Do or Don’t with DOAC Reversal Agents?

*The argument **against** a more **global** use of DOAC reversal agents, specific to the treatment of stroke patients.*

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Do or Don’t with DOAC Reversal Agents?

*The argument **for** a more **restricted** use of DOAC reversal agents, specific to the treatment of stroke patients.*

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I HAVE NO DISCLOSURES

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Is it safe?

Is it effective?

How much does it cost?

3 QUESTIONS YOU SHOULD BE ABLE TO ANSWER BEFORE RECOMMENDING ANY DRUG TO A PATIENT

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Is it safe?

Answer: We aren't really sure

Trial	Design	Thrombotic events Early	Thrombotic events Late
REVERSE-AD Group A N = 98 (ICH)	Prospective single cohort study of **idarucizumab** for debigatran reversal	2.3% at 5 days 7/301	4.8% at 30 days 14/301
UPRATE N = 59 (ICH)	Prospective use of **4F-PCC** for FXa reversal	0% at 72 hours 0/84	3% at 30 days 2/84
ANNEXA-4 Safety Population N = 227 (ICH)	Prospective open-label, single-group study of **andexanet** alpha for FXa reversal	3% at 5 days 11/352	10% at 30 days 34/352

REVERSE-AD. *NEJM*. 2017;377:431
UPRATE. *Blood*. 2017;130(15):1706
ANNEXA-4. *NEJM*. 2019;380:1326

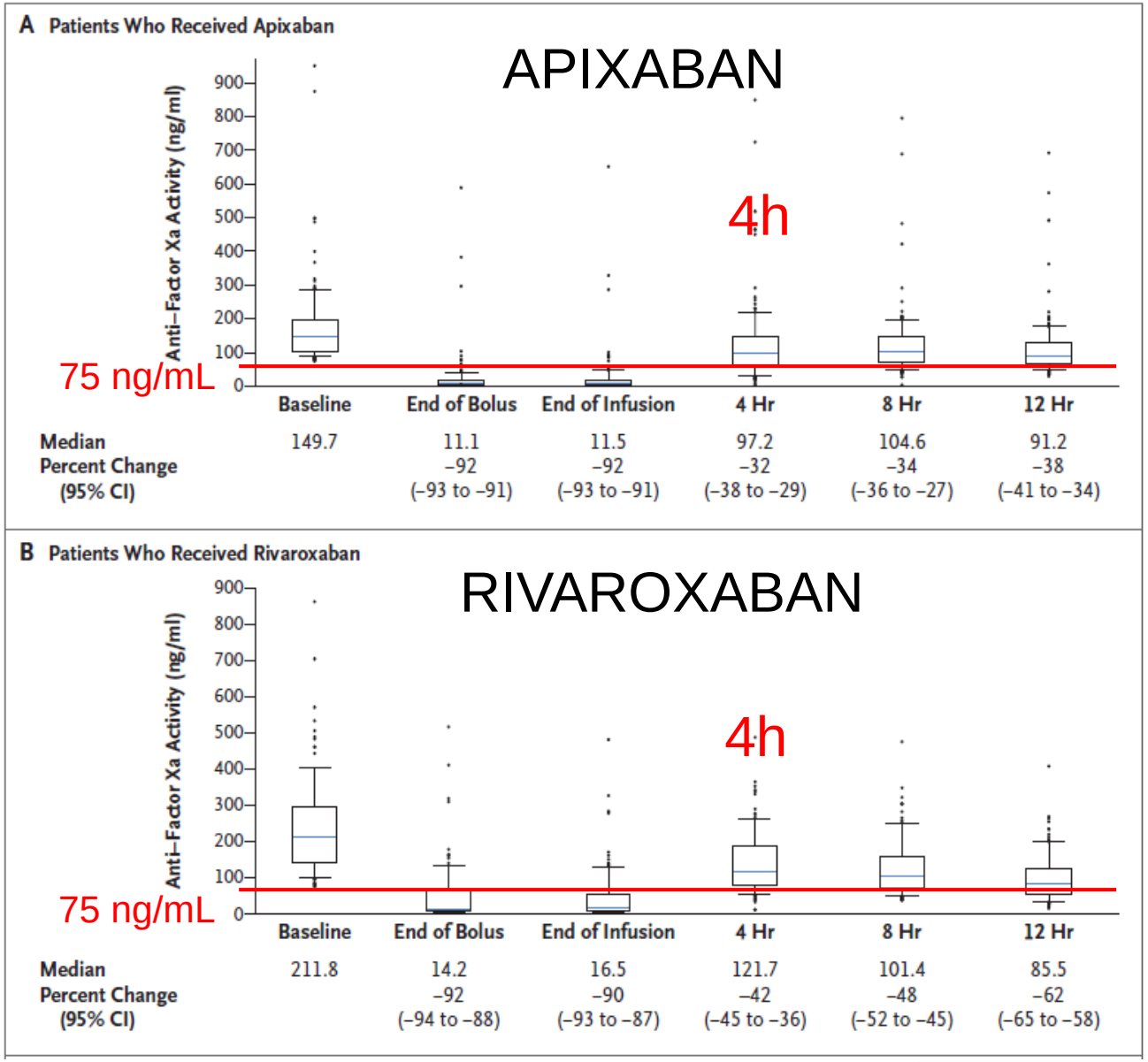
Is it effective?

