Question 14 evidence tables

Question 14: In patients with Novel Direct Oral Anticoagulant (NOAC) related acute intracerebral haemorrhage, do reversal methods (prothrombin complex concentrate-PCC, fresh frozen plasma –FFP, idarucizumab, andexanet alfa, tranexamic acid and Factor VIIa) improve functional outcome, mortality, haematoma expansion and normalise coagulation testing?

NB Any discrepancies between reviewers in evidence quality and comment were discussed at the corresponding evidence review meeting

DOAC = direct oral anticoagulant, PCC = prothombin complex concentrate, ISTH = International Society of Thrombosis and Haemostasis, MBE = major bleeding event, ICrH = intracranial haemorrhage, FFP = fresh frozen plasma, VKA = vitamin k antagonist, ICU = intensive care unit, HR = high risk. NOAC = novel oral anticoagulant, IVH = intraventricular haemorrhage, SAH = subarachnoid haemorrhage, BP = blood pressure, TXA = tranexamic acid, SR = systematic review, MA = meta-analysis, RCT = randomised controlled trial, IPDMA = individual patient data meta-analysis, MDT = multidisciplinary team, PICO = patient/population, intervention, comparison and outcomes, OR = odds ratio, CI = confidence interval, QoL = quality of life, ADL = activities of daily living, OR = odds ratio, RR = relative risk, aOR = adjusted odds ratio, cOR = crude odds ratio, CI = confidence interval, RoB = risk of bias, I2 = heterogeneity statistic.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
352	C. V. Pollack et al. (2015). Idarucizumab for dabigatran reversal. New England Journal of Medicine 373:511-520	Setting: Multicentre (184 sites in 35 countries) Design: Cohort study (prospective) Patients: 90 patients who had serious bleeding (group A, n=51, of whom 18 had intracranial haemorrhage) or required an urgent procedure (group B, n=39). >90% were taking Dabigatran for stroke prevention in AF. Median age 76.5y.	Intervention: 5g IV Idarucizumab which was administered as two 50-ml bolus infusions, each containing 2.5 g of idarucizumab, no more than 15 minutes apart Comparator: None	Outcome: maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after the administration of idarucizumab, on the basis of the determination at a central laboratory of the dilute thrombin time or ecarin clotting time Timepoint: text	100% reversal Normalised test results in 88-98% of patients, within minutes.	- No comparator group. 22 patients had baseline coagulation in the normal range. Minority of patients had ICH, and results weren't presented separately.
352	C. V. Pollack et al. (2015). Idarucizumab for dabigatran reversal. New England Journal of Medicine 373:511-520	Prospective cohort study, 90 patients (51 in group A (overt bleeding) and 39 in group B (requiring emergency surgery). Enrolled at 184 sites in 35 countries. 2014-2015.	Idarucizumab 5g IV..	Primary endpoint: Max % reversal of anticoagulant effect of dabigatran (dilute thrombin time or ecarin clotting time).	18 patients in Group A had ICH at baseline, no cases of ICH in Group B.	No control group. Small numbers of ICH patients.

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		Interim analysis (study ongoing)		Secondary endpoint: clinical outcomes (extent and severity of bleeding) and for ICH patients the mRS at 90 days.	68/90 patients had abnormal clotting times at study entry and amongst these, the median maximum % reversal of anticoagulation was 100% for both thrombin times and clotting times in blood samples taken immediately (within minutes) after first infusion of idarucizumab. This was associated with transient low levels of unbound dabigatran. Consequent increases in unbound dabigatran levels were associated with increases in clotting times. 5 patients had thrombotic events including 1/90 (1%) had a thrombotic event within 72 hours. None were receiving antithrombotic therapy when the events occurred.	
336	A. Agren et al. (2017). Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: A cohort study. *Blood,* 130:15 1706-1712	Prospective cohort study Jan 1 2014 – Oct 1 2016 in 25 Swedish hospitals (covering 2/3 Sweden) affiliated with the Coagulation Unit at Karolinska Institute who had been contacted about patients with major bleeding events (MBE) whilst taking apixaban or rivaroxaban. MBE defined using International Society of Thrombosis and Haemostasis (ISTH) definition of major bleeding in non-surgical patients. MBE was either evident	4-factor PCC at dose of 1500 IU or 2000 IU for body weight of less than or more than 65 kg, respectively (approx. 25 IU/kg)). An additional dose of PCC was allowed at discretion of treating physician.	For efficacy outcome, ISTH criteria used to ascertain effectiveness of haemostasis achievement. For ICH, clinical course, need for surgical intervention and, when available, repeat CT brain at 24 hours were recorded. Assessments covered out to 30 days post bleeding onset and were carried out by 2 independent	N=92 patients. N=8 excluded as PCC given for pre-operative DOAC reversal (n=4) and for non-receipt of PCC (n=4). Indication for DOAC was atrial fibrillation (75%). ICH was most common MBE (70.2%). Trauma associated 31%. Median interval from last dose of DOAC to PCC treatment 12.5 hrs (9-16 hrs) and from bleeding onset to PCC	Study methodology poor. Findings are hypothesis generating at best. No control group. No indication of how patients included compare with non-included patients.

