

Recent clinical trial update

RE-VERSE AD



Kwang-Yeol Park

Dep. of Neurology, Chung-Ang University, Seoul South Korea

Table of Contents

- 1 Atrial fibrillation and stroke
- 2 Stroke in Asia
- 3 When we need antidote for NOAC?
 - Hyperacute ischemic stroke
 - ICH
- 4 RE-VERSE AD
- 5 Summary

Section 1

Atrial fibrillation and stroke

Cardioembolic stroke

- 비판막성 심방세동
- 인공판막
- 좌심실 혈전증
- 점액종
- 감염성 심뇌막염

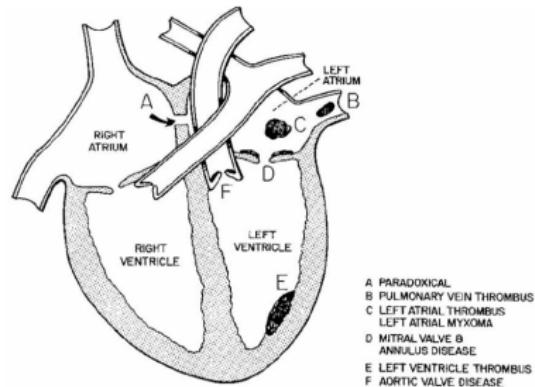
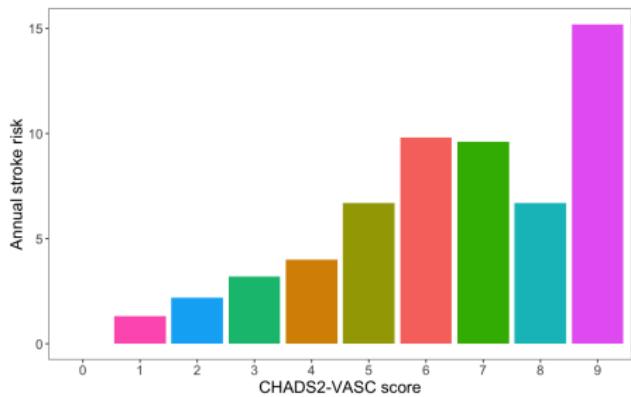


Figure 1. Cardiac causes of stroke (Adapted from Barnett et al)

Thromboembolic risk of AF

<i>CHA₂DS₂-VASc</i> criteria	Score
CHF	1
Hypertension	1
Age \geq 75 years	2
Diabetes mellitus	1
Stroke or TIA	2
Vascular disease	1
Age 65-74 years	1
Sex category (female)	1



Gage BF et al. JAMA 2001;285:2864-70; Lip G et al. Chest 2010;137:263-72

January C, T... et al. Circulation 2014

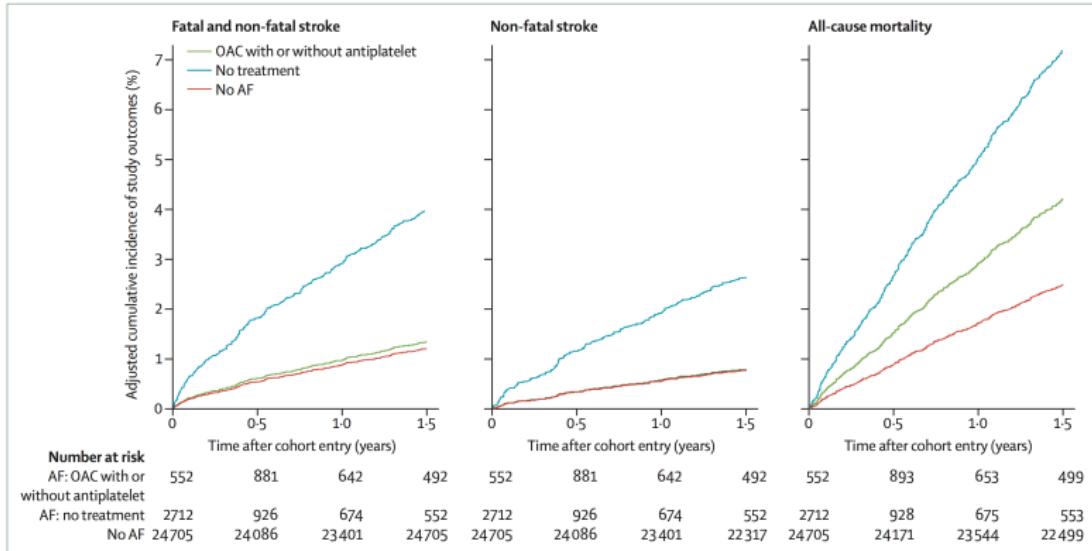
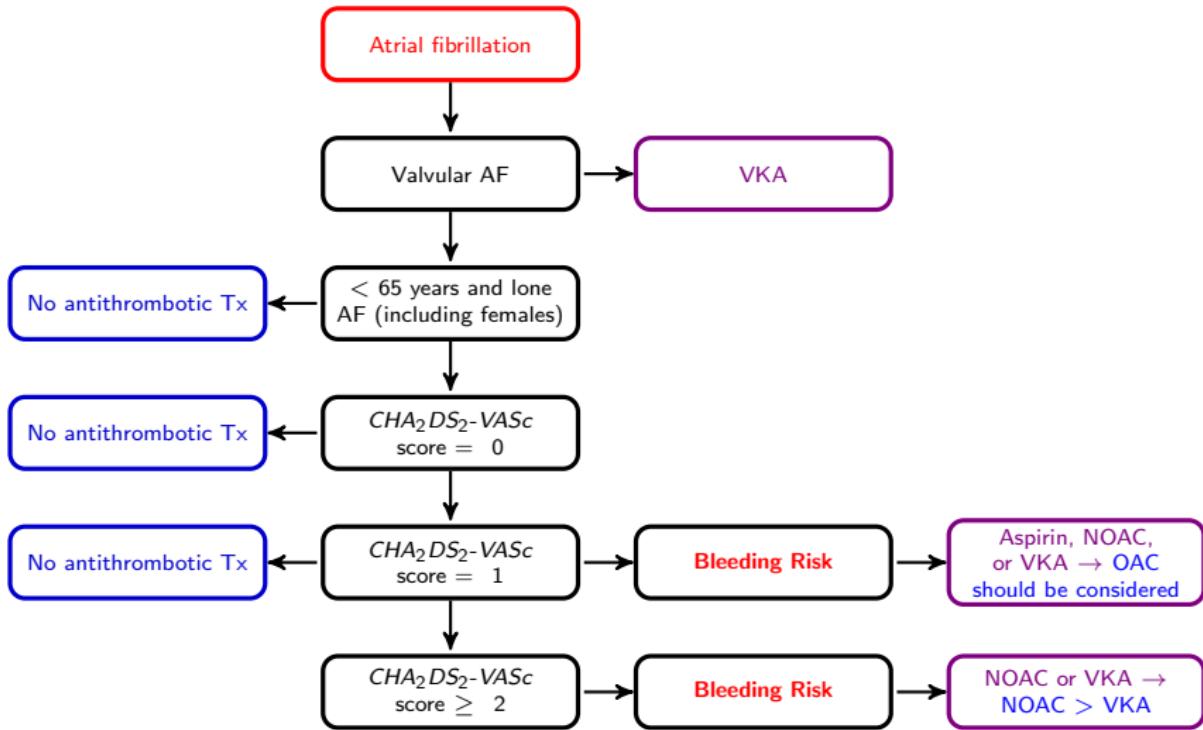


