ONLINE SUPPLEMENT: Summary of Clinical Trials on Direct-Acting Anticoagulant Reversal/Hemostatic Agents

Trial	Reversal Agent	Anticoagulant	Study Population	Dosing regimen	Design	Primary Endpoint	Clinical Outcomes	Additional Comments
RE-VERSE AD (1)	Idarucizumab	Dabigatran	• Patients with uncontrollable or life-threatening bleeding (n= 301) • Patients undergoing urgent surgery or other invasive procedure (n=202)	• 5 g IV (administered bolus infusions, of 2.5 g)	• Multicenter, prospective, open-label (n = 503)	• The primary endpoint was maximum percentage reversal of the anticoagulant effect of dabigatran within 4 h assessed by dTT or ecarin clotting time • Secondary end points included the restoration of hemostasis and safety	• Reversal of anticoagulant effect based on dTT or ecarin clotting time within 4 h was achieved in 100% of patients	• Median time to cessation of bleeding 2.5 h • Thrombotic events occurred in 6.3% of patients with uncontrollable bleeding and 7.4% in those undergoing surgery at 90 d. • Mortality rate was just over approximately 19% in both groups.
ANNEXA-4 (2)	Andexanet alfa	Apixaban, enoxaparin or rivaroxaban	• Patients ≥18 with acute major bleeding within 18 h of last dose of FXa inhibitor • 42% ICH • 49% GI bleeding	• **Low dose:** 400 mg IV bolus over 15 min, then 480 mg IV infusion over 2 h, if apixaban or >7 h from rivaroxaban • **High dose:** 800 mg IV bolus over 30 min, then 960 mg infusion over 2 h, if edoxaban, enoxaparin, or ≤7 h of rivaroxaban	• Multicenter, prospective, open-label single-group study (n=67)	• The primary endpoint was Percent change in anti-Xa activity and rate of good or excellent hemostasis 12 h after the infusion	• In patients with acute major bleeding, treatment with andexanet alfa markedly reduced anti–FXa activity, with 82% of patients having excellent or good hemostatic efficacy at 12 h.	• Thrombosis rate 10% within 30 d • Mortality 14% in 30 d
UPRATE (3)	4F- PCC*	Apixaban or rivaroxaban	• Major bleeding and direct Xa inhibitor use within 24 h • 70.2% ICH • 15.5% GI bleeding	• ~ 25 IU/kg	• Multicenter, prospective, observational study (n=84)	• The primary endpoint was the effectiveness of PCC when using the ISTH criteria for the assessment of effectiveness of major bleeding management	• Management with 4F-PCC was only effective in 69.1% of patients.	• Thrombosis rate 2.4% in 30 d • Mortality rate 32% within 30 d • The majority of patients in whom PCC was ineffective were those with ICH 61.5%.
PCC for major bleeding on FXa inhibitors (4)	4F- PCC	Apixaban or rivaroxaban	• Major bleeding and received 4F-PCC prior to plasma, platelets or other hemostatic agents • 55% ICH • 24% GI bleeding	• 2000 IU	• Multicenter, prospective, observational study (n=66)	• The primary endpoint was efficacy was based on the ISTH reversal criteria.	• Management of bleeding with 4F-PCC was effective in 68% of patients.	• Thrombosis rate 8% in 30 d • Mortality rate 14% by 30 d
4F-PCC versus plasma for rapid VKA reversal in patients needing urgent surgical or invasive interventions (5)	4F-PCC vs. plasma	Warfarin	• Patients 18 years or older needing rapid VKA reversal prior to an urgent surgical or invasive procedure	• Dose based on INR	• Multicenter, open-label, phase 3b randomized trial (n=181)	• The primary endpoint was effective hemostasis, with a coprimary end point of rapid INR reduction.	• Hemostatic efficacy was achieved in 90% of patients in the 4F-PCC group and in 75% of the plasma group. • Rapid INR reduction was achieved in 55% of patients receiving 4F-PCC and in 10% in the plasma group.	• Thromboembolic adverse events occurred in 7% of patients receiving 4F-PCC and 8% receiving plasma.

