Integrating the latest evidence surrounding reversal agents for direct oral anticoagulants for patients experiencing intracerebral haemorrhage into clinical practice

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The impact of ICH in patients receiving DOACs

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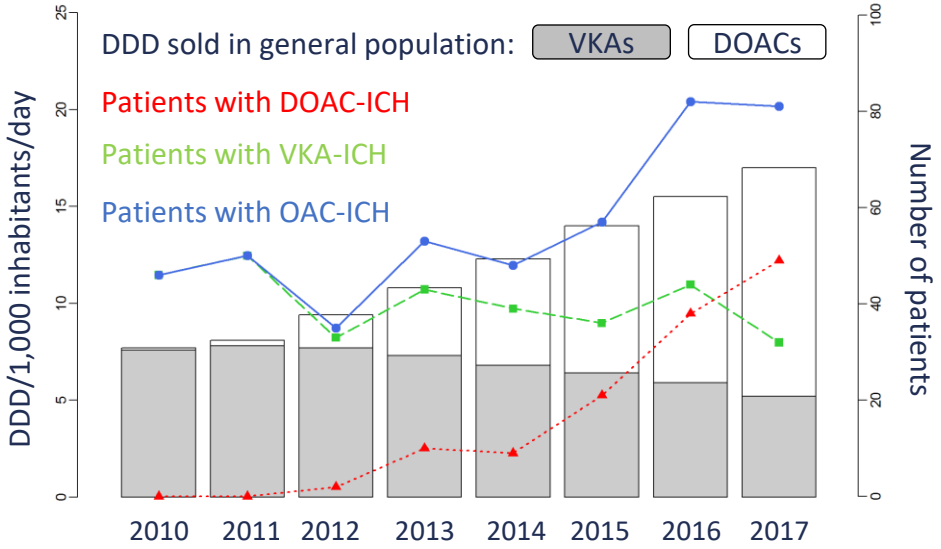
What is the burden of ICH in patients receiving DOACs?

Risk and impact on patients of DOAC-ICH

ICH association with anticoagulant drug use[1*]



30–90-day mortality rate:[2]

40–65%

Functional independence at 6 months:[3]

~20%

Increased use of DOACs, a potential widening of indications and ageing populations will most likely lead to a further increase of OAC-related ICH despite the relative risk reduction of ICH with DOACs[4]

*Analysis of 451 patients from the Capital Region Anticoagulation-related ICH study (COOL-ICH).

DDD, defined daily doses; DOAC, direct OAC; ICH, intracerebral haemorrhage; OAC, oral anticoagulant; VKA, vitamin K antagonist.

1. Grundtvig J, et al. *Eur Stroke J*. 2021;6:143–50; 2. Steiner T, et al. *Stroke*. 2017;48:1432–37; 3. Watson N, et al. *Front Aging Neurosci*. 2022;14:859067; 4. Christensen H, et al. *Eur Stroke J*. 2019;4:294–306.

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What are the barriers to improved clinical outcomes for patients with DOAC-ICH?

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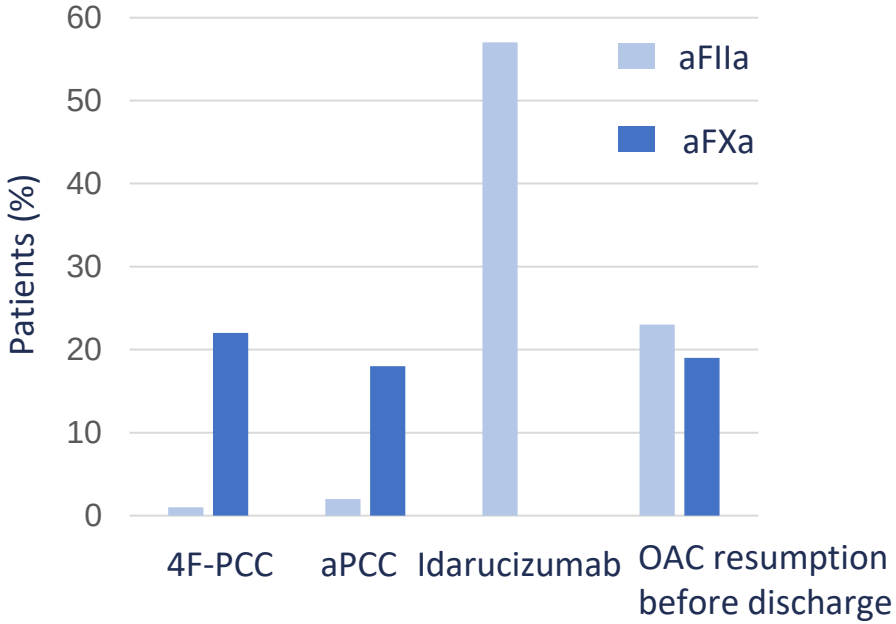
Clinical use of OAC reversal agents