Answer: Depends on what you mean by "effective"

	Definition of efficacy	Results
REVERSE-AD Group A N = 98 (ICH)	The maximum **percentage reversal** of the anticoagulant effect of dabigatran Clinical outcomes were "assessed by the treating clinician"	Normalized lab results in 100% of patients within minutes which persisted for 24 hours "The time to the cessation of bleeding could not be assessed in the 98 patients with intracranial bleeding, because there is dissociation between the clinical course and the extent of bleeding"
UPRATE N = 59 (ICH)	Follow-up CT within 24 hrs compared with the initial CT Change in neurological status and the need for surgical intervention	43/59 **(73%)** were determined to have effective hemostasis
ANNEXA-4 Efficacy Population N = 171 (ICH)	Reduced anti–factor Xa levels "Effective hemostasis"	Andexanet "markedly reduced" anti–factor Xa activity Achieved good or excellent effective hemostasis in 80% of patients with ICH

Andexanet reduced FXa activity *(for a little while, anyway)*

"The efficacy population included only patient in whom the baseline anti-factor Xa activity was later determined to be **75 ng/mL** or more"



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ANNEXA-4 Study Numbers

- Number of patients in the **Efficacy Population**: 254
- Number of patients in the Efficacy Population with **intracranial bleeding**: 171
  - Intraparenchymal 104
  - SDH 58, SAH 43
  - Multicompartmental 54
- **Intraparenchymal hematoma** volume in patients in the efficacy population:
  - ≤ 10 mL: n = 66
  - 11-60 mL: n = 38

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What is “effective” ICH hemostasis?

- **Excellent hemostasis**: **≤20%** increase in hematoma volume compared to baseline on a repeat CT scan performed at the end infusion + 1 hour and at 24-hours
- **Good hemostasis**: **>20% to ≤35%** increase in hematoma volume compared to baseline on a repeat CT scan performed at 24-hours
- The authors did not provide the data on how many ICHs were adjudicated as excellent vs. good hemostatic efficacy – these were **lumped** together

Is a ≤ 35% increase in hematoma volume clinically meaningful?

(< 3.5 mL in 2/3 of ICH patients)

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Lessons from the past

- **FAST**: The mean estimated increase in volume of the ICH at 24 hours was **26%** in the placebo group vs. **11%** in the 80 mcg/kg FVII group (P<0.001) and the growth in volume of the ICH was reduced by **3.8 mL**, but there was no significant difference in clinical outcome (and an increase in thromboembolic serious adverse events – 9% vs. 4%. P=0.04)
- **INTERACT**: Relative risk of hematoma growth of **33%** was 36% lower (p=0.05) and there was **3.15 mL** less mean absolute hematoma growth in the intensive BP control group than in the guideline group, however, this did not alter the risks of adverse events or secondary clinical outcomes at 90 days.