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		clinically as active blood loss or intracranial haemorrhage. Last dose of DOAC within 24 hours. Patients recommended PCC by the Coagulation Unit at Karolinska were included in the study. There was no control group.		assessors. Discordant findings were resolved by discussion. Safety outcomes: Primary was occurrence of objectively documented arterial or venous thrombosis post treatment with PCC within 30 days. Death within 30 days was also recorded.	treatment was 6 hours (2-10 hrs). Median PCC dose 2000 IU. A second dose of 500-1500 IU given in 3 cases. Additional treatments given included plasma (n=13), platelets (n=10) and tranexamic acid (n=56). Haemostatic effectiveness n=58, 69.1.%). For ICH, 72.9%. No difference comparing traumatic vs non-traumatic bleeding. Of those with ineffective haemostasis 16/26 61.5% had ICH. 3/84 patients (3.6%) had thromboembolic event within 30 days (I PE and 2 ischemic stroke). 27 patients died within 30 days (32%) of which 74.1% had ICH.	
336	A. Agren et al. (2017). Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: A cohort study. *Blood,* 130:15 1706-1712	Prospective, observational study conducted by Karolinska University Hospital, (covering 25 hospitals as a tertiary referral centre) in Sweden from 2014-16. 84 patients were referred to the centre and when the unit recommended PCC, the patient was included in the study (consent waived). All patients had major bleeding events, 59	Patients who were felt to need PCC treatment by the team received treatment with a 4-factor PCC. There was no control population. Dose of 1500 IU if < 65 kg, 2000 IU if > 65 kg.	Data collected by note review 30 days after PCC treatment. Outcomes: Effectiveness by ISTH criteria. For ICrH, this is all 4 of (1) ICH Vol on CT is stable or < 35% increase by 12 h (6-24 h range).	PCC 'effective' in 43/59 ICrH patients but 16 had no follow up CT because they improved, 9 more had no CT because they deteriorated quickly and died (all 9 assumed to be ineffective). 3 thromboembolic events noted, all over 70 with AF. 2 strokes at 5 & 10 days, 1 PE at	- No control group. Outcomes not prospectively or robustly collected – notes review only.

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		with intracranial haemorrhage. Patients took rivaroxaban or apixaban in last 24 h. The exclusion criteria included patients with a do-not-resuscitate order, preoperative reversal of rivaroxaban or apixaban, and patients with acute coronary syndrome or ischemic stroke within the past 30 days.		No deterioration in eGOS. No need for further haemostatic agents or blood products by 48 h (4) No neurological deterioration at discharge/30 d as assessed by 'any validated scoring system'. Occurrence of an objectively verified arterial (stroke, myocardial infarction, or arterial thromboembolism) or venous thromboembolism (deep venous thrombosis or pulmonary embolism) after treatment with a PCC Death up to 30 days.	15 days (but never verified on imaging).	
337	R. Al-Shahi Salman et al. (2018). Haemostatic therapies for acute spontaneous intracerebral haemorrhage. *Cochrane Database of Systematic Reviews,* 2018:4 CD005951	Cochrane systematic review and meta-analysis	Haemostatic therapies vs placebo/control in patients with spontaneous ICH	Primary: mRS 4-6	1 RCT of blood clotting factors vs FFP in anticoagulant-associated ICH (n=5)	**++**
337	R. Al-Shahi Salman et al. (2018). Haemostatic therapies for acute spontaneous intracerebral haemorrhage. *Cochrane Database of*	Setting: Multicentre Design: Systematic review and meta-analysis of RCTs Patients: We included 12 RCTs involving 1732 participants.	Intervention: See below Comparator: See below 7 RCTs of blood clotting factors versus	Outcome: text Timepoint: text	In one RCT of platelet transfusion versus open control for acute spontaneous ICH associated with antiplatelet drug use, there was a significant increase in death or dependence	**++** Cochrane review. We were unable to include two eligible RCTs because they presented aggregate data for adults with ICH and other types of

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	Systematic Reviews, 2018:4 CD005951		placebo or open control involving 1480 participants 3 RCTs of antifibrinolytic drugs versus placebo or open control involving 57 participants 1 RCT of platelet transfusion versus open control involving 190 participants 1 RCT of blood clotting factors versus fresh frozen plasma involving five participants.		(modified Rankin Scale score 4 to 6) at day 90 (70/97 versus 52/93; risk ratio (RR) 1.29, 95% CI 1.04 to 1.61, one trial, 190 participants, moderate-quality evidence). All findings were non-significant for blood clotting factors versus placebo or open control for acute spontaneous ICH with or without surgery (moderate-quality evidence), for antifibrinolytic drugs versus placebo (moderate-quality evidence) or open control for acute spontaneous ICH (moderate-quality evidence), and for clotting factors versus fresh frozen plasma for acute spontaneous ICH associated with anticoagulant drug use (no evidence).	intracranial haemorrhage. Across all seven criteria in the 12 included RCTs, the risk of bias was unclear in 37 (44%), high in 16 (19%), and low in 31 (37%). Only one RCT was at low risk of bias in all criteria.
338	T. Apostolaki-Hansson et al. (2020). Reversal Treatment in Oral Anticoagulant-Related Intracerebral Hemorrhage—An Observational Study Based on the Swedish Stroke Register. *Frontiers in Neurology,* 11:	Riksstroke, Swedish Stroke Register cohort, consecutive cases, registered Jan 1st-31st Dec 2017, covers 90% of admitted Swedish stroke cases. Adults age > 18 years, ICH in setting of prior VKA, apixaban, rivaroxaban or dabigatran included. Baseline demographics, ICH details recorded. Level of consciousness scale (RLS-85) used as proxy of stroke severity.	DOAC reversal consisted of PCC (82.2%), idarucizumab 5.9%, 1 patient received both.	Primary outcomes were mortality and functional outcome (mRS) at 90 days.	Patients receiving reversal treatment were younger, more often independent pre-stroke, had less severe strokes, more likely treated in Stroke Unit/ICU setting. All cause mortality at 90 days was 33.6% in those receiving reversal treatment vs 52.7% in those not. In DOAC cases, HR for death 1.41, 0.88-2.24).	LOC (RLS-85) used as proxy of initial ICH severity. 14% of cases lost to f/u for functional outcome at 90 days. Significant imbalances in baseline variables for treated vs not-treated ICH cases. Suggestion that DOAC reversal may be of benefit. Findings hypothesis generating at best .