Figure 2: Effect of treatment on incidentally detected atrial fibrillation

AF=atrial fibrillation. OAC=oral anticoagulant. Reproduced with permission from Freedman and colleagues.²¹



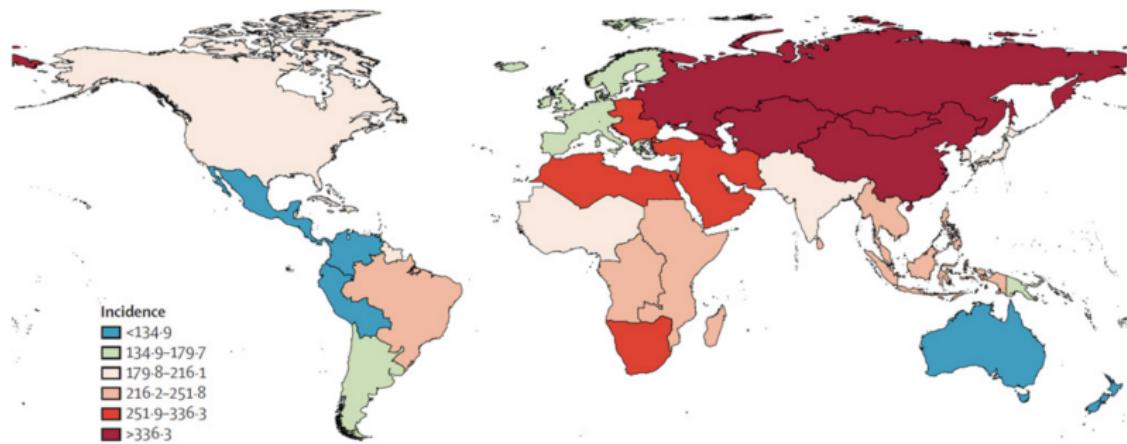
Camm, A. J., et al. Eur Heart J. 2012; Meschia, J. F., et al. Stroke 2014; Kirchhof et al. Eur Heart J 2016

Section 2

Stroke in Asia

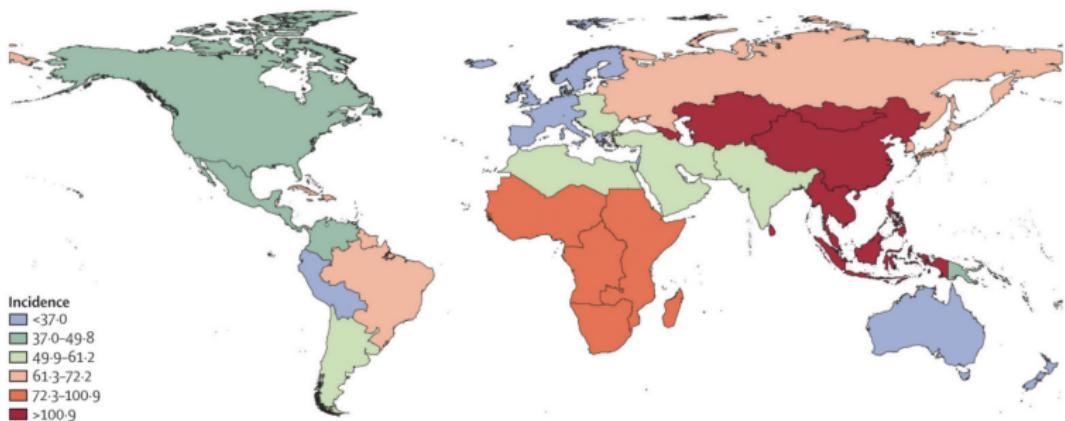
Age-standardised stroke incidence

per 100 000 person-years for 2010



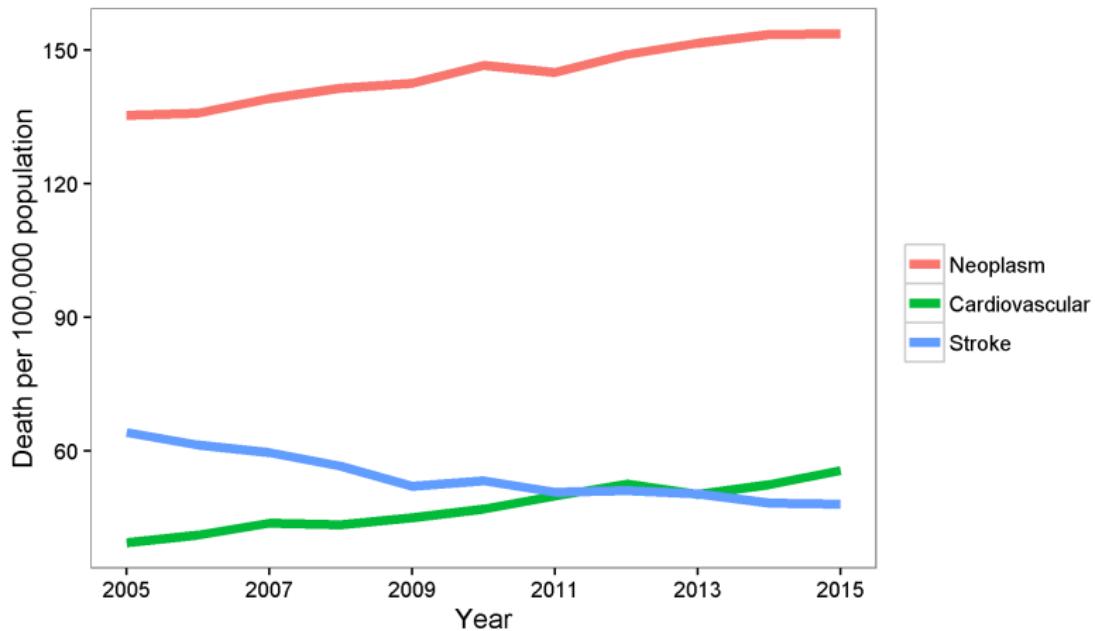
Lancet Neurol. 2014 383(9913): 245–254.

