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

Data updates
January 2025

Date of preparation: 28 January 2025

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Additional data on the risk of ICH with anticoagulant use (1/2)

	SAFETY AND EFFECTIVENESS OF DOACS VS WARFARIN FOR VTE[1]	RISK OF ICH WITH DOAC VS ANTIPLATELET THERAPY[2]
Aims	**To assess the effectiveness and safety of DOACs compared with warfarin using data from real-world practice settings**	**To determine whether DOAC therapy, vs single-agent antiplatelet therapy, was associated with an increased risk of ICH and major haemorrhage**
Methods and outcomes	• A systematic review and meta-analysis of observational studies of DOACs vs warfarin in patients with acute VTE (680,695 patients) • Effectiveness: risk of VTE recurrence • Safety outcomes: major bleeding, clinically relevant non-major bleeding, intracranial haemorrhage, gastrointestinal bleeding and all-cause mortality	• A systemic review and meta-analysis of randomized controlled trials (45,494 patients) • Primary outcome: ICH • Secondary outcomes: major haemorrhage, fatal haemorrhage, GI haemorrhage, ischaemic stroke and cardiovascular mortality
Results	• Risk of VTE recurrence (DOACs vs warfarin): **24% reduction** • Safety: ICH risk (DOAC vs warfarin): **31% reduction** ; however, no significant difference in incidence of ICH in studies reporting number of events/arm	• DOAC therapy not associated with significantly higher odds of ICH vs antiplatelet therapy: **0.55% vs 0.48%, OR 1.15** • DOAC therapy was associated with significantly higher odds of major haemorrhage vs antiplatelet therapy: **2.41% vs 1.76%, OR 1.39**
Conclusions	**DOACs demonstrate favourable effectiveness and safety vs warfarin but clinicians should evaluate pts for bleeding risk factors before initiating DOAC therapy**	**DOAC therapy was not associated with a significantly higher risk of ICH vs antiplatelet therapy, but was associated with a higher risk of major haemorrhage**

DOAC, direct oral anticoagulant; ICH, intracranial haemorrhage; OR, odds ratio; VTE, venous thromboembolism.

1. Alshahrani WA, et al. *Am J Cardiovas Drugs*. 2024;24:823–39; 2. Coyle, M et al. *JAMA Network Open.* 2024;7:e2449017.

Additional data on the risk of ICH with anticoagulant use (2/2)

	ICH IN PATIENTS TAKING DIFFERENT TYPES OF OAC[1]	CDM FOR RISK FOR ANTICOAGULANT-INDUCED ICH[2]	REAL-WORLD PHARMACOVIGILANCE STUDY OF OAC-INDUCED ICH[3]
Aims	**To assess outcomes in patients with ICH according to prior OAC or no anticoagulation**	**To investigate incidence and risk factors for OAC-induced sICH in a real-world setting**	**To describe the national post-market cases of OAC-induced ICH**
Methods and outcomes	• Observational study using two prospective national stroke registries (11,349 patients) • Main outcomes: favourable functional outcome (modified Rankin scale 0–2) and mortality at 3 months	• A retrospective study of the clinical data warehouse from the SNUH (12,821 patients) • Used a CDM to analyse incidence and risk factor of sICH	• Analysis of the FAERS-reported cases of OAC-related ICH (11,201 cases)
Results	• Favourable outcome (DOAC vs no anticoagulation): **adjusted OR 0.64** • 3-month mortality (DOAC vs no anticoagulation): **adjusted OR 1.28**	• Incidence of sICH: **warfarin 0.5%** and **NOAC 0.2%** • Risk factors: warfarin over NOAC, hypertension, diabetes, brain tumours, decreased duration of OAC	• Median time to onset: **181 days** • Median age at onset of ICH: **75 years** • After adjusting for confounding factors, lower ICH risks observed with DOACs vs VKAs
Conclusions	**Prior DOAC is independently associated with lower odds of a favourable outcome and higher odds of 3-month mortality**	**NOACs demonstrated a lower risk of sICH vs warafarin in a real-world setting; use of a CDM may be beneficial in clinical studies**	**DOACs demonstrated a robust lower risk of ICH vs VKAs. The majority of OAC-induced ICH occurred within 5 months and in elderly patients**

CDM, common data model; CI, confidence interval; DOAC, direct oral anticoagulant; FAERS, US Food and Drug Administration Adverse Event Reporting System; ICH, intracranial haemorrhage; NOAC, novel oral anticoagulant; OAC oral anticoagulant; OR, odds ratio; pts, patients; s, spontaneous; SNUH, Seoul National University Hospital; VKA, vitamin K antagonist.