Use of reversal agents in OAC-related acute haemorrhage[1]



Difference in use of pharmacological intervention between men and women following OAC-related ICH (adjusted odds ratio):[2]

0.52

(95% CI 0.32–0.84)

Use of OAC reversal agents in daily clinical practice is heterogeneous[1,2]

4F-PCC, 4-Factor PCC; aFIIa, anti-Factor IIa; aFXa, anti-Factor Xa; aPCC, activated PCC; CI, confidence interval; ICH, intracerebral haemorrhage; OAC, oral anticoagulant; PCC, prothrombin complex concentrate.

1. Pollack CV Jr, et al. *Am J Emerg Med.* 2020;38:1163–70; 2. Grundtvig J, et al. *Front Neurol*. 2022;13:832903.

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Can the functional outcomes of patients be predicted in the event of DOAC-ICH?

Improving the prognosis of DOAC-ICH

- Reversal may reduce haematoma expansion, which may be associated with a lower risk of death and probability of poor neurological outcomes[1]

- Non-contrast computed tomography predictors of haematoma expansion include blend sign, black hole sign, island sign, satellite sign and swirl sign[2]

- Blood pressure reduction and adequate stroke unit care are best practice and may reduce future disability[3]

The safety and outcome data of DOAC reversal agents in ICH are limited[4]

DOAC, direct oral anticoagulant; ICH, intracerebral haemorrhage.

1. Huttner HB, et al. *Stroke*. 2022;53:532–43; 2. Li Z, et al. *Front Neurol*. 2020;11:702; 3. Paroutoglou K, Parry-Jones AR. *Clin Med (Lond)*. 2018;18(Suppl. 2):s9–12;
4. Chaudhary R, et al. *JAMA Netw Open*. 2022;5:e2240145.

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Efficacy and safety data associated with reversal agents for treatment of DOAC-ICH