FAST3. *NEJM*. 2008;358:2127
INTERACT. *Stroke*. 2010;41:307

What does it co$t?

- 4 Factor PCC - ~$3,000 for 2,000 unit dose
- Idarucizumab - ~$3,500 for 5 gm dose
- Andexanet alfa
  - "low dose" (last dose <7h) **$24,750**
  - "high dose" (last dose >7h) **$49,500**

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Summary: What I am *for*

- Before reversal consider some variables: time LKW, time last dose of DOAC taken, renal function, size of hematoma, labs (TT, aPTT, INR)
- Idarucizumab for reversal of DTI only if:
  - Last dose taken within 18 hours (assuming normal renal function)
  - Thrombin time is elevated
- 4F-PCC for FXa reversal
  - Last dose taken within 18 hours (assuming normal renal function)
- Further study on a specific FXa reversal agent

Reversal of DAICH vs. WAICH #1

- Prospective study of 161 consecutive patients with non-traumatic OAICH at 13 tertiary stroke centers over a 12 month period
- DAICH 47, WAICH 114 (INR 2.9±1.14)
- Reversal agents used in WAICH **87%**
  - FFP (27%), PCC (60%), vitamin K (72%)
- Reversal agents used in DAICH **53%**
  - FFP (6%), vitamin K (11%), PCC (34%), idarucizumab (2%)
- Despite ~ ½ receiving any reversal agent, DAICH had **less hematoma expansion** at 24 hours (23% DAICH vs. 37% WAICH)
- AND had **better 3-month clinical outcomes**

Tsivgoulis et al., Neurology.2017;89:1142-1151

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Reversal of DAICH vs. WAICH #2

- Prospective study of 196 consecutive patients with non-traumatic OAICH at 15 tertiary stroke centers over a 12-month period
- DAICH 62, WAICH 134 (mean INR 3.05±1.3)
- Reversal agents used in WAICH **86%**:
  - FFP (20%), PCC (63%), vitamin K (80%)
- Reversal agents used in DAICH: **48%**
  - FFP (6%), vitamin K (10%), PCC (44%), andexanet alpha (1.6%)
- Despite less than ½ receiving any reversal agent, DAICH had **less hematoma expansion** (17% DAICH vs. 37% WAICH)
- AND had a trend toward **better 3-month function outcomes**

Lioutas et al., Stroke.2018;49:2309-2316

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Lack of hematoma expansion = Effective hemostasis

Significant hematoma expansion defined as: absolute increase by 12.5 mL or relative increase of > 33%

Excellent/good hemostasis defined as: ≤35% increase in hematoma volume

	Hematoma expansion	"Effective hemostasis"
Tsivgoulis et al.	23% →	77%
Lioutas et al.	17% →	83%
UPRATE (PCC)		73%
ANNEXA-4 (FXaI)		80%

We don't even *know* if reversal is necessary for DAICH

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“IT'S WHAT WE THINK WE KNOW THAT KEEPS US FROM LEARNING.”

— Claude Bernard

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DTI & reversal

- T1/2 is longest (12-17h)
- Renal clearance is 80%
- Some ability to rapidly assess presence of anticoagulant effect (aPTT will be elevated if supratherapeutic, TT and ECT could be used for monitoring)
- Idarucizumab is a Fab fragment of hu Ab vs. dabigatran
- Administered as a 2.5mg bolus q15m x2 (i.e. fast)
- Reversal is rapid and permanent (a true antidote)

FXa inhibitors & reversal

- T1/2 are shorter (6-12h)
- Lower renal clearance
- FXa levels are not readily available for clinical decision making
- Andexanet is a recombinant hu FXa “decoy” of native FXa
- Bolus followed by 2 hour infusion (requires reconstitution and can take up to 45 min from order to initiation)
- Once infusion stops, FXa levels begin to rise (t1/2 is 1 hour)