1. Siepen BM, et al. *Stroke Vas Neurol*. 2024;9:e002813; 2. Hong, N et al. *J Clin Neurosci.* 2025;8:133:111039.

Real-world evidence for the effectiveness and safety of andexanet alfa

	EFFECTIVENESS OF ANDEXANET ALFA (ASTRO-DE STUDY)[1]	EFFECTIVENESS OF ANDEXANET ALFA IN AN ITALIAN POPULATION[2]
Aims	**To assess the real-world evidence for AA in mitigating haematoma expansion and altering the prognosis rivaroxaban- or apixaban-treated patients with ICH**	**To review outcomes for Italian patients treated with AA as a reversal agent for FXaI-related major bleedings**
Methods and outcomes	• Prospective, non-interventional cohort study (137 patients) • Primary outcomes: HVC; proportion of patients with haematoma growth ≤33% within 12-72h or until first control imaging • Secondary outcomes include in-hospital TE; mortality up to 90 days	• Retrospective collection of real-world data of FXaI-related haemorrhage (51 patients) • Predominant bleeding type: ICH, particularly intracerebral: 68.6%
Results	• At first control imaging: mean HVC **2.3 mL** and haematoma growth ≤33% **90.3% of patients** • Within 12-72h: mean HCV **1.8 mL** and haematoma growth ≤33% **90.5% of patients** • TEs: **8.0%** (n=11/137) and 90-day mortality: **36.7%** (n=47/128)	• In patients with ICH, median haematoma volume expansion was **12.34%** • Successful haemostasis rate: **77%** of patients (**53.7%** with intracerebral haemorrhage) • OR for 30-day mortality in patients with ICH: **1.87** • TEs: **9.8%**
Conclusions	**Treatment with AA showed favourable haemostasis and minimal mean haematoma volume growth in patients with ICH and DOAC treatment**	**This analysis provide a comprehensive overview of FXaI-related bleeding events in Italy managed with AA and contribute to the existing evidence**

AA, andexanet alfa; DOAC, direct oral anticoagulant; FXaI, Factor Xa inhibitor; h, hours; HVC, haematoma volume change; ICH, intracranial haemorrhage; OR, odds ratio; TE, thromboembolic events.

1. Diener H-C, et al. *Int J Stroke*. 2025 Jan 20: doi: 10.1177/17474930251317385 (Online ahead of print); 2. Simioni P, et al. *Thrombosis Res*. 2025: 245:109241.

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Additional data for the efficacy and safety of andexanet alfa and other DOAC reversal agents

	EFFICACY AND SAFETY ANDEXANET ALFA VS SOC*[1]	A UK-BASED AUDIT OF THE USE OF DOAC-REVERSAL AGENTS (ANDEXANET ALFA, PCC OR IDARUCIZUMAB)[2]
Aims	**To evaluate the efficacy and safety of AA vs SOC* for the reversal of DOAC-induced ICH**	**To assess the use of DOAC-reversal agents, as well as associated mortality and thrombosis rates**
Methods and outcomes	• A systematic review and meta-analysis using prospective or retrospective cohort studies or RCTs (4,330 patients) • Primary efficacy outcome: haemostatic efficacy • Primary safety outcomes: rates of thrombotic complications; mortality	• A retrospective, observational audit of patients who received AA, PCC or idarucizumab for DOAC reversal (2,477 patients) • Primary outcome: patients receiving a reversal agent who had major bleeding defined by ISTH criteria • Secondary outcomes: 90-day mortality; 30-day TE rate
Results	• Haemostatic efficacy, pooled RR: **1.1** favouring AA • TE, pooled RR: **1.22** • Mortality, pooled RR: **0.81** • Subgroup analysis of AA vs 4F-PCC: similar results for haemostatic efficacy and thrombotic complications, but significant mortality risk reduction favouring AA	• **40.8%** of patients had an ICH • **91.1%** of treated patients fulfilled ISTH criteria • 13.0% received AA,† 82.3% PCC and 4.7% idarucizumab • 90-day mortality rate: **45.8%** in patients with ICH • 30-day TE rate: **3.0%**
Conclusions	**Treatment with AA offers improved haemostatic efficacy vs SoC, with no effect on thrombotic complications and mortality rates**	**Most patients fulfilled the ISTH definition of major bleeding; high mortality rates confirm the cohort is enriched for severe presentations of bleeding**