Age-standardised incidence of haemorrhagic stroke per 100 000 person-years for 2010



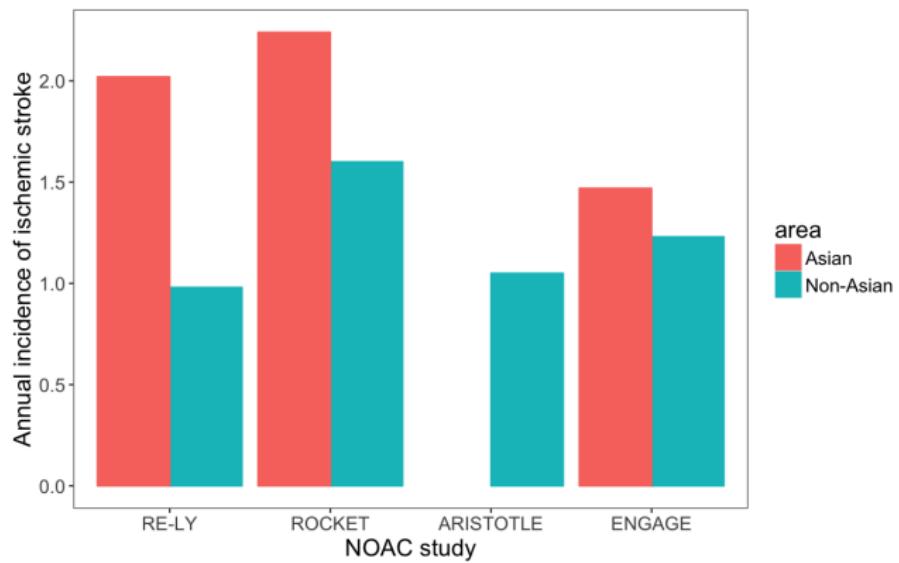
Lancet Glob Health. 2013 Nov; 1(5): e259-e281.

Secular trend of mortality in Korea



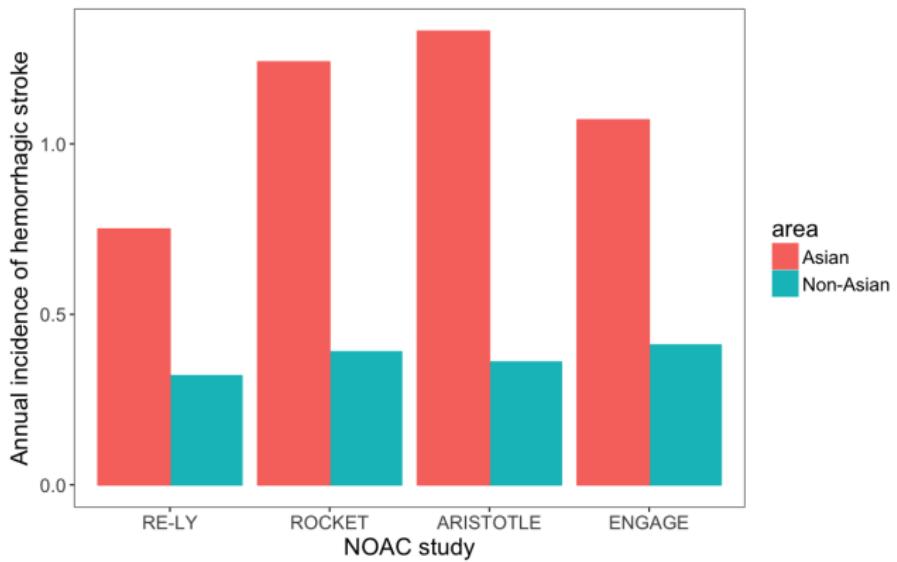
http://www.index.go.kr/potal/main/EachDtlPageDetail.do?idx_cd=1012 accessed on Nov 03, 2016

Ischemic stroke on warfarin



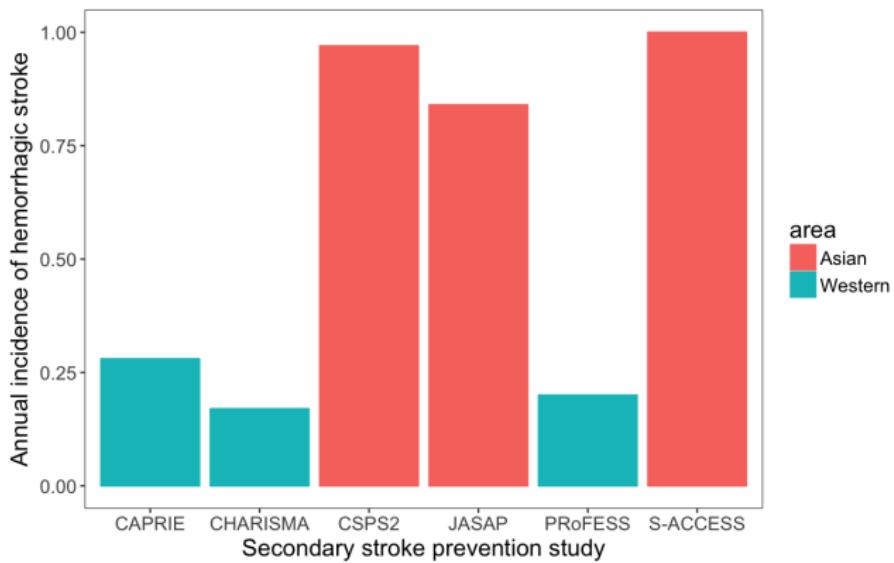
Lip GYH et al, Int J Cardiol 2015;180:246

hemorrhagic stroke on warfarin



Lip GYH et al, Int J Cardiol 2015;180:246

Incidence of Cerebral Hemorrhage with Aspirin



1. Kim JS, et al. Int J Stroke 2015;10 Suppl 1:1-9.

Section 3

When we need antidote for NOAC?

