

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



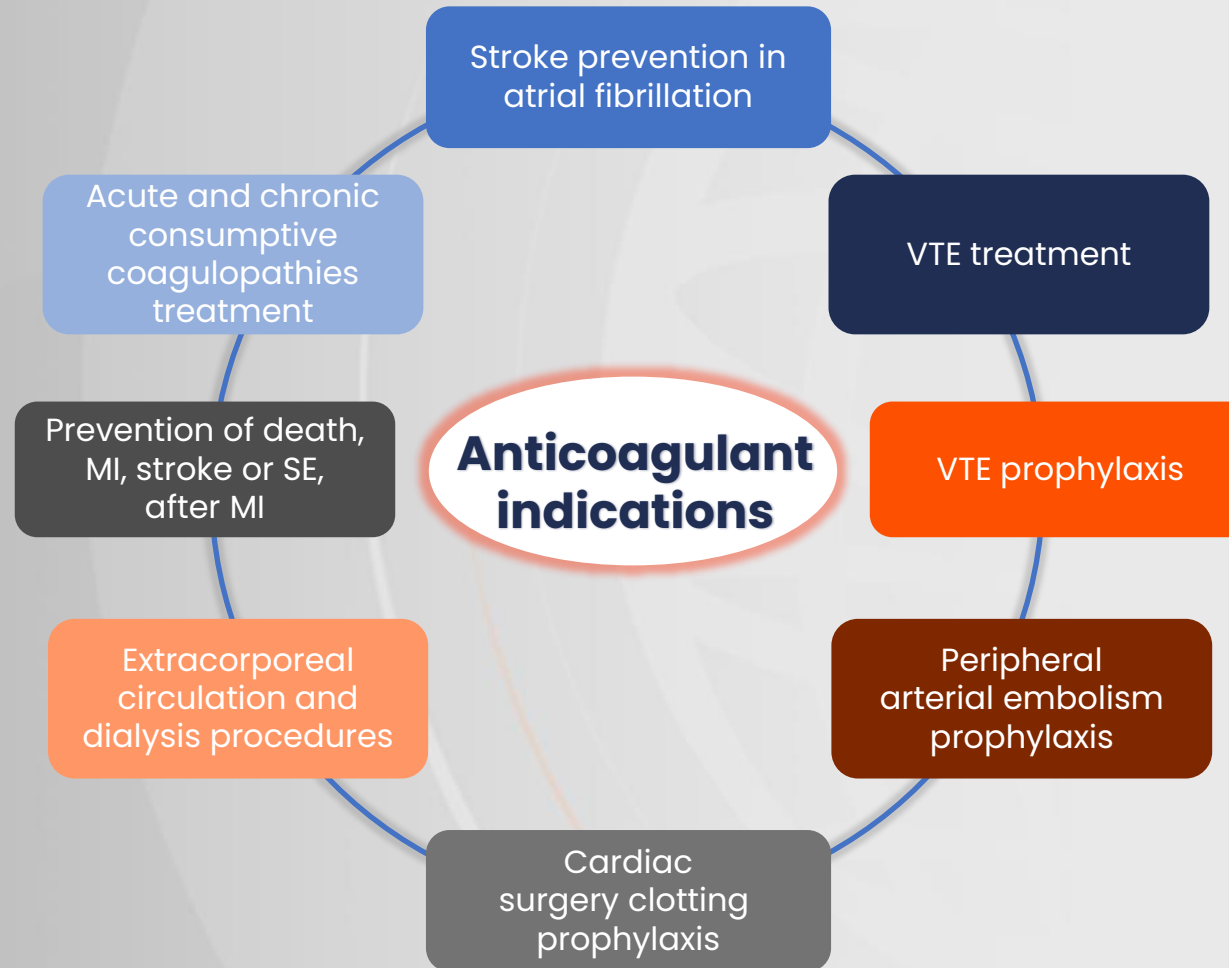
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University Hospital Carl Gustav Carus Dresden,  
Germany