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		N=572 with anticoagulant associated ICH N=369(64.5%) received reversal treatment of which 118 (32%) were on DOAC. 50.2% of DOAC ICH cases received reversal treatment.			Trend seen of better functional outcomes (mRS) at 90 days in DOAC ICH cases given reversal treatment.	
338	T. Apostolaki-Hansson et al. (2020). Reversal Treatment in Oral Anticoagulant-Related Intracerebral Hemorrhage—An Observational Study Based on the Swedish Stroke Register. *Frontiers in Neurology,* 11:	Secondary analysis of Swedish Stroke Register (Riksstroke) including analysis of 572 oral-anticoagulant associated ICHs during 2017.	Reversal (n=369) Or non-reversal (n=203). Choice of treatment non-randomised, at clinicians' discretion. Reversal of NOACs was 82.2% treated with PCC, 5.9% received Idarucizumab, and one patient received both PCC and Idarucizumab. Missing data for 11%.	90-day mortality mRS at 90 day Cox regression adjusted for adjusted for age, sex, diabetes, hypertension, atrial fibrillation, pre-stroke dependency, anticoagulant reversal, hemorrhage location (supratentorial vs. infratentorial), intraventricular hemorrhage, and neurosurgery. Level of consciousness used as a stratification variable.	NOAC-ICH were 235 of cases and 118 had treatment and 117 did not. 15 received dabigatran, the rest apixaban or rivaroxaban. For NOAC-ICH, no reversal therapy not associated with higher hazard of death (HR 1.41 [0.88 to 2.24]; p=0.15). No adjusted analysis for mRS.	+ Observational design prevents any firm conclusions.
339	A. T. Cohen et al. (2020). 30 Day Mortality Following Andexanet Alfa In Annexa-4 Compared With Prothrombin Complex Concentrate (PCC) Therapy In The Orange Study For Life Threatening Non-Vitamin K Oral Anticoagulant (NOAC) Related Bleeding.	Comparison of 30 day mortality in life threatening bleeding for andexanet alpha in the ANNEXA-4 cohort study vs PCC in ORANGE Cohort Study of major anticoagulant associated bleeding, including life-threatening bleeding ICH cases n=258 Propensity score matching used to derive 2 cohorts with life-	PCC vs andexanet alpha.	30 day mortality.	ICH sub-group mortality 48.94% with PCC vs 15.31% with andexanet alpha.	Reject due to severe methodological shortcomings.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Journal of the American College of Cardiology, 75:11 2242	threatening bleeding whilst on DOACs treated with either andexanet alpha or PCC				
339	A. T. Cohen et al. (2020). 30 Day Mortality Following Andexanet Alfa In Annexa-4 Compared With Prothrombin Complex Concentrate (PCC) Therapy In The Orange Study For Life Threatening Non-Vitamin K Oral Anticoagulant (NOAC) Related Bleeding. *Journal of the American College of Cardiology,* 75:11 2242	Comparison of 2 independent datasets. ANNEXA-4 (single arm, open label, North America and Europe 63 sites, 2015-2018) (excluded GCS<7, ICH vol >60 cc)) with ORANGE (observational prospective study of 2192 patients with major bleeds associated with OACs from 32 hospitals in UK 2013-2016)	Anticoagulation reversal with Andexanet alfa versus PCC.	30 day mortality by type of bleed (ICH, GI bleed and other major bleed).	322/352 ANNEXA-4 patients (64.9% were ICH) were matched with 88/2192 ORANGE patients (67.1% were ICH). Groups included GI bleeds as well as ICH. Adj 30 day mortality lower with andexanet alfa (16.4% versus 34.1%). In ICH subgroups (after matching) mortality lower with andexanet alfa (15.3% versus 48.9%)	0 Groups were propensity score-matched based on demographic and clinical characteristics. Could not account for GCS, haematoma volume (not measured in ORANGE), expected survival. High risk of bias.
340	C. I. Coleman et al. (2021). Real-world management of oral factor Xa inhibitor-related bleeds with reversal or replacement agents including andexanet alfa and four-factor prothrombin complex concentrate: A multicenter study. *Future Cardiology,* 17:1 127-135	Multi-centre retrospective analysis of electronic medical records from 45 US hospitals 2016-2019 to extract 3030 FXa inhibitor associated major bleed hospitalisations.	From 507 ICrH, 67 treated with andexanet alfa (13%), 170 treated with 4F-PCC 24%) , 146 treated with FFP (29%), 11 (22%) treated with 'other' reversal and 47 (9%) with no reversal treatment.	In hospital mortality, hospital length of stay, ICH length of stay.	ICH bleeds treated with andexanet alfa (n = 67) had a 9% in hospital mortality rate, which was the lowest rate across all agents. Rates were higher for other commonly used agents, including 4F-PCC (n = 170, 25%) and FFP (n = 146, 27%), no reversal (23%).	Considerable bias in this study. Observational retrospective data analysis only. No description of case mix of ICH or haematoma reduction/expansion or factor X a activity. High risk of bias as a result of this.