Case 1, F/75

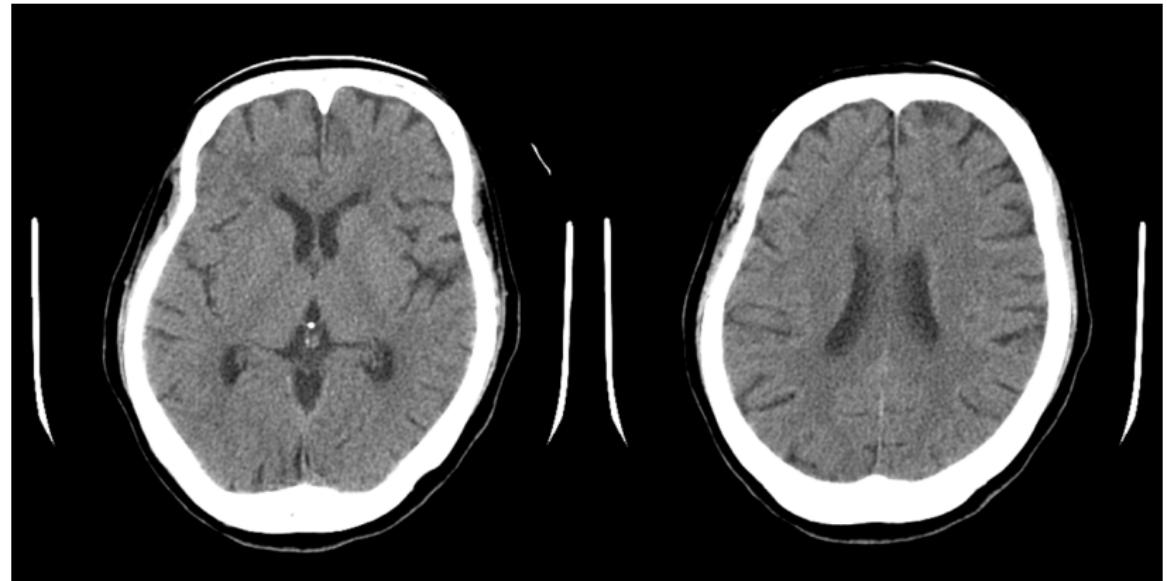
내원일 저녁 10시30분경 혼자서 TV 보던중 갑자기 말이 어둔해지고, 좌측 팔다리에 힘이 빠져서 11시 5분 응급실 내원함.

NIHSS 10

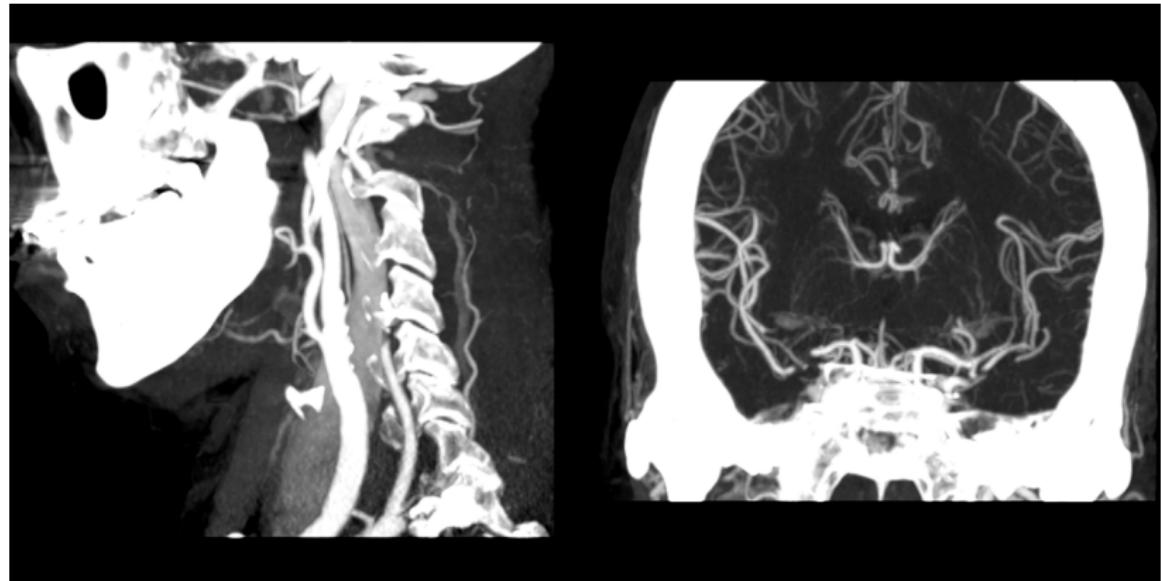
Lt. central type facial palsy, dysarthria, neglect Lt. hemiparesis (U/Ex I, L/Ex IV-)

HTN, AF on NOAC (She skipped medication that day.)

Brain CT, 51min



Brain CTA



How to treat this patient?

How to treat this patient?

- ① Consider IV thrombolysis
- ② Consider IA thrombectomy
- ③ No reperfusion therapy

Hyperacute ischemic stroke in patients on NOAC

- No prospective data exist!
- The use of rtPA is not recommended according to official labelling.
- If patients took the last dose of NOAC 48 hours ago and coagulation assay (e.g. aPTT for Dabigatran) is within normal range, the use of fibrinolytics can be considered.
- Mechanical thrombectomy may be considered as an alternative option.



Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials

Mayank Goyal, Bijoy K Menon, Wim H van Zwam, Diederik W J Dippel, Peter J Mitchell, Andrew M Demchuk, Antoni Dávalos, Charles B L M Majeski, Aad van der Lugt, María A de Miquel, Geoffrey A Donnan, Yvo B W E M Roos, Alain Bonafe, Reza Jahan, Hans-Christoph Dietrich, Lucie A van den Berg, Elad I Levy, Olivier A Berkhemer, Vitor M Pereira, Jeremy Rempel, Mónica Millán, Stephen M Davis, Daniel Roy, John Thornton, Luis San Roman, Marc Ribó, Debbie Beumer, Bruce Stouch, Scott Brown, Bruce C V Campbell, Robert J van Oostenbrugge, Jeffrey L Saver, Michael D Hill, Tudor G Jovin, for the HERMES collaborators

Summary

Background In 2015, five randomised trials showed efficacy of endovascular thrombectomy over standard medical care in patients with acute ischaemic stroke caused by occlusion of arteries of the proximal anterior circulation. In this meta-analysis we, the trial investigators, aimed to pool individual patient data from these trials to address remaining questions about whether the therapy is efficacious across the diverse populations included.

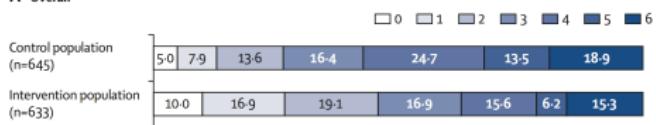
Lancet 2016; 387: 1723-33

Published Online

February 18, 2016

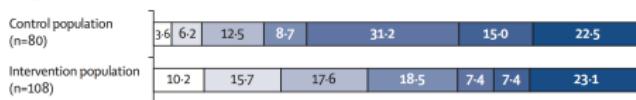
[http://dx.doi.org/10.1016/S0140-6736\(15\)00263-X](http://dx.doi.org/10.1016/S0140-6736(15)00263-X)

