

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

**Data updates
January 2025**

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	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Analysis of the FAERS-reported cases of OAC-related ICH (11,201 cases)
Results	<ul style="list-style-type: none"> Favourable outcome (DOAC vs no anticoagulation): adjusted OR 0.64 3-month mortality (DOAC vs no anticoagulation): adjusted OR 1.28 	<ul style="list-style-type: none"> Incidence of sICH: warfarin 0.5% and NOAC 0.2% Risk factors: warfarin over NOAC, hypertension, diabetes, brain tumours, decreased duration of OAC 	<ul style="list-style-type: none"> 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 warfarin 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

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	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Retrospective collection of real-world data of FXaI-related haemorrhage (51 patients) • Predominant bleeding type: ICH, particularly intracerebral: 68.6%
Results	<ul style="list-style-type: none"> • 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) 	<ul style="list-style-type: none"> • 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.

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	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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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**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 _a 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