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340	C. I. Coleman et al. (2021). Real-world management of oral factor Xa inhibitor-related bleeds with reversal or replacement agents including andexanet alfa and four-factor prothrombin complex concentrate: A multicenter study. *Future Cardiology,* 17:1 127-135	Observational cohort study using records from 45 US hospitals to detect hospitalisations for major bleeding events N=3030 factor Xai associated major bleeds	Andexanet alfa vs 4 factor PCC vs FFP vs others	In-hospital mortality Length of stay	In-hospital mortality: andexanet 4%; PCC 10%; FFP 11%; others 8% Length of stay: ICU length of stay andexanet 2 days vs other agents 3 days	+
341	S. J. Connolly et al. (2016). Andexanet alfa for acute major bleeding associated with factor xa inhibitors. *New England Journal of Medicine,* 375:12 1131-1141	Setting: Multicentre Design: Cohort study (prospective) Patients: Acute major bleeding within 18h of administration of a factor Xa inhibitor (n=67 [28 (42%) had intracranial haemorrhage], of whom only 47 were in the efficacy analyses). Average age 77y. Mean time to bolus 4.8h.	Intervention: Andexanet bolus and 2h infusion Comparator: None.	Outcome: measures of anti–factor Xa activity and were assessed for clinical hemostatic efficacy Timepoint: 12 hours. Followed for 30 days.	After the bolus administration, the median anti–factor Xa activity decreased by 89%. 12h after the andexanet infusion, clinical haemostasis was adjudicated as excellent or good in 37 of 47 patients in the efficacy analysis (79%; 95% CI, 64 to 89); excellent / good haemostasis achieved for 80% (56–94) of 20 with ICH. Thrombotic events occurred in 12 of 67 patients (18%) during the 30-day follow-up.	- Comment: No comparator group. Only 47/67 in efficacy analyses. 28 (42%) had intracranial haemorrhage.
341	S. J. Connolly et al. (2016). Andexanet alfa for acute major bleeding associated with factor xa inhibitors. *New*	ANNEXA-4 Study. Multicentre prospective open label single group study.	Bolus andexanet followed by 2 hour infusion (doses depended on type of FXAI and time since taken).	Change in anti-FXA activity on pharmacokinetic studies at different time points pre and post bolus of andexanet.	iCH in 28 (42%) After bolus administration, anti FXA activity fell by 89% (rivaroxeban group) and 93% (apixaban group)	**-/+** Preliminary report of ongoing cohort study.

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	England Journal of Medicine, 375:12 1131-1141	67 participants with acute major bleeding within 18 hours of taking a FXAI (apixaban, edoxaban enoxaparin or riveroxeban). Since 2015, centres in Europe and North America. Excluded patients with GCS<7 or ICH volume of >60 ml. Ongoing study		Clinical haemostatic efficacy. mRS and imaging used to monitor ICH patients. Adverse events collected for 30 days.	Partial return to pretreatment values at 4-4.5 hours after initiation of adexanet 12 hours after infusion, clinical haemostasis was excellent or good in 37/47 (79%) in efficacy analysis. Thrombotic events in 12/67 (18%) during 30 day follow up.	Insufficient numbers enrolled so far to determine relationship between reduction in anti-factor XA activity and clinical outcomes.
342	A. M. Demchuk et al. (2021). Hemostatic Efficacy and Anti-FXa (Factor Xa) Reversal with Andexanet Alfa in Intracranial Hemorrhage: ANNEXA-4 Substudy. *Stroke,* : 2096-2105	Sub-study within ANNEXA-4 examining effect of andexanet alpha in intra-cranial ICH. Single-arm open label prospective study in adults > 18 years with ingestion of Factor Xa inhibitor < 18 hours N=227 safety analysis N=171 in efficacy analysis ICH spontaneous or traumatic. Exclusions: GCS < 7, ICH vol > 60 cc, expected survival < 1 month. Mean age 79.3 years, 51.5% male, prior atrial fibrillation 85% Median GCS 15, median NIHSS 3.0, median mRS 3.0. Apixaban 61.7%, rivaroxaban 30.4%. Median time from symptom onset or trauma to initial scan 3.3	Andexanet alpha bolus IV followed by 2 hour infusion	Co-primary end-points: Percent change from baseline to lowest level in Factor Xa activity measured at beginning of treatment and within 10 mins of infusion completion. The percentage of patients achieving good or excellent haemostasis at 12 hours after treatment defined as follows: <20% increase in ICH volume at both 2 and 12 hours after infusion = excellent haemostasis >20% but < 35% increase between baseline and 12 hours = good haemostasis.	Median percent change in anti-FXa level 93.8% for apixaban patients and 92.6% for rivaroxaban patients. Level remain suppressed throughout the infusion and slowly increased out to 12 hours but remain below baseline level. For spontaneous ICH, haemostasis excellent or good in 78.6%. For traumatic ICH, haemostasis excellent or good in 83%. Minimal change in ICH volume between baseline and 12 hours. Thrombotic events within 30 days 9.3%, occurring a median	Single arm study, gives no indication of effect of andexanet alpha vs current best medical therapy.