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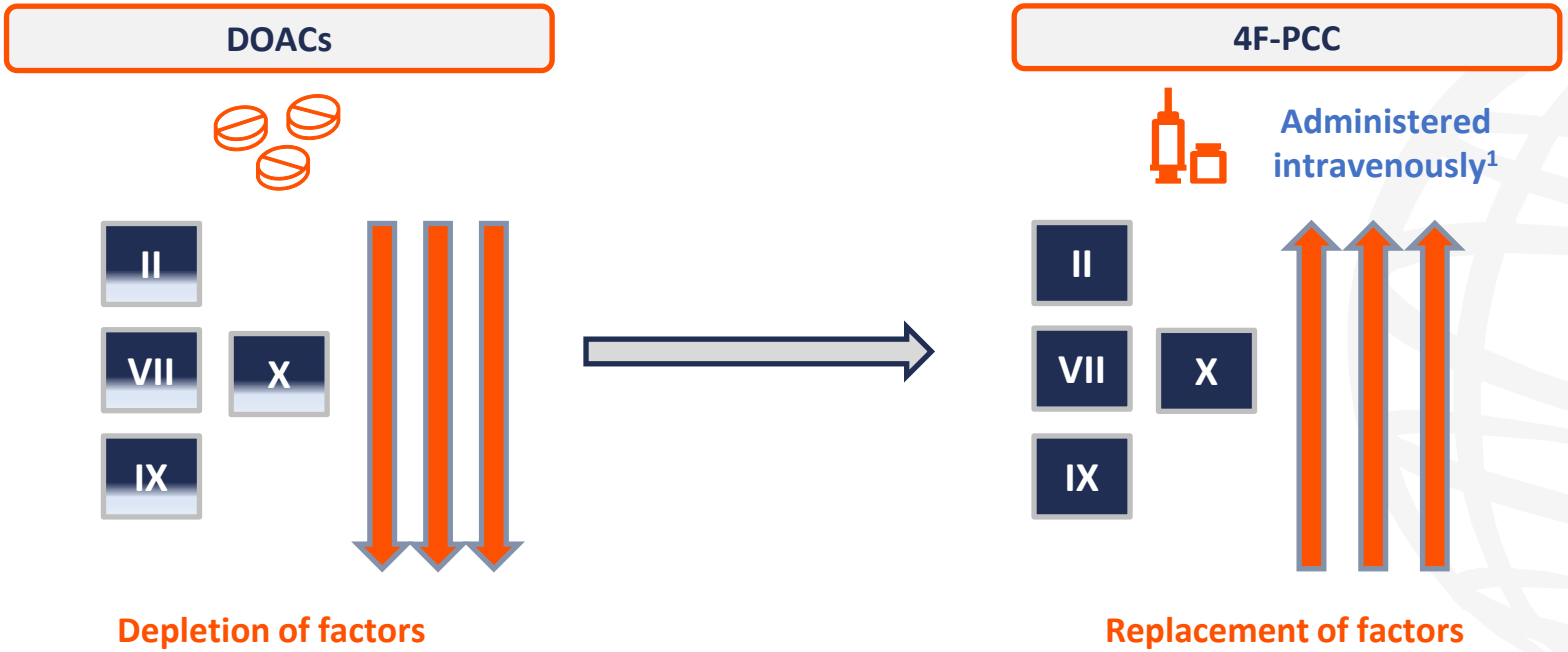
How have prothrombin complex concentrate strategies been used to manage DOAC-ICH?

Mechanism of action of 4F-PCC



4F-PCC (used off-label to manage DOAC-ICH) replaces depleted coagulation factors[2]

4F-PCC, four-factor prothrombin complex concentrate; DOAC, direct oral anticoagulant; ICH, intracranial haemorrhage.

1. FDA. Prothrombin complex concentrate PI. Available at: www.fda.gov/media/85512/download (accessed 11 July 2023); 2. Whaley PM, et al. *J Pharm Pract*. 2022:8971900221148034.

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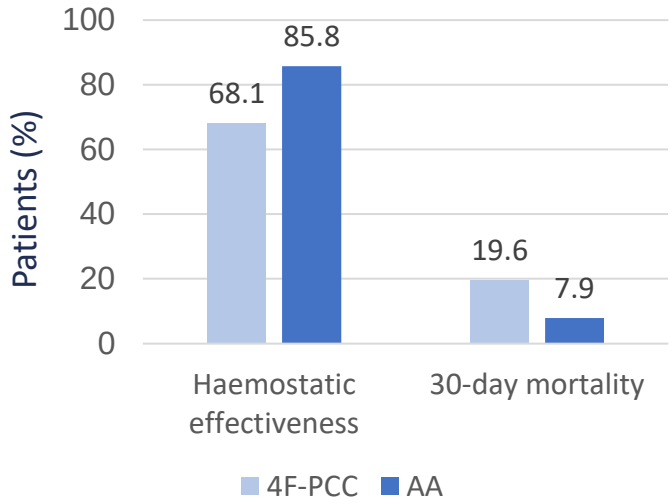
Trial evidence of 4F-PCC

Indirect comparison of haemostatic effectiveness and safety of 4F-PCC vs AA



- Retrospective study
- FXa inhibitor-associated ICH
- N=202 (4F-PCC: n=95; AA: n=107)

Haemostatic effectiveness (odds ratio):

2.73

30-day mortality (odds ratio):

0.36

4F-PCC is associated with a lower rate of haemostatic effectiveness and a higher rate of 30-day mortality compared with AA in patients with FXa inhibitor-associated ICH

4F-PCC, four-factor prothrombin complex concentrate; AA, andexanet alfa; FXa, Factor Xa; ICH, intracranial haemorrhage.