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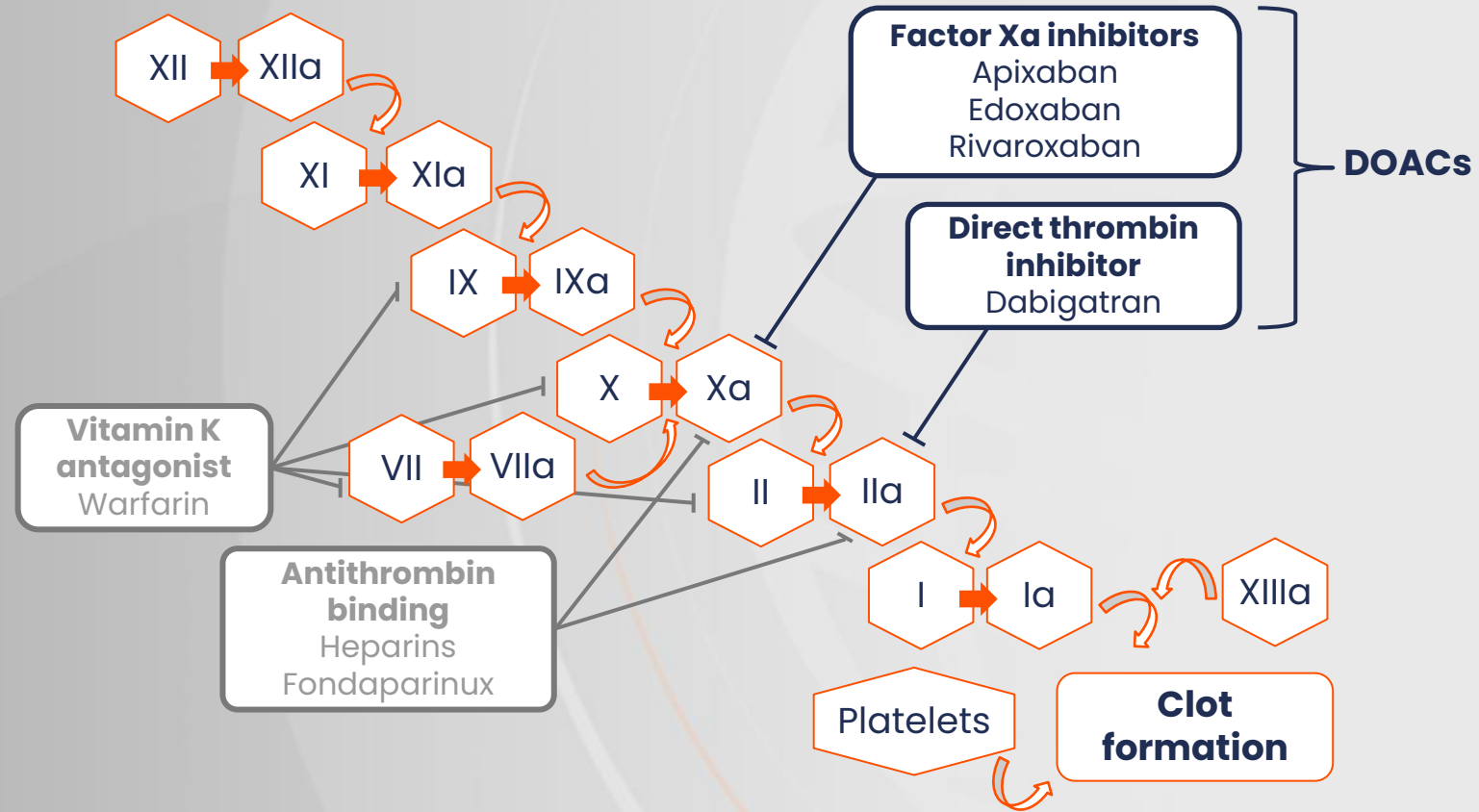
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# Balancing risk: DOACs in the real world