A Overall

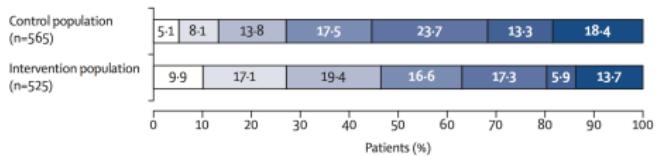


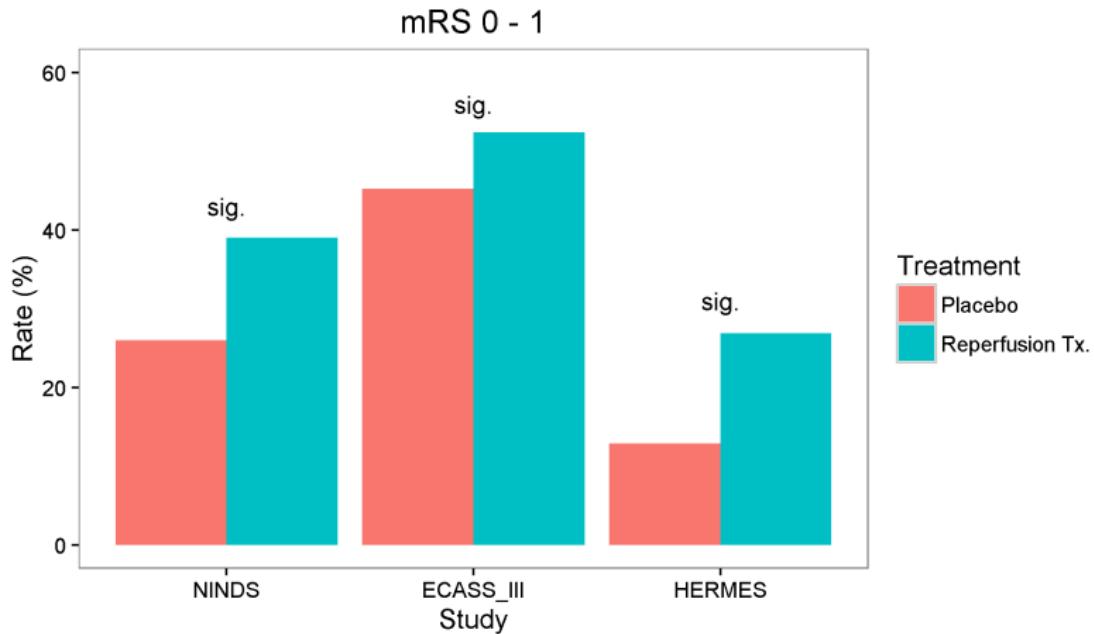
B

Ineligible for alteplase

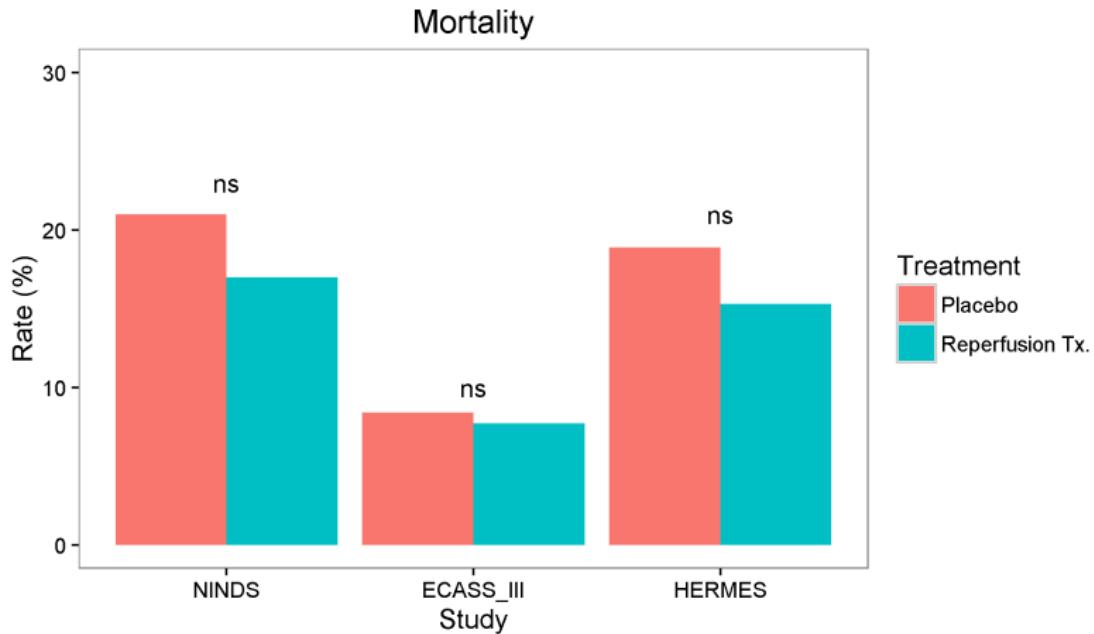


Received alteplase





NINDS study group NEJM 1995; Hacke W et al. NEJM 2008; Goyal M et al. Lancet 2016



NINDS study group NEJM 1995; Hacke W et al. NEJM 2008; Goyal M et al. Lancet 2016

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

Humanized antibody fragment (Fab)

Specific to dabigatran

Binding affinity for dabigatran ~350x higher than dabigatran to thrombin, resulting in essentially irreversible binding

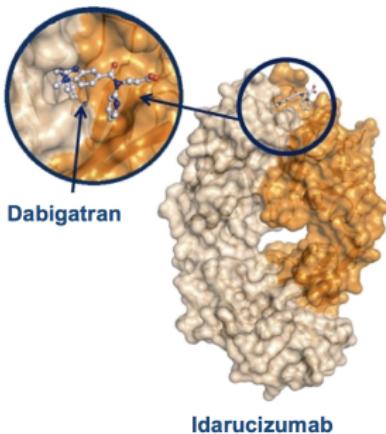
No endogenous targets

Ready to use solutions for IV administration

Immediate onset of action

No intrinsic procoagulant or anticoagulant activity

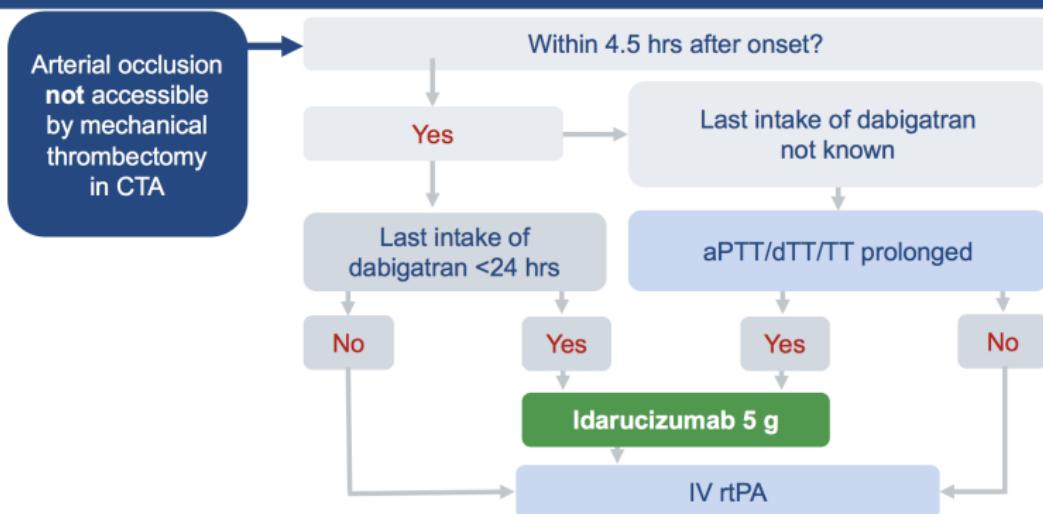
Idarucizumab–dabigatran complex is eliminated quickly (within a few hours)