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		hrs, median time from scan to andexanet alpha 2.0 hrs.		>35% increase = poor haemostasis. Safety outcomes were death, thromboembolic events within 30 days.	of 11 days post treatment, 66.7% occurring > 6 days. Mortality within 30 days 15%, mostly due to CV causes, 76.5% of deaths occurred > 6 days. 62.1% of the safety population (141/227) resumed anticoagulation a median of 3 days post treatment. No thrombotic events occurred post same.	
342	A. M. Demchuk et al. (2021). Hemostatic Efficacy and Anti-FXa (Factor Xa) Reversal with Andexanet Alfa in Intracranial Hemorrhage: ANNEXA-4 Substudy. *Stroke,* : 2096-2105	Single arm open label sub study of ANNEXA 4 study (2019) testing the haemostatic efficacy and safety of Andexanet alfa in patients with ICH (spontaneous and traumatic). Total of 227 patients (128 spontaneous and 99 traumatic). Patients were required to have an episode of ICH/IVH/Subdural or SAH within 18 hours of taking Factor Xa inhibitor (Apixaban, rivaroxaban, edoxaban or enoxaparin). Excluded if required neurosurgery or had volumes > 60 cc	Bolus and 2-hour infusion of andexanet intravenous	Efficacy outcomes: 1. Change in baseline anti factor X activity levels to nadir 2. Reduction of haematoma increase < 20% (excellent) and >20 < 35% (good) at 12 hours compared to baseline Safety outcomes: 1. Mortality and thrombotic events at 30 days 2. Rankin at 30 days	227 patients recruited Efficacy population 171 patients Safety population 227 patients Of note: Median Baseline volumes for ICH/IVH were 9.5 mls for spontaneous ICH) 27% of ICH > 20 mls Efficacy: Median % decrease from baseline to nadir was 92.6 % for rivaroxaban treated patients and 93.8% for apixaban treated patients Efficacy in spontaneous ICH was 78.6% (excellent	Open label single arm study with no comparator and no outcome data beyond 30 days. Excludes patients with large volume haematoma > 60 cc, life expectancy < 1 month (in practice difficult to predict this when treatment needs to be given rapidly).

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					haemostasis) and effects were consistent across a number of subgroups Efficacy in spontaneous ICH was 83 % (excellent haemostasis) and effects were consistent across a number of subgroups Median mRS at 30 days was 4 (spontaneous) and 1 (traumatic). Safety: Thrombotic event (9.3%) Mortality 15%	
343	A. Filippatou et al. (2018). Fatal oral anticoagulant-related intracranial hemorrhage: a systematic review and meta-analysis. *European Journal of Neurology,* 25:10 1299-1302	Systematic review and meta-analysis to evaluate risk of fatal NOAC-related intracranial haemorrhage vs fatal VKA-related intracranial haemorrhage. 4 RCTs, 2 open-label trials of NOAC-specific reversal agents.	N/A	Fatal intracranial haemorrhage.	NOACS had a lower risk of fatal intracranial haemorrhage vs VKAs: RR 0.46, 95% CI 0.36-0.58. In indirect analysis, case fatality rate of NOAC-related intracranial haemorrhage treated with specific reversal agents was lower compared with remainder of pts.	+
343	A. Filippatou et al. (2018). Fatal oral anticoagulant-related intracranial hemorrhage: a systematic review and meta-analysis.	Setting: Text Design: Systematic review and meta-analysis of RCTs and observational studies. Patients: 4 RCTs and 2 observational studies.	Intervention: NOAC-specific reversal agent (idarucizumab or andexanet alpha) Comparator: No NOAC-specific reversal agent.	Outcome: Death. Timepoint: Not specified.	In the indirect analysis case fatality rate of NOAC-related ICH in patients treated with specific reversal agents was lower compared to the rest	- Mixed RCT and observational studies. Abstract/poster only – insufficient.

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	European Journal of Neurology, 25:10 1299-1302				(17%, 95%CI: 11%-24% vs. 41%, 95%CI: 34-49%; p<0.001; Figure 3).	
344	S. T. Gerner et al. (2021). Hematoma Expansion and Clinical Outcomes in Patients With Factor-Xa Inhibitor-Related Atraumatic Intracerebral Hemorrhage Treated Within the ANNEXA-4 Trial Versus Real-World Usual Care. *Stroke,* : STROKEAHA121034572	Indirect comparative analysis from 2 different study designs Comparison of two separate study populations. Apixeban and riveroxeban related ICH patients (n=85) in North America and Europe from Single arm trial ANNEXA-4 (subjects enrolled 2015-2018) (treatment with Andexanet alfa) versus 97 patients receiving usual care in a German multicentre (19 tertiary centres subjects enrolled between 2011-2015) in an observational cohort study (RETRACE-II) (19 tertiary centres between 2011-2015).	Andexanet Alfa (low or high dose) versus "usual care" (75% .patients received PCC, 5% received Vit K)	ICH volume on quantitative computer based assessment or formula calculations; on scan at baseline versus scan up to 12h (ANNEXA 4) and up to 36 h (RETRACE-II) later. Haematoma expansion defined as increase volume >=35% radiologically. Mean change in ICH volume. In hospital mortality. Functional outcome (mRS) at discharge or day 30 if still inpatient.	HE occurred in 11/80 (14%) andexenat alfa treated group versus 21/67 (36%) in the usual care cohort with radiological outcomes available (P=0.005, after adjusting for differences in baseline characteristics). Andexanet alfa associated with reduced HE (adj risk ratio 0.44, 0.22-0.87, P=0.017). Mean change in ICH volume lower in andexanet alfa group (adj P=0.0013). In hospital mortality non-significant trend in favour of andexanet alfa on adjusted analysis (0relative risk 0.49, 0.24 -1.04, P=0.06). Functional outcomes were similar between the two groups.	– Groups similar demographics at baseline but this was not a RCT Some differences between groups in type of OAC, prior use of antiplatelets (higher in andexanet group), BP on admission (higher in usual care group), intraventricular haemorrhage (higher in usual care group), meant time since OAC taken (longer in andexanat group). Second scan times were more delayed in RETRACE-II. Differences in assessment of imaging/study period. Significant potential for bias despite statistical adjustment.
344	S. T. Gerner et al. (2021). Hematoma Expansion and Clinical Outcomes in Patients With Factor-Xa Inhibitor-Related	Comparative study of patients with apixaban or rivaroxaban associated non-traumatic ICH extracted from multi-centre, single-arm prospective ANNEXA-4 study compared with similar	Comparison of IV andexanet alpha in ANNEXA-4 vs usual care in RETRACT-II which consisted	Primary outcome: proportion of patients with haematoma expansion (HE) 12 hours post baseline in ANNEXA-4 and at the first follow-up	RETRACE-II subjects GCS was 13.5 vs 13.0, MAP 99.0 vs 118.0 mm Hg, initial ICH vol 13.95 vs 16.08 cc, IVH extension 12.9 vs 40%,	Likely residual confounding factors make comparison between the 2 groups problematic.