# Oral and parenteral anticoagulants have a range of indications



# Anticoagulants target various components of the coagulation cascade<sup>1,2</sup>

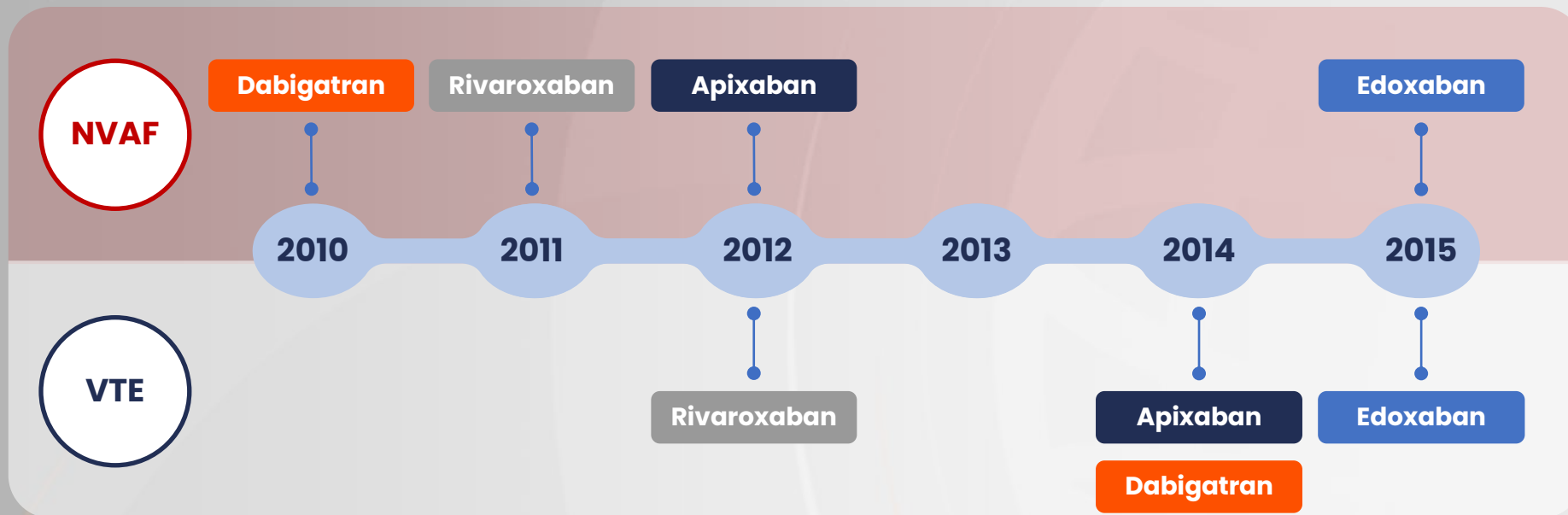


DOAC, direct oral anticoagulant.

1. Akhrass R, et al. *J Card Surg.* 2022;37:214–22; 2. Heestermans M, et al. *Cells.* 2022;11:3214.

# DOACs have been widely approved for multiple indications

## Timeline of key FDA approvals for DOAC indications<sup>1</sup>



### Other approved indications:<sup>2-4</sup>

- DVT prophylaxis after hip and/or knee surgery: apixaban, dabigatran, rivaroxaban
- CV risk reduction in patients with CAD: rivaroxaban
- Paediatric VTE treatment and secondary prophylaxis: dabigatran, rivaroxaban

CAD, coronary artery disease; CV, cardiovascular; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; FDA, US Food and Drug Administration; NVAF, non-valvular atrial fibrillation; VTE, venous thromboembolism.

1. Arora P, et al. *Res Social Adm Pharm*. 2023;19:1424–31; 2. FDA. Apixaban PI. 2021. Available at: [www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/202155s0341bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202155s0341bl.pdf) (accessed 3 May 2024); 3. FDA. Dabigatran PI. 2023. Available at: [www.accessdata.fda.gov/drugsatfda\\_docs/label/2023/022512s0471bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2023/022512s0471bl.pdf) (accessed 3 May 2024); 4. FDA. Rivaroxaban PI. 2023. Available at: [www.accessdata.fda.gov/drugsatfda\\_docs/label/2023/022406s0411bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2023/022406s0411bl.pdf) (accessed 3 May 2024).

# DOACs have a range of benefits compared with other anticoagulants

DOACs are more effective in reducing the risk of stroke/SEE, mortality and recurrent VTE vs VKA therapy

## AF population<sup>1</sup>

### Composite stroke/SEE\*

15%

N=77,011  
OR 0.85  
(95% CI 0.75–0.98)

### All-cause mortality\*

14%

N=77,011  
OR 0.86  
(95% CI 0.82–0.91)

## VTE population<sup>2</sup>

### Recurrent VTE or death\*\*

12%

N=22,040  
OR 0.88  
(95% CI 0.75–1.03)