Costa OS, et al. *Crit Care*. 2022;26:180.

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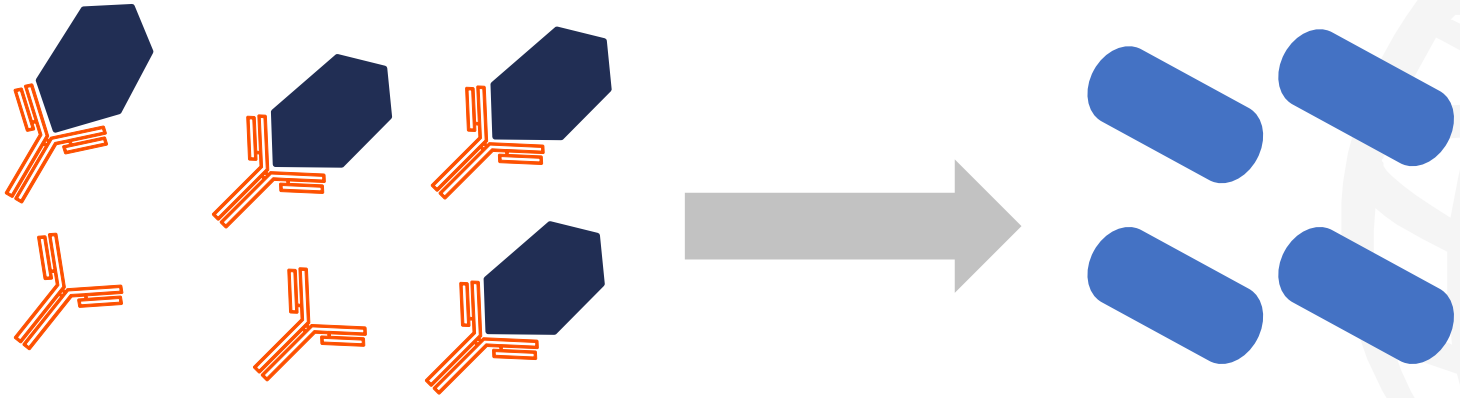
What reversal agents are available for Factor IIa inhibitor-induced ICH and what evidence informs clinicians of their use in this setting?

Mechanism of action of idarucizumab



Idarucizumab binds with dabigatran

Formation of fibrin

Idarucizumab binds with dabigatran with high affinity and specificity to reverse anticoagulant effects

Kermer P, et al. *Int J Stroke*. 2020;15:609–18.