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	Atraumatic Intracerebral Hemorrhage Treated Within the ANNEXA-4 Trial Versus Real-World Usual Care. *Stroke,* : STROKEAHA12103457 2	patients in the German-wide multicentre observational RETRACE-II cohort. Propensity score weighted indirect comparison. ANNEXA-4 cases enrolled April 2015-May 2018. RETRACE-II cases treated at 19 German centres between Jan 2011-Dec 2015. DOAC intake < 18 hours pre hospital admission. Other exclusions: GCS < 7, ICH vol > 60 cc. 182 patients available for analysis, 85 in ANNEXA-4 and 97 in RETRACE-II. Mean time since last DOAC intake in ANNEXA-4 11.5 hrs vs 7.8 hrs in RETRACE-II. In ANNEXA-4, all patients received andexanet alpha. In RETRACE-II, 76.3% received PCC, mean dose 32.88 IU/kg.	mainly of PCC 25 iu/kg IV.	imaging in RETRACE-II. HE defined according to International Society of Thrombosis and Haemostasis criteria as > 35% increase in ICH volume between baseline and follow up imaging. Secondary outcomes: mean absolute change in haematoma volume between initial and f/u imaging, in hospital mortality and functional outcome (mRS) at discharge. Propensity score modelling used to balancefor differences in baseline variables in both groups.	absence of f/u imaging 5.9 vs 30.1%, respectively. Primary outcome: HE 14% in ANNEXA-4 vs 36% in RETRACE-II unadjusted. In the propensity score modelling adjusted analysis, HE was significantly reduced with andexanet alpha (aRR 0.40, (0.20-0.78). In a similar analysis looking at absolute change in ICH volume, andexanet alpha was associated with lower mean ICH volume change -7.12 cc (-11.41- -2.83). Adjusted hospital mortality rate was lower for andexanet alpha (HR 0.49, 0.24-1.04, p=0.06). Adjusted analysis functional outcome was not significantly differen.t between the 2 groups Thromboembolic compilcations within 30 days ANNEXA-4 12.9% vs 10.1% in RETRACE-II.	No difference in functional outcome or mortality despite apparent lower haematoma expansion with andexanet alpha notable.
345	S. T. Gerner et al. (2018). Association of prothrombin complex concentrate	Retrospective cohort study.	N/A	Primary: Association of PCC with haematoma enlargement.	N=146 NOAC-ICH patients. Haematoma enlargement occurred in 33.6%.	+

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	administration and hematoma enlargement in non-vitamin K antagonist oral anticoagulant-related intracerebral hemorrhage. *Ann Neurol,* 83:1 186-196	N=190 with NOAC-associated intracerebral haemorrhage (ICH) at 19 Hospitals across Germany.		Secondary: in-hospital mortality; functional outcome at 3 months (mRS).	PCC administration was not associated with a reduced rate of haematoma enlargement.	
345	S. T. Gerner et al. (2018). Association of prothrombin complex concentrate administration and hematoma enlargement in non-vitamin K antagonist oral anticoagulant-related intracerebral hemorrhage. *Ann Neurol,* 83:1 186-196	Retrospective cohort study including individual patient data for 190 patients with NOAC-associated ICH over a 5-year period (2011–2015) at 19 departments of neurology across Germany.	PCC administration in great majority of cases, at clinician's discretion.	1. Haematoma enlargement. 2. In-hospital mortality. 3. Functional outcome 3 months.	PCC administration prior to follow-up imaging was not significantly associated with a reduced rate of hematoma enlargement either in overall NOAC-related ICH or in patients with factor Xa inhibitor intake (NOAC: risk ratio [RR]51.150, 95% confidence interval [CI]50.632–2.090; factor Xa inhibitor: RR51.057, 95% CI50.565–1.977), regardless of PCC dosage given or time interval until imaging or treatment. PCC administration had no effect on mortality and functional outcome either at discharge or at 3 months.	**+** Observational design and lack of randomisation prevents any causal inference. Good adjustment for confounders, but still a major risk of confounding by indication.
351	P. L. Gross et al. (2018). Prothrombin Complex Concentrate for Major Bleeding on Factor Xa Inhibitors: A Prospective Cohort Study. *Thrombosis and Haemostasis,* 118:5 842-851	Prospective, multicentre observational study at 9 Canadian hospitals. Patients on apixaban or rivaroxaban with a major bleed were recruited to the study.	Treated as part of standard care with 2000 IU of PCC then recruited for a 30 day follow up. No comparator. 11 of the 33 ICrH patients were also given TXA.	The treating physician evaluated the haemostatic effectiveness as observed during the first day as good, moderate or poor/ none, using an assessment guide. Safety outcomes were thromboembolism or death.	66 patients recruited, 36 had ICrH, of which 18 intracerebral, 7 subdural, 4 subarachnoid haemorrhages and 7 with combinations. 11 (48%) ICHs had a volume of less than 10 mL, 6 (26%) had a volume of 11 to 44 mL, 5 (22%) had a volume of greater	**+** Prospective observational study. No control group, no standardisation of repeat imaging, criteria for 'effective' haemostasis open to interpretation. Prospective follow up at 30 days with