## Practical advantages of DOACs over warfarin and other VKAs<sup>3</sup>



Fixed dosing



No need for routine anticoagulation-level monitoring



Rapid onset and short half-life



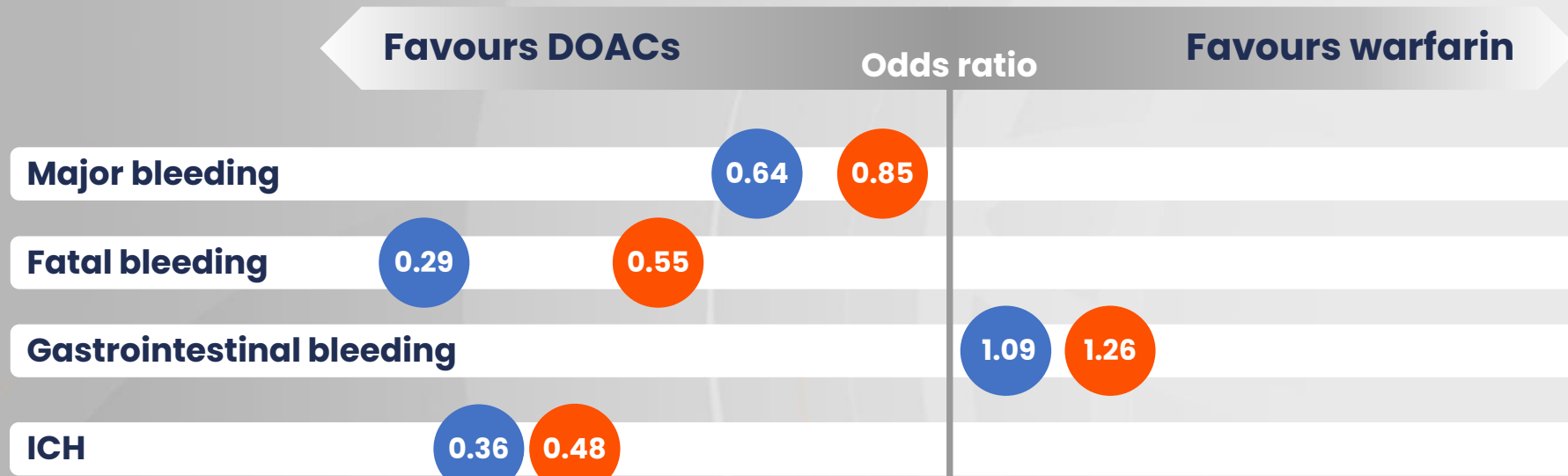
Fewer drug-drug and drug-food interactions

\*Meta-analysis data from 12 studies in patients with AF. \*\*Meta-analysis data from 5 studies in patients with acute VTE.

AF, atrial fibrillation; CI, confidence interval; DOAC, direct oral anticoagulant; OR, odds ratio; SEE, systemic embolic event; VKA, vitamin K antagonist; VTE, venous thromboembolism.

1. Hicks T, et al. *Open Heart*. 2016;3:e000279; 2. Makam RCP, et al. *PLoS One*. 2018;13:e0197583; 3. Julia S, James U. *Eur Cardiol*. 2017;12:40–5.

# Bleeding rates with DOACs are generally lower than with warfarin



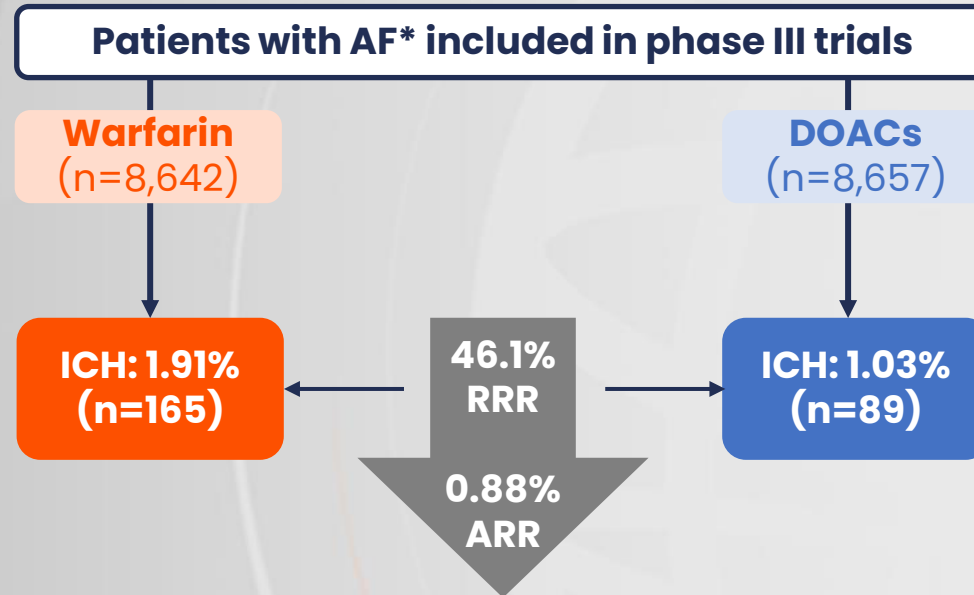
● Patients with VTE in clinical trials (N=22,040)

● Patients with AF in clinical trials (N=58,271)



