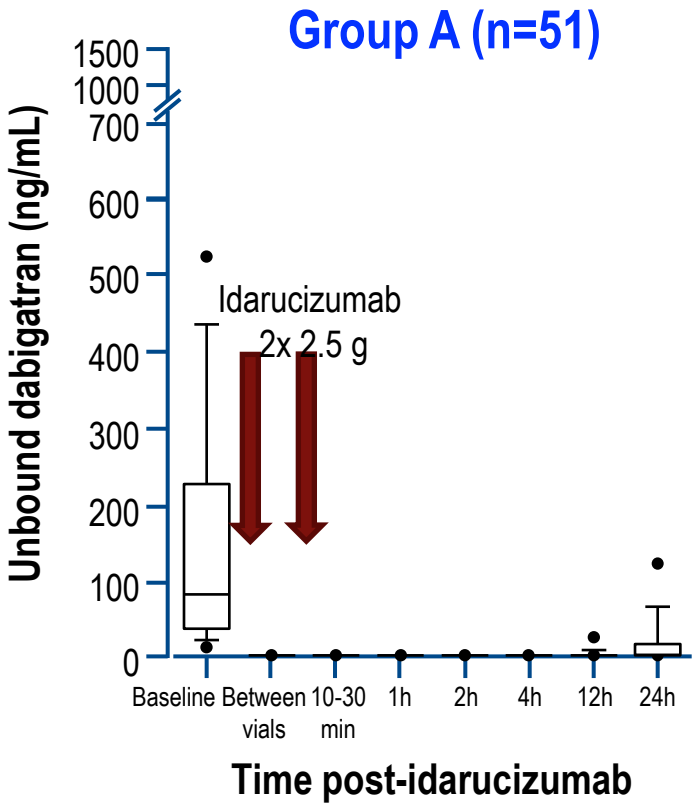
Assay upper limit of normal

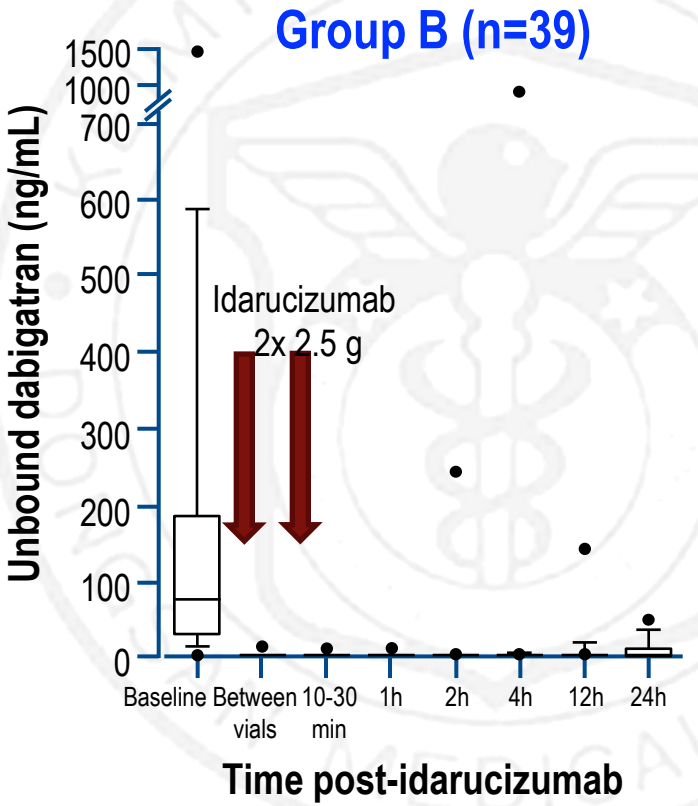


Pollack CV Jr, et al. N Engl J Med 2015;373:511

Dabigatran levels before/after treatment with Idarucizumab

- Dabigatran levels were below 20 ng/mL in 89/90 patients already after infusion of first vial
- Unbound dabigatran concentrations were below 20 ng/mL in 77/83 and 62/78 patients at 12 and 24 hours, respectively





Pollack CV Jr, et al. N Engl J Med 2015;373:511

Secondary Endpoint: Restoration of hemostasis

Group A
51 Patients → Assessable in 38 patients → Median local investigator-determined time to bleeding cessation **11.4 hours***

Group B
39 Patients → Surgery performed in 36 patients → Intraoperative hemostasis:
- **33 normal (~92%)**
- 2 mildly abnormal
- 1 moderately abnormal

*Assessment of bleeding cessation may be difficult in internal bleeding into confined space such as intramuscular or intracranial bleeding

Pollack CV Jr, et al. N Engl J Med 2015;373:511

Idarucizumab for Dabigatran Reversal

- Among 68 patients with an elevated dTT & 81 with an elevated ECT at baseline, Median maximum reversal ***within 4 hours was 100% for both dTT and ECT (95% CI, 100–100)***, evident after first vial of idarucizumab
- ***dTT normalized in 98% and 93%*** of Group A and B patients, respectively
- ***ECT normalized in 89% and 88%*** of Group A and B patients, respectively
- Concentrations of unbound dabigatran remained ***below 20 ng per milliliter*** at ***24 hours in 79%*** of the patients; sustained reversal of dabigatran effect over 12 hours was observed in at least 90% of patients

Pollack CV Jr, et al. N Engl J Med 2015;373:511

Idarucizumab for Dabigatran Reversal

CONCLUSIONS

Idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes.

Pollack CV Jr, et al. N Engl J Med 2015;373:511

US FDA approved Praxbind®

10-16-2015

U.S. Department of Health and Human Services

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

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FDA News Release

FDA approves Praxbind, the first reversal agent for the anticoagulant Pradaxa

Praxbind approved for specific emergency situations

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

For Immediate Release October 16, 2015

Release

The U.S. Food and Drug Administration today granted accelerated approval to Praxbind (idarucizumab) for use in patients who are taking the anticoagulant Pradaxa (dabigatran) during emergency situations when there is a need to reverse Pradaxa's blood-thinning effects.

"The anticoagulant effects of Pradaxa are important and life-saving for some patients, but there are situations where reversal of the drug's effects is medically necessary," said Richard Pazdur, M.D., director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research. "Today's approval offers the medical community an important tool for managing patients taking Pradaxa in emergency or life-threatening situations when bleeding can't be controlled."

The FDA approved Pradaxa in 2010 to prevent stroke and systemic blood clots in patients with atrial fibrillation, as well as for the treatment and prevention of deep venous thrombosis and pulmonary embolism. Praxbind is the first reversal agent approved specifically for Pradaxa and works by binding to the drug compound to neutralize its effect. Praxbind solution is for intravenous injection.

Inquiries

Media

Sarah Peddicord
301-796-2805

Consumers

888-INFO-FDA

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Prescription Drug Labeling of Praxbind ®

- **투여 방법**
  약(2.5 g/50 mL) 바이알 두 개*(5 g)를 정맥투여*하며, 두 바이알 각각 *5분 ~ 10분에 걸쳐 연속적으로 점적투여하거나 또는 일시투여*한다.
- *권장 투여량은 5 g*으로, 50 mL 바이알 두 개(각 2.5 g)가 1회 용량에 해당한다. 1일 최대용량에 대해서는 연구되지 않았다
- 항혈전제를 사용하지 않으면 환자가 기저질환 또는 기저상태의 혈전성 위험에 노출될 수 있다.
- *신장애, 간장애, 고령자 (>65세): 용량 조절은 필요하지 않다*

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Thank You for Your Attention !

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