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

8

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, CT angiography; dTT, diluted thrombin time; rtPA, recombinant tissue plasminogen activator; TT, thrombin time

Adapted from: Diener HC et al. Int J Stroke 2016; Pradaxa®: EU SPC, 2016; Praxbind®: EU SPC, 2015; Actilyse®: EU SPC, 2015

47

Case 2 (M/63) and Case 3 (F/78)



ARTICLES

Published Ahead of Print on April 5, 2017 as 10.1212/WNL.0000000000003886

Outcome of intracerebral hemorrhage associated with different oral anticoagulants

OPEN

Duncan Wilson, MD

David J. Seiffge, MD

Christopher Traenka,
MDGhazala Basir, MBBS,
FCPSJan C. Purrucker, MD
Timolaos Rizos, MD
Oluwaseun A. Sobowale,
MD

Hanne Sallinen, MD

Shin-Jou Yeh, MD

Teddy Y. Wu, MD

Marc Ferrigno, MD

Rik Houben, MD

Floris H.B.M. Schreuder,
MD

Luke A. Perry, BSc

Jun Tanaka, MD

Marion Boulanger, MD

Rustum Al-Shahi Salman,
FRCP EdinHans R. Jäger, MD,
FRCR**ABSTRACT**

Objective: In an international collaborative multicenter pooled analysis, we compared mortality, functional outcome, intracerebral hemorrhage (ICH) volume, and hematoma expansion (HE) between non-vitamin K antagonist oral anticoagulation-related ICH (NOAC-ICH) and vitamin K antagonist-associated ICH (VKA-ICH).

Methods: We compared all-cause mortality within 90 days for NOAC-ICH and VKA-ICH using a Cox proportional hazards model adjusted for age; sex; baseline Glasgow Coma Scale score, ICH location, and log volume; intraventricular hemorrhage volume; and intracranial surgery. We addressed heterogeneity using a shared frailty term. Good functional outcome was defined as discharge modified Rankin Scale score ≤ 2 and investigated in multivariable logistic regression. ICH volume was measured by ABC/2 or a semiautomated planimetric method. HE was defined as an ICH volume increase $>33\%$ or >6 mL from baseline within 72 hours.

Results: We included 500 patients (97 NOAC-ICH and 403 VKA-ICH). Median baseline ICH volume was 14.4 mL (interquartile range [IQR] 3.6–38.4) for NOAC-ICH vs 10.6 mL (IQR 4.0–27.9) for VKA-ICH ($p = 0.78$). We did not find any difference between NOAC-ICH and VKA-ICH for all-cause mortality within 90 days (33% for NOAC-ICH vs 31% for VKA-ICH [$p = 0.64$]; adjusted Cox hazard ratio [for NOAC-ICH vs VKA-ICH] 0.93 [95% confidence interval (CI) 0.52–1.64] [$p = 0.79$]), the rate of HE (NOAC-ICH $n = 29/48$ [40%] vs VKA-ICH $n = 93/140$ [34%] [$p = 0.45$]), or functional outcome at hospital discharge (NOAC-ICH vs VKA-ICH odds ratio 0.47; 95% CI 0.18–1.19 [$p = 0.11$]).

Conclusions: In our international collaborative multicenter pooled analysis, baseline ICH volume, hematoma expansion, 90-day mortality, and functional outcome were similar following NOAC-ICH and VKA-ICH. *Neurology®* 2017;88:1–8

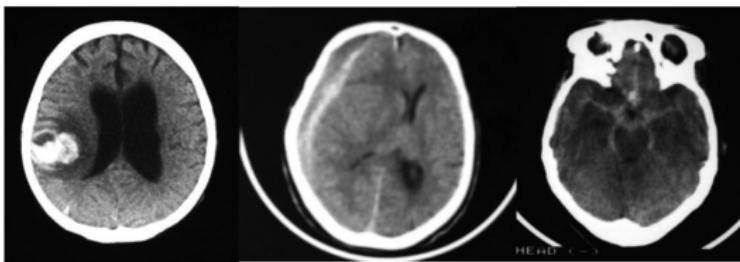
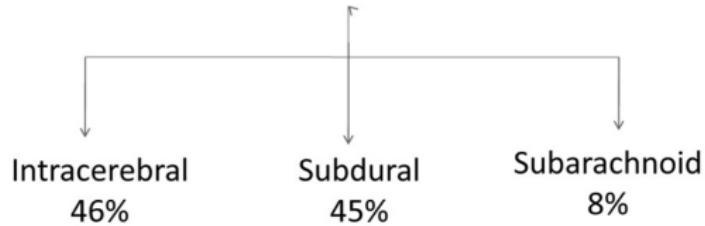
	ICH during NOAC n=97	ICH during VKA n=403	p value
ICH volume	14.4mL	10.6mL	0.78
Hematoma expansion	40%	34%	0.45
All-cause mortality (< 30 d)	33%	31%	0.64

NOAC: apixaban(13), dabigatran(13), and rivaroxaban(69).

ICH during anticoagulation

Intracranial Hemorrhages in RE-LY

n = 154



ICH during anticoagulation

	Warfarin	Dabigatran 150mg	Dabigatran 110mg
ICH, %/y	0.76	0.31	0.23
Mortality	36%	35%	41%
Fatal ICH	32	13	11

Independent predictors of ICH

- Assignment to warfarin (RR 2.9, p<0.001)
- Aspirin use (RR 1.6, p=0.01)
- Age (RR 1.1 per year, p<0.001)
- Previous stroke or TIA (RR 1.8, p=0.001)

