

Intracranial haemorrhage related to direct oral anticoagulant medications: Latest evidence for reversal strategies

**Data updates
October 2024**

There is new evidence for the efficacy and safety of DOAC reversal agents and for monitoring their efficiency

	EFFICACY AND SAFETY OF 4F-PCC ¹	EFFICACY AND SAFETY OF ANDEXANET ALFA VS 4F-PCC ²	MONITORING THE EFFICIENCY OF REVERSAL ON ANTI-FX α DOACs ³
Aims	To evaluate outcomes in patients treated with PCC for FXaI-associated bleeding or urgent surgery	To assess the comparative efficacy and safety of AA and 4F-PCC in the reversal of FXaI-associated ICH	To assess point-of-care viscoelastic testing as a method of detecting DOAC concentrations before/after reversal
Methods	<ul style="list-style-type: none"> Single-centre retrospective study Patients receiving 4F-PCC* for FXaI-associated major bleeding or surgery Primary outcome: haemostatic efficacy Safety outcome: 30-day risk of TE 	<ul style="list-style-type: none"> Systematic review and meta-analysis of studies until 16 May 2024 (N=2,977) Primary outcomes: Haemostatic efficacy; overall mortality; TE events REM used to pool data 	<ul style="list-style-type: none"> Case series of three patients requiring DOAC reversal for bleeding POC VET lab assays (RVV clotting time test) used to measure DOAC effects after reversal with AA
Results	<ul style="list-style-type: none"> FXaI-associated bleeding, n=83[†] <ul style="list-style-type: none"> 32 (39%) had ICH Effective haemostasis in 67% of patients with bleeding 30-day risk of TE was 8% overall 	<ul style="list-style-type: none"> Haemostatic efficacy in favour of AA: RR 1.10, 95% CI 1.01–1.20 (p=0.02) Lower overall mortality with AA: RR 0.67, 95% CI 0.51–0.88 (p=0.004) More TE events with AA: RR 1.47, 95% CI 1.01–2.15 (p=0.046) 	RVV clotting time assays were able to: <ul style="list-style-type: none"> Detect and quantify DOACs Confirm haemostatic effect of reversal agents (<i>clotting time after AA infusion: 90–91s[‡]</i>) Identify late DOAC rebound
Conclusions	PCC for FXaI-associated bleeding was associated with haemostatic efficacy in two-thirds of patients; 30-day TE event rate was <10%	AA is superior to 4F-PCC in terms of haemostatic efficacy and reducing overall mortality. More TE events are associated with use of AA vs 4F-PCC	If confirmed in large validation studies, utilization of RVV-CT in routine emergency care will streamline the care of DOAC patients

*25–50 IU/kg; [†]Urgent surgery, n=22; [‡]Results for patients 1 and 3; patient 2 received low-dose AA as rescue therapy.

4F-PCC, four-factor of prothrombin complex concentrate; AA, andexanet alfa; DOAC, direct oral anticoagulant; FXaI, Factor Xa inhibitor; GI, gastrointestinal; ICH, intracranial haemorrhage; POC, point-of-care; REM, random effects model; RR, risk ratio; RVV, Russell viper venom; TE, thromboembolism; VET, viscoelastic testing.

1. Shaw JR, et al. *Thromb Res*. 2024;243: 109172; 2. Sarhan K, et al. *Neurocrit Care*. 2024. DOI: <https://doi.org/10.1007/s12028-024-02130-y>. Online ahead of print;

3. Heubner L, et al. *Thromb J*. 2024;22:89.

INTERACT trial updates demonstrate the importance of blood pressure and blood sugar control in ICH







	POOLED ANALYSIS OF ALL FOUR INTERACT TRIALS¹ <i>Impact of timing of blood pressure lowering</i>	INTERACT3 TRIAL SUBANALYSIS² <i>Impact of blood glucose levels</i>
Aims	To assess the heterogeneity in the treatment effect of BP lowering, based on treatment time in ICH	To determine associations of BG and unfavourable functional outcome in patients with ICH without diabetes
Methods	<ul style="list-style-type: none"> Individual patient data pooled analysis of INTERACT1, 2, 3 and 4 trials N=2,921 patients with ICH Ordinal logistic regression model used to define heterogeneity in treatment effect on 90-d efficacy (mRS) 	<ul style="list-style-type: none"> Post hoc analysis of INTERACT3, an RCT where BL characteristics were collected at ICH hospital admission Logistic regression models used to determine associations of BG as continuous and categorical exposures and 6-month functional outcome (mRS)*
Results	<ul style="list-style-type: none"> Treatment, n=1,467; control, n=1,454 Significant heterogeneity in treatment effect by treatment time (p for interaction, 0.005) More benefit if BP-lowering therapy given within 3 hours of onset 	<ul style="list-style-type: none"> n=6,306; median BG 7.1 mmol/L No association between BG and functional outcome: aOR 1.01, 95% CI 0.98-1.04 (p=0.64) Higher BG increased the risk of death: aOR 1.08, 95% CI 1.04-1.12 (p<0.0001) <ul style="list-style-type: none"> BG >10mmol/L group: aOR 1.50, 95% CI 1.15-1.96 vs the <7.8 mmol/L group (p=0.0019)
Conclusions	Individual patient data pooling aims to provide robust evidence for informing clinical guidelines regarding early BP lowering	In patients with ICH without diabetes, very high BG (>10.0 mmol/L) is associated with death over 6 months. Glycaemic control should be applied in such patients

*Adjusted for study-design, patient and management variables. aOR, adjusted odds ratio; BG, blood glucose; BL, baseline; BP, blood pressure; CI, confidence interval; d, day; ICH, intracranial haemorrhage; INTERACT, Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trials; mRS, modified Rankin Scale; RCT, randomized controlled trial.

1. Ren X. Presented at the 16th World Stroke Congress, 23-26 October 2024, Abu Dhabi, UAE. Available at: <https://cslide.ctimeetingtech.com/wsc24/attendee/confcal/session/list> (accessed 24 October 2024); 2. Ouyang M. Presented at the 16th World Stroke Congress, 23-26 October 2024, Abu Dhabi, UAE. Available at: <https://cslide.ctimeetingtech.com/wsc24/attendee/confcal/session/list> (accessed 24 October 2024).

The Scientific and Standardization Committee of the ISTH has updated its guidance on reversal of DOACs

2024 update to the prior 2016 guidance includes:

-  DOAC reversal agents
-  Comparisons among reversal agents
-  Reversal strategies under investigation
-  Potential indications for reversal
-  Laboratory testing
-  Hospital use and administration