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				For ICrH: Good - < 20% increase on repeat CT, OR stabilisation of deterioration OR Neurological improvement Moderate – 20-35% increase, OR 'minimal' deterioration Poor > 35% increase OR deterioration OR death	than 44 mL, and 1 (4%) had IVH. Of there with ICrH, 67% had 'good' effectiveness of haemostasis, 17% had 'moderate' and 17% has 'poor'. There were 9 deaths by 30 days overall ad 5 (8%) had a major thromboembolic event.	adjudication for thrombotic complications.
351	P. L. Gross et al. (2018). Prothrombin Complex Concentrate for Major Bleeding on Factor Xa Inhibitors: A Prospective Cohort Study. *Thrombosis and Haemostasis,* 118:5 842-851	Prospective cohort study of patients on apixaban or rivaroxaban suffering a major bleed at 9 Canadian hospitals.	PCC.	Haemostatic effectiveness assessed by treating physician as good, moderate or poor/none.	N=66 Good: 65% Moderate: 20% Poor/none: 15% Intracranial haemorrhage =36 Good: 67% Moderate: 17% Poor/none: 17%	- Treating physician recorded outcome.
346	T. Jaspers et al. (2021). A meta-analysis of andexanet alfa and prothrombin complex concentrate in the treatment of factor Xa inhibitor-related major bleeding. *Research and Practice in Thrombosis and Haemostasis,* 5:4 e12518	Setting: 21 studies Design: Systematic review and meta-analysis of single-arm even rates (no comparative studies). Patients: FXia-related bleeding (45-100% had ICH). 17 PCC studies, 3 andexanet studies and 1 study describing PCC and andexanet both were included, comprising 1428 PCC-treated patients and 396 andexanet-treated patients.	Intervention: Andexanet Alpha Comparator: PCC.	Outcome: Primary objective was haemostatic effectiveness. Secondary objectives were thromboembolic event rate and mortality. Timepoint: Variable, up to 30d.	In subgroup analysis, the pooled proportion of patients with effective haemostasis in studies that used Annexa-4 criteria demonstrated a haemostatic effectiveness of 0.85 (95% CI 0.80-0.90) in PCC and 0.82 (95% CI 0.78-0.87) in andexanet studies. The pooled proportion of patients with thromboembolic events was 0.03 (95% CI, 0.02-0.04) in PCC and 0.11 (95% CI,	- None of the studies had a control group. No comparative studies. Well conducted review, but poor quality primary studies. Conclusions based on indirect comparisons.

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					0.04-0.18) in andexanet studies.	
346	T. Jaspers et al. (2021). A meta-analysis of andexanet alfa and prothrombin complex concentrate in the treatment of factor Xa inhibitor-related major bleeding. *Research and Practice in Thrombosis and Haemostasis,* 5:4 e12518	Systematic review and meta-analysis of observational studies describing effectiveness and/or safety of PCC or andexanet in patients with major bleeding on FXaIs	PCC or andexanet.	Haemostatic effectiveness as assessed in the included studies Thrombembolic events and mortality.	21 studies included (17 were PCC studies, 3 were andexanet studies and 1 both) 11 studies included patients with ICH only. No difference in haemostatic effectiveness observed in PCC studies vs andante studies but incidence of thromboembolic events higher in andexanet studies.	**0/-** Very few studies for andexanet Most studies medium or high risk of bias. No studies had comparator groups. Few studies were prospective with consecutive recruitment. Different definitions of outcome variables. No strong conclusions can be made about the difference in thromboembolic events PCC vs andante.
347	C. Luo et al. (2021). Prothrombin complex concentrates and andexanet for management of direct factor Xa inhibitor related bleeding: A meta-analysis. *European Review for Medical and Pharmacological Sciences,* 25:6 2637-2653	Meta-analysis of prospective or retrospective studies examining outcomes in patients treated with either andexanet alpha or 4 factor PCC and which reported rates of haemostasis achieved or rates of thromboembolic events or mortality. N=22 studies selected from 484 unique citations found on literature search. No control group in any study, most were retrospective.	IV andexanet alpha or 4 factor PCC.	Good to excellent haemostatic control (no specific definition given). Thromboembolic events within 90 days. Mortality within 90 days.	In intra-cranial haemorrhage cases: Good to excellent haemostasis with andexanet alpha 78% (66-89%) and 75% (68-83%) for 4 factor PCC. Thrombotic complications post andexanet alpha in ICH cases 18% (2-34%) and 4% (3-5%) within 90 days post 4 factor PCC.	No uniform definition of 'good to excellent haemostasis' used, high heterogeneity, variation in doses of andexanet alpha and 4 factor PCC noted. Not possible to assess comparative efficacy or safety on the basis of this study.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					Mortality in ICH cases post andexanet alpha 34% (22-47%) and 22% (15-29%)	
347	C. Luo et al. (2021). Prothrombin complex concentrates and andexanet for management of direct factor Xa inhibitor related bleeding: A meta-analysis. *European Review for Medical and Pharmacological Sciences,* 25:6 2637-2653	Meta-analysis of studies (all non randomised) assessing the efficacy, safety and mortality of PCC and andexanet for direct factor Xa inhibitor related bleeding including patients with ICH. No direct comparison made between both treatment modalities and in total 22 studies included. Mostly retrospective, single arm studies and case reviews. 50% studies from USA.	Combination of PCC and andexanet.	Haemostasis outcomes (varied with reduction in increase in haematoma expansion dependent when imaging was perfomed). Thrombotic complications. Mortality (varied in hospital and 30 days).	Excellent haemostatic control observed in patients with ICH with andexanet (78%) Excellent haemostatic control observed in patients with ICH with 4-PCC (75%) Thrombotic events ICH with andexanet 18% vs 4% 4-PCC 90 day mortality 34% with andexanet vs 22% 4-PCC	- All observational, retrospective and small studies (some studies n=2). No comparator group and no head to head comparison between both interventions. Heterogeneity in terms of haemostatic outcomes (different imaging procedures) , activity and mortality leading to considerable bias in studies presented.
348	N. G. Panos et al. (2020). Factor Xa Inhibitor-Related Intracranial Hemorrhage: Results from a Multicenter, Observational Cohort Receiving Prothrombin Complex Concentrates. *Circulation,* : 1681-1689	Multicentre, retrospective, observational cohort study. Apixaban or rivaroxaban related intracranial haemorrhage who received PCC 2015-2019.	N/A	Safety: Occurrence of a thrombotic event at hospital discharge or 30 days after PCC. Haemostatic efficacy: At least 1 follow-up image within 24hrs of PCC. Primary efficacy outcome: % with excellent or good haemostasis using modified Sarode criteria.	N=663 N=443 for haemostatic efficacy. Primary efficacy outcome: 81.8%. 26 thrombotic events (3.8%).	+
348	N. G. Panos et al. (2020). Factor Xa Inhibitor-Related	Setting: Multicentre. Design: Observational cohort study (retrospective).	Intervention: PCC. Comparator: None.	Outcome: haemostatic efficacy and clinical safety outcomes.	433 patients met criteria for haemostatic efficacy	-

