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

Data updates
October 2024

Date of preparation: 30 October 2024

touch™ CARDIO

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-FXa 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	• 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	• 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	• 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	• FXaI-associated bleeding, n=83†
	  • **32 (39%)** had ICH
	  • Effective haemostasis in **67%** of patients with bleeding
	• 30-day risk of TE was **8%** overall
		• 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:
			• Detect and quantify DOACs
			• Confirm haemostatic effect of reversal agents *(clotting time after AA infusion:* ***90–91s***‡*)*
			• 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.

touch™ CARDIO

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

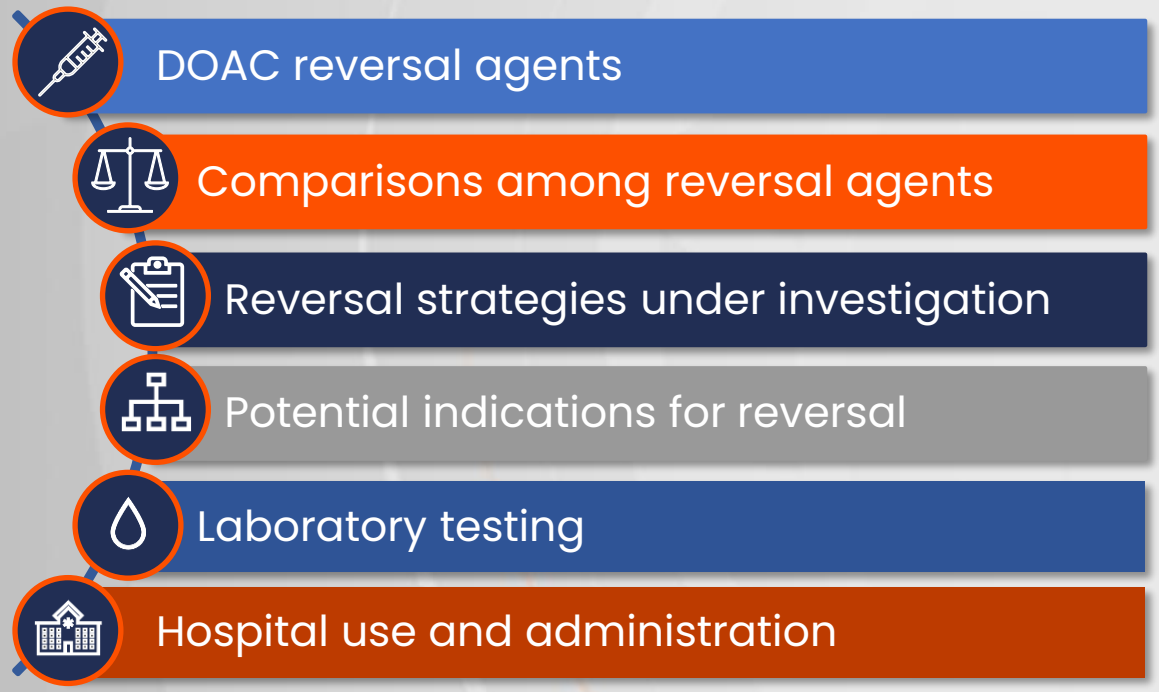
	POOLED ANALYSIS OF ALL FOUR INTERACT TRIALS[1] *Impact of timing of blood pressure lowering*	INTERACT3 TRIAL SUBANALYSIS[2] *Impact of blood glucose levels*
Aims	**To assess the heterogeneity in the treatment effect of BP lowering, based on treatment time in ICH**	**To determine associations of BG and unfavourable functional outcome in patients with ICH without diabetes**
Methods	• 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)	• 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	• 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	• 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)** • 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 internal; 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, direct oral anticoagulant; ISTH, International Society on Thrombosis and Haemostasis.

Levy JH, et al. *J Thromb Haemost.* 2024;22:2889–99.