Trial	Reversal Agent	Anticoagulant	Study Population	Dosing regimen	Design	Primary Endpoint	Clinical Outcomes	Additional Comments
Efficacy and safety of a 4F-PCC concentrate in patients on VKA presenting with major bleeding (6)	4F-PCC or plasma	Warfarin	• Patients with acute nonsurgical major bleeding	• Dose based on INR	• Multicenter, open-label, noninferiority trial (n=212)	• The primary endpoint was if 4F-PCC was noninferior to plasma for the coprimary end points of 24-h hemostatic efficacy from start of infusion and INR correction (≤1.3) at 30 min following the end of infusion	• Hemostatic efficacy achieved in 72.4% of the 4F-PCC group compared with 65.4% of the plasma group • Reduction in INR to <1.3 within 30 min occurred in 62.2% for 4F-PCC versus 9.6% for plasma	
Safety, efficacy, and cost of 4F-PCC in patients with FXa inhibitor-related bleeding (7)	4F-PCC	Apixaban or rivaroxaban	• Major bleeding secondary to FXa inhibitors • ICH (58%) • Pericardial effusion (16%) • Musculoskeletal (12.9%)	• Weight based dosing – 25 U/kg (38/7%) – 50 U/kg – (51.6%)	• Observational, retrospective review (n=31)	• The primary endpoint was effectiveness of 4F-PCC for FXa major bleeding based on ISTH criteria	• Weight-based 4F-PCC achieved hemostasis in 80.6% of patients receiving a direct Xa inhibitor.	• No thrombotic events reported at 7 d
Evaluation of fixed-dose 4F-PCC for emergent warfarin reversal (8)	Fixed-dose 4F-PCC	Warfarin	• Emergent warfarin reversal • ICH 71.8% • Median INR on presentation 3.3	• 1500 IU	• Retrospective review (n=39)	• The primary endpoint was Successful reversal (INR <2.0) occurred in 92.3% of patients and 71.8% achieved an INR of ≤1.5.	• Fixed-dose 4F-PCC leads to a high rate of warfarin reversal. • Median INR following a single dose of 1500 IU was 1.4.	• No thrombotic events reported at 7 d
Fixed versus variable dosing of PCC in VKA-related ICH (9)	PCC	Warfarin	• Emergent reversal of warfarin in patients with ICH • Median INR 3.3 in the fixed-dose and 3.1 in the weight based group	• 1000 U fixed-dose versus weight based	• Before and after design (n=53)	• The primary endpoint was achievement of INR ≤1.5.	• In the fixed-dose group, 68% achieved an INR ≤1.5 compared with 96 % in the weight-based dose fixed cohort	• The fixed-dose protocol necessitated additional infusions of PCC more frequently to achieve a target INR ≤1.5.
Evaluation of fixed-dose 4F-PCC for emergent warfarin reversal in patients with ICH (10)	Fixed-dose 4F-PCC	Warfarin	• Patients with ICH • Baseline INRs of 2.98 in the weight based group and 2.84 in the fixed-dose group	• 1000-unit fixed dosing compared with weight based dosing	• Before and after design (n=61)	• The primary end point was achieving an INR <1.5.	• An INR of <1.5 was achieved in 71% of in the weight-based group compared with 53% in the fixed-dose group. • Overall, there was a nonstatistically significant difference in warfarin reversal to an INR goal of <1.5 when comparing the 2 treatment strategies.	• No difference in mortality
Fixed-dose 4F-PCC for the emergent reversal of warfarin (11)	Fixed-dose 4F-PCC	Warfarin	• Patients needing emergent warfarin reversal • Median INR pretreatment 3.06	• 1500 IU	• Retrospective (n=37)	• The primary endpoint was successful reversal with an attainment of an INR ≤1.5	• Fixed-dose 4F-PCC resulted in 75% of patients reaching an INR ≤1.5 and 100% achieving and INR ≤2.	• A fixed dose of 1500 IU of 4F-PCC demonstrated efficacy in adequately reversing the INR in most patients.

4F-PCC= 4-factor prothrombin complex concentrate; ANNEXA-4 =Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors; dTT = dilute thrombin time; FXa = factor Xa; GI = gastrointestinal; ICH = intracranial hemorrhage; INR = international normalized ratio; ISTH = International Society on Thrombosis and Haemostasis; IU = international unit; IV = intravenous; PCC = prothrombin complex concentrate; REVERSE-AD = Reversal Effects of Idarucizumab on Active Dabigatran; UPRATE = Unactivated Prothrombin Complex Concentrates for the Reversal of Anti-Factor Ten Inhibitors; VKA = vitamin K antagonist

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