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	Intracranial Hemorrhage: Results from a Multicenter, Observational Cohort Receiving Prothrombin Complex Concentrates. *Circulation,* : 1681-1689	Patients: 663 apixaban- or rivaroxaban-related ICH who received PCCs between January 1, 2015, and March 1, 2019.		Timepoint: text	evaluation. We observed excellent or good haemostasis in 354 patients (81.8% [95% CI, 77.9–85.2]). Twenty-five (3.8%) patients had a total of 26 thrombotic events.	Retrospective, no comparison group
349	C. V. Pollack et al. (2017). Idarucizumab for dabigatran reversal -full cohort analysis. *New England Journal of Medicine,* 377:5 431-441	Multicenter, prospective, open-label study to determine whether 5 g of intravenous idarucizumab would be able to reverse the anticoagulant effect of dabigatran in patients who had uncontrolled bleeding (group A) or were about to undergo an urgent procedure (group B).	5 g of intravenous idarucizumab, no control arm.	The primary end point was the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after the administration of idarucizumab, on the basis of the diluted thrombin time or ecarin clotting time. Secondary end points included the restoration of hemostasis and safety measures.	A total of 503 patients were enrolled: 301 in group A, and 202 in group B. The median maximum percentage reversal of dabigatran was 100% (95% confidence interval, 100 to 100), on the basis of either the diluted thrombin time or the ecarin clotting time. In group A, 137 patients (45.5%) presented with gastrointestinal bleeding and 98 (32.6%) presented with intracranial hemorrhage; among the patients who could be assessed, the median time to the cessation of bleeding was 2.5 hours. At 90 days, thrombotic events had occurred in 6.3% of the patients in group A and in 7.4% in group B, and the mortality rate was 18.8% and 18.9%, respectively. There were no serious adverse safety signals.	+ Well conducted, prospective observational study. Lack of a control group prevents any firm conclusions regarding haemostasis and clinical outcomes.
349	C. V. Pollack et al. (2017). Idarucizumab for dabigatran reversal	Multicentre, prospective, open-label study N=503 on Dabigatran	Idarucizumab.	Primary: Maximum % reversal of the anticoagulant effect of	Group A n=301 Group B n=202	+

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	-full cohort analysis. *New England Journal of Medicine,* 377:5 431-441	Group A: uncontrolled bleeding Group B: about to undergo an urgent procedure.		Dabigatran within 4 hrs of administration of idarucizumab (diluted thrombin time or escarin clotting time).	Group A: 45.5% GI bleeding, 32.6% intracranial haemorrhage. Primary: median max % reversal of dabigatran was 100%. Thrombotic events occurred in 6.3% in group A and 7.4% in group B.	
350	J. C. Purrucker et al. (2016). Early clinical and radiological course, management, and outcome of intracerebral hemorrhage related to neworal anticoagulants. *JAMA Neurology,* 73:2 169-177	Setting: multicentre at 38 stroke units in Germany. Design: Prospective observational cohort study Patients: 61 consecutive patients with nontraumatic. NOAC-associated ICH, of whom 45 (74%) qualified for the haematoma expansion analysis.	Intervention: PCC. Comparator: No PCC.	Outcome: text. Timepoint: text.	Overall, 57%(35 of 61) of the patients received prothrombin complex concentrate, with no statistically significant effect on the frequency of substantial hematoma expansion (43%[12 of 28] for prothrombin complex concentrate vs 29% [5 of 17] for no prothrombin complex concentrate, P = .53), or on the occurrence of an unfavorable outcome (modified Rankin Scale score, 3-6) (odds ratio, 1.20; 95%CI, 0.37-3.87; P = .76).	**+** Observational, not randomised.
350	J. C. Purrucker et al. (2016). Early clinical and radiological course, management, and outcome of intracerebral hemorrhage related to neworal anticoagulants. *JAMA*	Observational study, 38 stroke units in Germany, 2012-2014. 61 patients with non-traumatic NOAC-associated ICH of whom 45 qualified for haematoma expansion analysis.	N/A (usual care at discretion of physician).	Haematoma expansion, intraventricular haemorrhage, reversal in acute phase. Functional outcome (mRS) at 90 days.	35 (67%) received PCC but this was not associated with differences in haematoma expansion or functional outcomes (mRS 3-6).	**0** Potential for selection bias as not consecutive recruitment and missing data e.g. only 45 patients had serial imaging to detect haematoma expansion.

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	Neurology, 73:2 169-177					Study not designed or powered to test efficacy of PCC.