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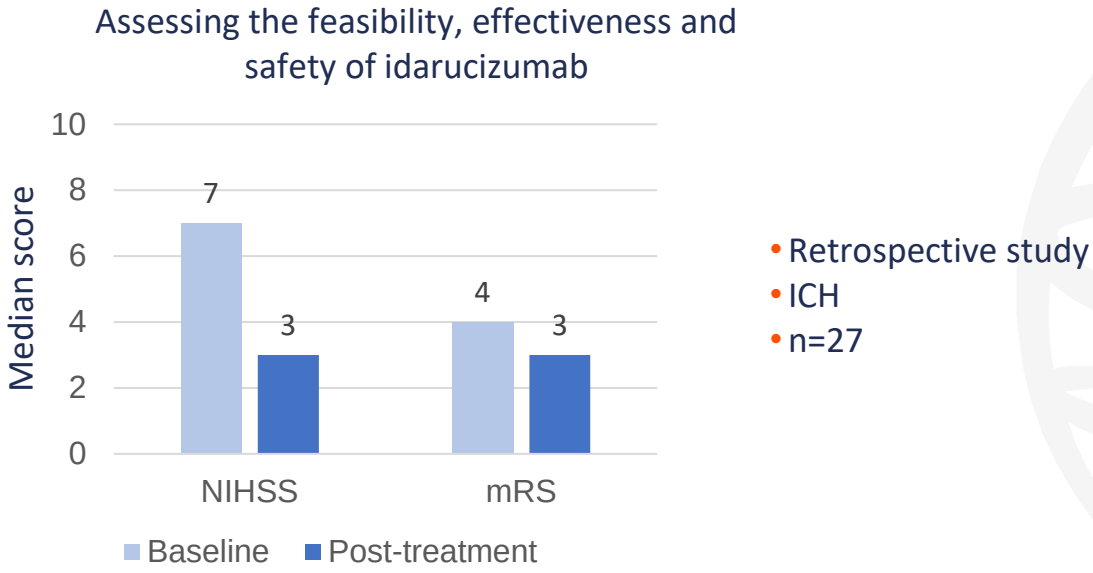
Trial evidence of idarucizumab in ICH



Idarucizumab is associated with improved outcomes and reduced risk of haematoma growth and mortality in patients with ICH

ICH, intracerebral haemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.
Kermer P, et al. *Int J Stroke*. 2020;15:609–18.

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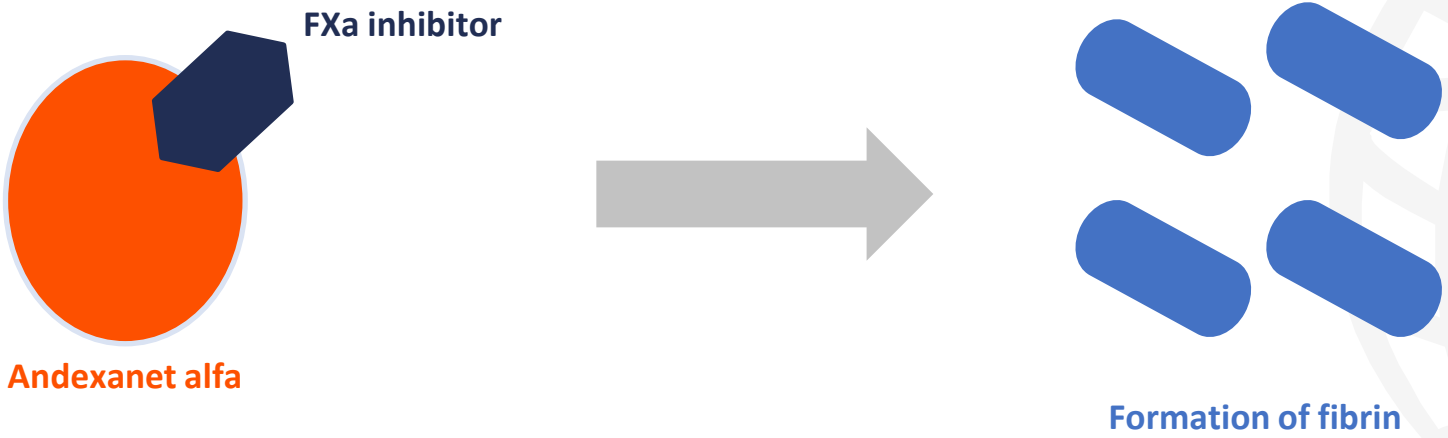
How should clinicians reverse ICH in patients who had received a Factor Xa inhibitor?

Mechanism of action of andexanet alfa



Andexanet alfa is administered intravenously and binds specifically with FXa inhibitors to reverse anticoagulant effects

FXa, Factor Xa.

Momin JH, et al. *P T*. 2019;44:530–49.