*Standard of care in included trials was 4- or 3-factor PCC, activated PCC or tranexamic acid. †AA use restricted to gastrointestinal haemorrhage in most of the UK.
AA, andexanet alfa; DOAC, direct oral anticoagulant; ICH, intracranial haemorrhage; ISTH, International Society of Thrombosis and Haemostasis; PCC, prothrombin complex concentrate; RCT, randomized control trial; RR, risk ratio; SOC, standard of care; TE, thromboembolism.
1. Xiang AJ, et al. *Blood*. 2024;144 (Suppl. 1):5089–90; 2. Buka, RJ, et al. *Blood*. 2024;144 (Suppl. 1):2637–8.

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October 2024

Date of preparation: 30 October 2024

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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.

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

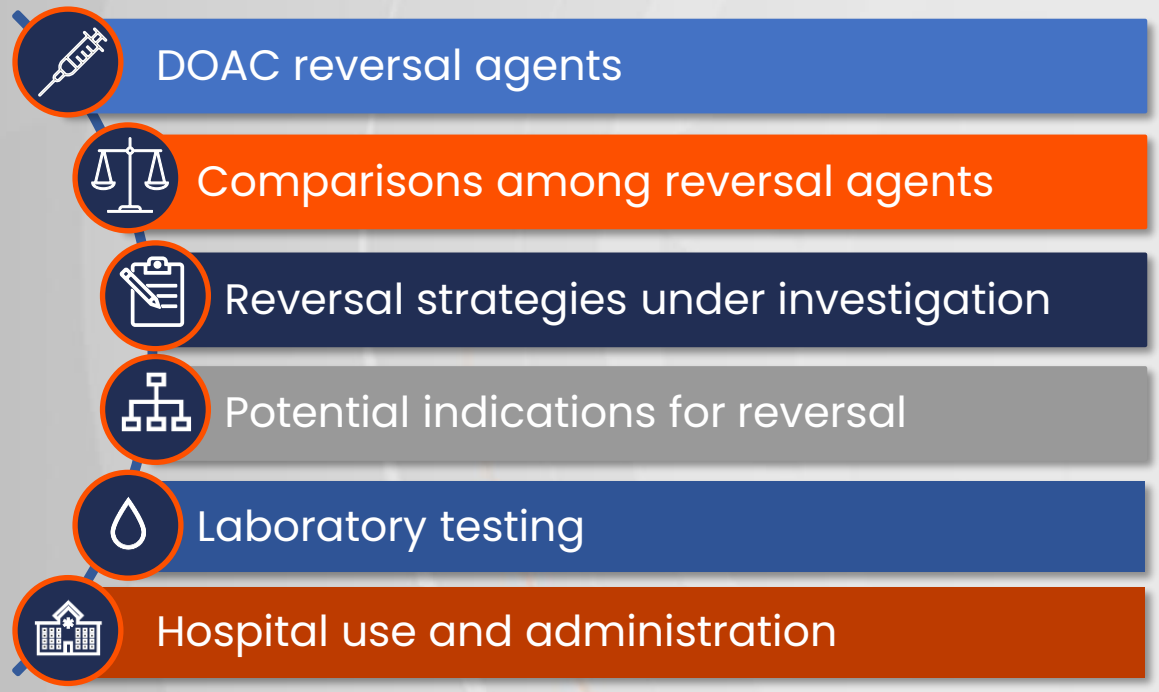
	POOLED ANALYSIS OF ALL FOUR INTERACT TRIALS[1] *Impact of timing of blood pressure lowering*	INTERACT3 TRIAL SUBANALYSIS[2] *Impact of blood glucose levels*
Aims	**To assess the heterogeneity in the treatment effect of BP lowering, based on treatment time in ICH**	**To determine associations of BG and 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.