Management of bleeding complication

Table 9 Possible measures to take in case of bleeding

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, and rivaroxaban)
None life-threatening bleeding	<p>Inquire last intake + dosing regimen.</p> <p>Estimate normalization of haemostasis:</p> <ul style="list-style-type: none"> Normal renal function: 12–24 h CrCl 50–80 mL/min: 24–36 h CrCl 30–50 mL/min: 36–48 h CrCl < 30 mL/min: ≥48 h <p>Maintain diuresis.</p> <p>Local haemostatic measures.</p> <p>Fluid replacement (colloids if needed).</p> <p>RBC substitution if necessary.</p> <p>Platelet substitution (in case of thrombocytopenia $\leq 60 \times 10^9/L$ or thrombopathy).</p> <p>Fresh frozen plasma as plasma expander (not as reversal agent)</p> <p>Tranexamic acid can be considered as adjuvants.</p> <p>Desmopressin can be considered in special cases (coagulopathy or thrombopathy)</p> <p>Consider dialysis (preliminary evidence: –65% after 4 h).¹²²</p> <p>Charcoal haemoperfusion can be considered (based on preclinical data)</p>	<p>Inquire last intake + dosing regimen.</p> <p>Normalisation of haemostasis: 12–24 h</p> <p>Local haemostatic measures.</p> <p>Fluid replacement (colloids if needed).</p> <p>RBC substitution if necessary.</p> <p>Platelet substitution (in case of thrombocytopenia $\leq 60 \times 10^9/L$ or thrombopathy).</p> <p>Fresh frozen plasma as plasma expander (not as reversal agent)</p> <p>Tranexamic acid can be considered as adjuvants.</p> <p>Desmopressin can be considered in special cases (coagulopathy or thrombopathy)</p>
Life-threatening bleeding	<p>All of the above.</p> <p>Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) (but no clinical data).</p> <p>Activated PCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available.</p> <p>Activated factor VII (rFVIIa; 90 µg/kg) no data about additional benefit + expensive (only animal evidence)</p> <p>Idarucizumab 5 g IV (approval waiting)</p>	<p>All of the above.</p> <p>Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) (healthy volunteer data)</p> <p>Activated PCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available.</p> <p>Activated factor VII (rFVIIa; 90 µg/kg) no data about additional benefit + expensive (only animal evidence)</p>

RBC, red blood cells; CrCl, creatinine clearance; PCC, prothrombin complex concentrate.

Section 4

RE-VERSE AD

Anticoagulated patients may experience life-threatening bleeding or require urgent surgery

In RE-LY®...



2.0%
required urgent surgery
or procedures¹

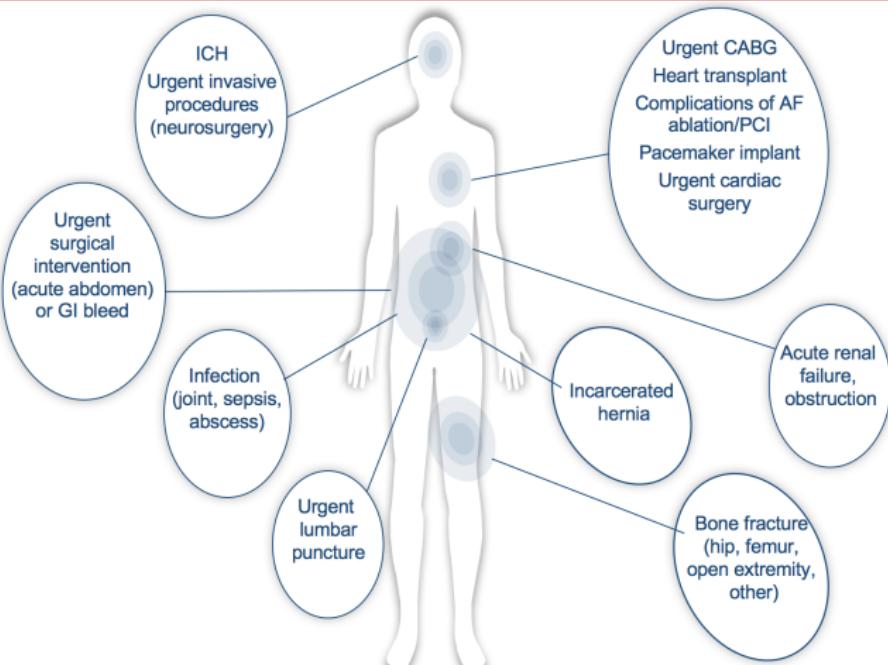


Life-threatening
bleeding reported for:²
1.2% on D110
1.5% on D150
1.9% on warfarin

D110, dabigatran 110 mg BID, D150, dabigatran 150 mg BID

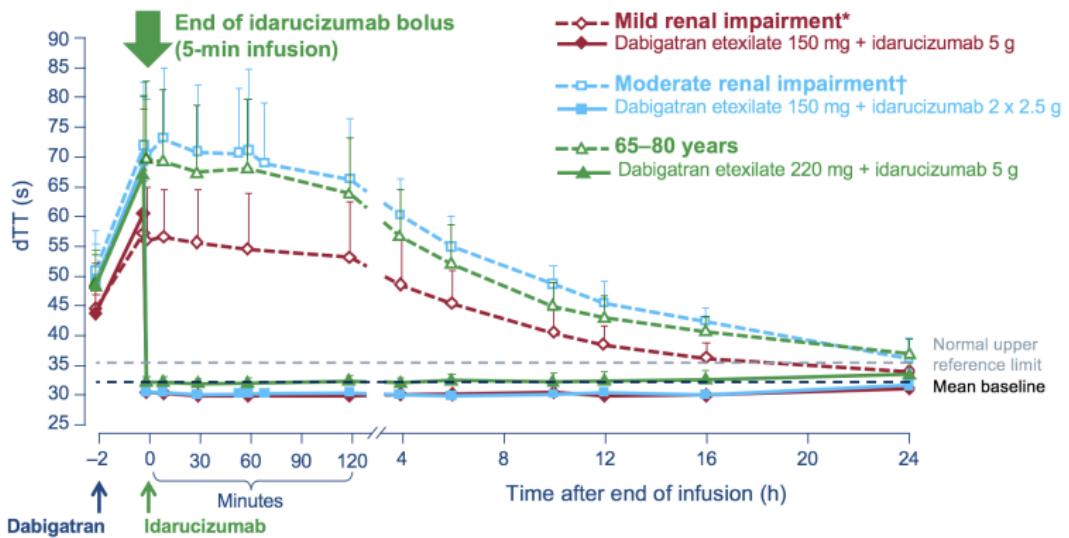
1. Douketis et al. Thromb Res 2016; 2. Connolly et al. N Engl J Med 2014

Where might specific NOAC reversal agents be used?



CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention

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

9

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

CV Pollack Jr, MA, MD; PA Reilly, PhD; J van Ryn, PhD; J Eikelboom, MD;
S Glund, PhD; RA Bernstein, MD, PhD; R Dubiel, PharmD;
MV Huisman, MD, PhD; EM Hylek, MD; PW Kamphuisen, MD, PhD;
J Kreuzer, MD; JH Levy, MD; FW Sellke, MD; J Stangier, PhD;
T Steiner, MD, MEE; B Wang, PhD; C-W Kam, MD; JI Weitz, MD

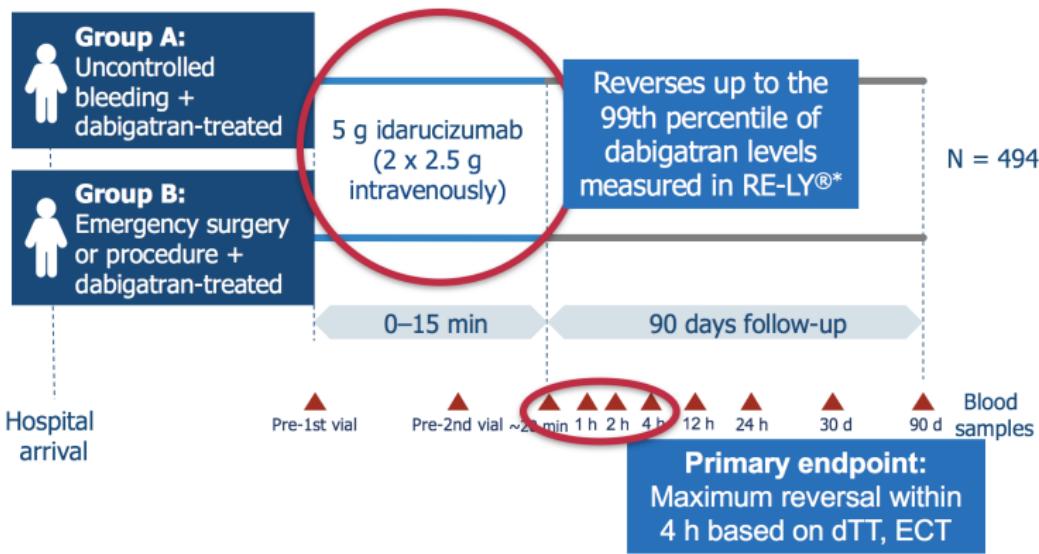
On behalf of the RE-VERSE AD™ Investigators



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

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.

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

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 BID, twice daily; dTT, diluted thrombin time; ECT, ecarin clotting time.	5/298 (1.7)	2/196 (1.0)	7/494 (1.4)

in patients on active dabigatran

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

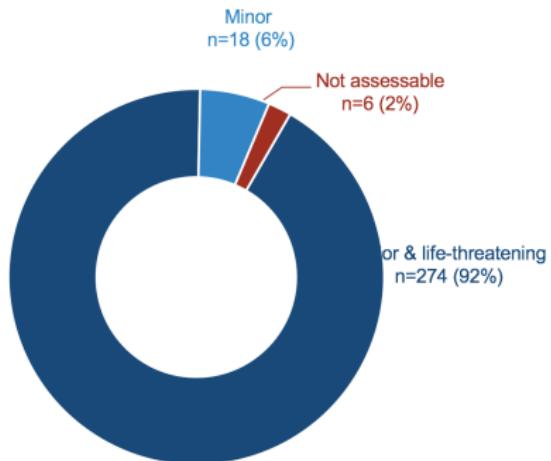
*Calculated for patients with elevated levels at baseline

Pollack et al. AHA 2016

RE-VERSE AD™ group A (n=298): patients were enrolled due to major bleeding events

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

ISTH bleeding severity determined locally upon patient entry (n=298)

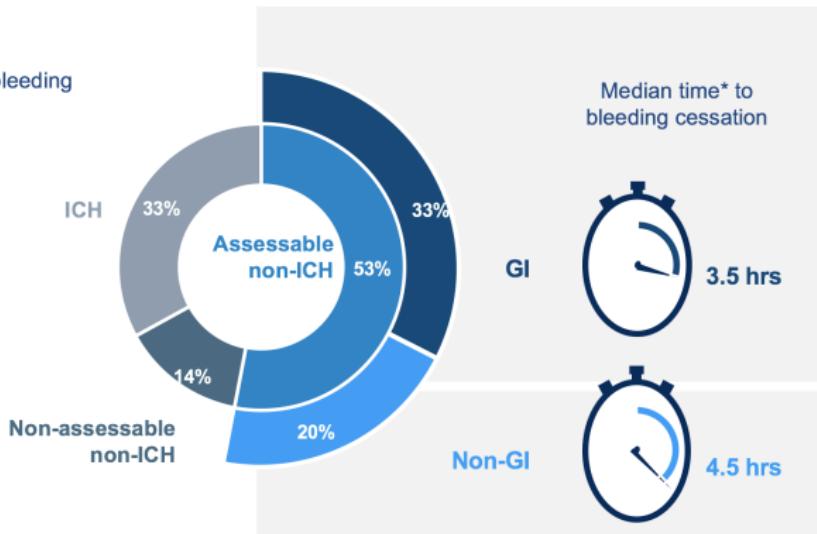


*Bleeding may occur at more than one site
Pollack et al. AHA 2016

Group A: bleeding stopped within 3–5 hours in patients with extracranial haemorrhage

Group A

298 patients with bleeding type classed as:



*Local investigator-determined time to bleeding cessation
Pollack et al. AHA 2016

RE-VERSE AD™ group B (n=196): patients were enrolled due to a variety of conditions requiring emergency procedures

Indication/procedure	Frequency (n)
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

MI, myocardial infarction

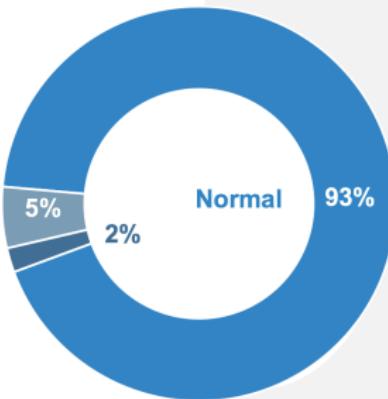
Pollack et al. AHA 2016

Group B: most patients had normal haemostasis during surgery

Group B

191/196 (97.4%) patients underwent surgery/procedure with periprocedural haemostasis classed as:

Mildly abnormal
Moderately abnormal
0% Severely abnormal



Overall median time from first vial to procedure



Pollack et al. AHA 2016

Adjudicated post-reversal thromboembolic events through 90 days

- In total, 35 thrombotic events occurred in 31 of 494 patients (6.3%) at 90 days
 - 15 of these events were classed as VTE (3.0%)
 - 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
Ischaemic stroke	8
MI	7
Systemic embolism	1

VTE, venous thromboembolism
Pollack et al. AHA 2016



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

Pollack et al. AHA 2016



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 ADTM: 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

Section 5

Summary

Summary

1

A specific reversal agent for dabigatran is now widely available in Europe, the USA, and other countries

2

Idarucizumab immediately reverses the anticoagulant activity of dabigatran and is easy to use

3

The availability of a specific reversal agent for dabigatran adds more control and is an important factor in NOAC choice