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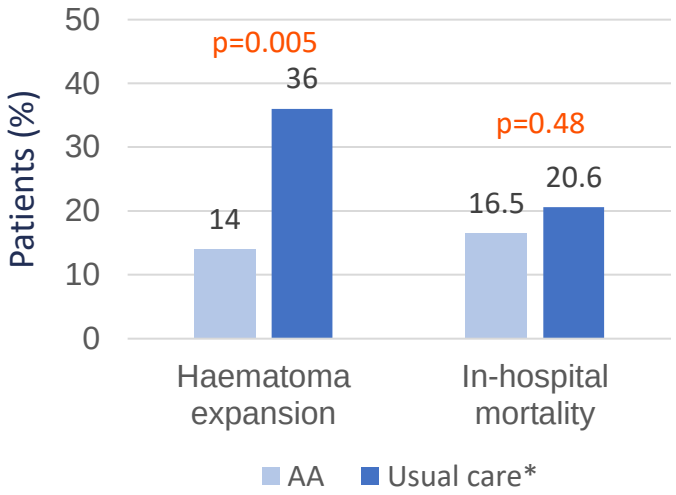
Trial evidence of andexanet alfa

Effectiveness and safety of AA vs usual care*



- Indirect comparative study of RETRACE-II cohort study vs post-hoc analysis of ANNEXA-4 clinical trial
- FXa inhibitor-related ICH
- N=182
  (AA: n=85; usual care: n=97)

AA was associated with a lower rate of both haematoma expansion and in-hospital mortality compared with usual care. However, the improvement in clinical outcomes was not significant

*Usual care was comprised of treatment according to the physician's discretion and haemostatic treatment based on available international guidelines during the RETRACE-II study period (2011–2015).
AA, andexanet alfa; FXa, Factor Xa; ICH, intracerebral haemorrhage.
Huttner HB, et al. *Stroke*. 2022;53:532–43.

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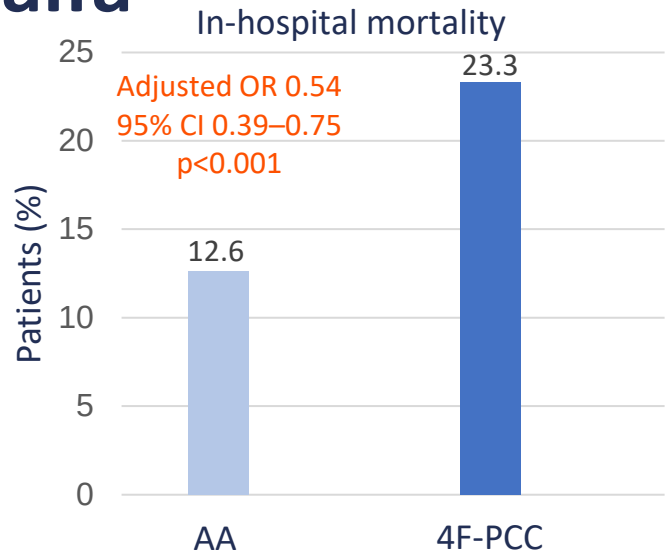
Real-world data exploring the use of andexanet alfa



- Comparison of in-hospital mortality in patients treated with andexanet alfa vs 4F-PCC
- FXa inhibitor-related ICH
- AA (n=666); 4F-PCC (n=662)

AA was associated with a 50% lower likelihood of in-hospital mortality compared with 4F-PCC in patients with rivaroxaban- or apixaban-associated major bleeds

4F-PCC, four-factor prothrombin complex concentrate; AA, andexanet alfa; CI, confidence interval; FXa, Factor Xa; ICH, intracerebral haemorrhage; OR, odds ratio.
Dobesh PP, et al. Presented at: ISTH 2023 Congress, Montreal, Canada. 24–28 June 2023. Abstr OC 31.2.

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What are the limitations of the current treatment options and unmet needs?

Improving treatment outcomes of patients receiving reversal agents for DOAC-ICH

- Individualization of the reversal strategy for DOAC-ICH should consider severity of ICH and time window for reversal

- More data from randomized clinical trials are needed to help determine optimal reversal strategies

It is challenging to determine the risk of haematoma expansion due to insufficient information from studies involving a heterogeneous cohort of patients with DOAC-ICH

DOAC, direct oral anticoagulant; ICH, intracerebral haemorrhage.

Chaudhary R, et al. *JAMA Netw Open*. 2022;5:e2240145.

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Optimizing haemostatic stabilization and subsequent health outcomes

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What are the guideline recommendations for the use of reversal agents in patients with DOAC-ICH?

Current guidelines on DOAC-ICH reversal agents

	ESO 2019[1]	ACC 2020[2]	AHA/ASA 2022[3]
AA	• Rivaroxaban and apixaban over no treatment (weak recommendation)	• Rivaroxaban and apixaban if critical site bleeding	• FXa inhibitors
Idarucizumab	• Dabigatran	• Dabigatran if life-threatening/ uncontrolled bleeding	• Direct thrombin inhibitors
PCC	• Edoxaban • Rivaroxaban and apixaban if AA not available	• May be used if specific inhibitors are not available*	• May be used if specific inhibitors are not available*

*Specific inhibitors include idarucizumab and andexanet alfa.

AA, andexanet alfa; ACC, American College of Cardiology; AHA, American Heart Association; ASA, American Stroke Association; DOAC, direct oral anticoagulant; ESO, European Stroke Organisation; FXa, Factor Xa; ICH, intracerebral haemorrhage; PCC, prothrombin complex concentrate.

1. Christensen H, et al. *Eur Stroke J*. 2019;4:294–306; 2. Tomaselli GF, et al. *J Am Coll Cardiol*. 2020;76:594–622; 3. Greenberg SM, et al. *Stroke*. 2022;53:e282–361.

What individual patient characteristics should clinicians consider when using reversal agents for the management of DOAC-ICH?

Key considerations for individualizing care

- ICH severity
- Immediate need for surgical decompression
- Creatinine clearance
- Anticipated risk of haematoma expansion
- Time since the last dose of DOAC
- Availability of specific DOAC reversal agents at the treating facility

Pragmatic patient selection is required for DOAC reversal following ICH and should be performed over a time window based on clinical presentation and rate of deterioration

DOAC, direct oral anticoagulant; ICH, intracerebral haemorrhage.

Chaudhary R, et al. *JAMA Netw Open*. 2022;5:e2240145.

How should the haemostatic effectiveness of the reversal agents be defined and measured in the clinic?

Haemostatic effectiveness criteria

ISTH SSC subcommittee on Control of Anticoagulation 2021

12 h

Haematoma stable or increased <35%

24 h

No deterioration of GOS-E or any validated scoring system

48 h

No need for further treatment with haemostatic agents*

48 h

No unscheduled (re-)interventions are needed for bleeding management

No invasive interventions/carried out without exceeding expected blood loss

No neurologic deterioration/ dysfunction at discharge

*Also includes coagulation factors or transfusion of blood products.

GOS-E, Extended Glasgow Outcome Scale; h, hours; ISTH, International Society on Thrombosis and Haemostasis; SSC, Scientific and Standardization Committee.

Khorsand N, et al. *J Thromb Haemost*. 2021;19:1112–5.

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When should treatment with DOACs be resumed following ICH?

Resumption of DOACs following ICH

In patients with spontaneous ICH and conditions placing them at high risk of thromboembolic events, early resumption of anticoagulation to prevent thromboembolic complications is reasonable

In patients with non-valvular AF and spontaneous ICH, the resumption of anticoagulation to prevent thromboembolic events and reduce all-cause mortality may be considered based on weighing benefit and risk

In patients with AF and spontaneous ICH in whom the decision is made to restart anticoagulation, initiation of anticoagulation ≈7–8 weeks after ICH may be considered after weighing specific patient characteristics to optimize the balance of risks and benefits

AF, atrial fibrillation; DOAC, direct oral anticoagulant; ICH, intracerebral haemorrhage.

Greenberg SM, et al. *Stroke*. 2022;53:e282–361.

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