# ICH is an important complication in patients treated with DOACs

DOACs are associated with a lower incidence of ICH vs warfarin<sup>1</sup>



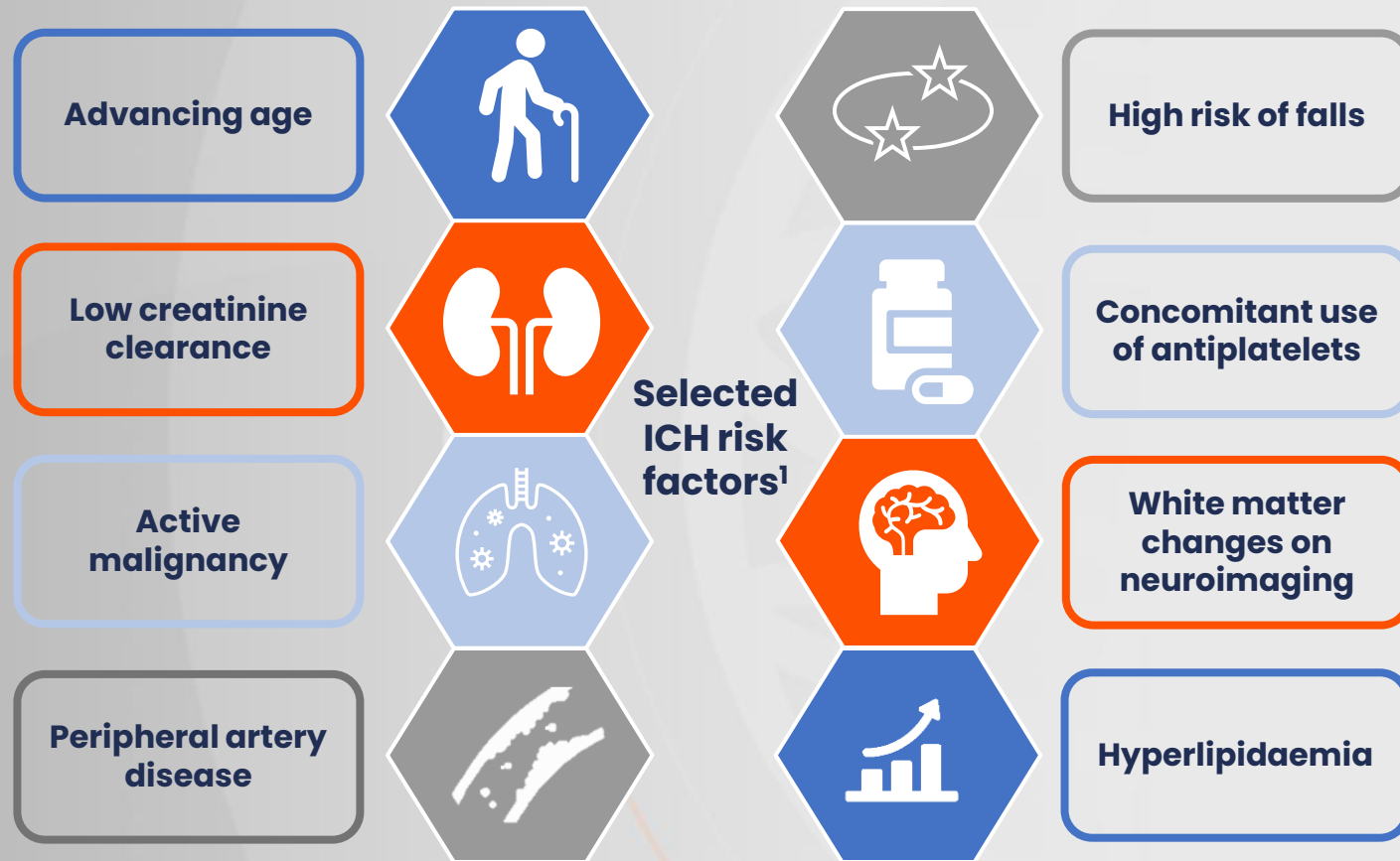
- Although the risk of ICH is lower with DOACs compared with warfarin therapy,<sup>2</sup> this remains an important potential complication
- Incidence of ICH is likely to increase given the rise in use of DOACs and the ageing population<sup>3</sup>

\*Patients with AF and a history of stroke/transient ischaemic attack.

AF, atrial fibrillation; ARR, absolute risk reduction; DOAC, direct oral anticoagulant; ICH, intracranial haemorrhage; RRR, relative risk reduction.

1. Ntaios G, et al. *Int J Stroke*. 2017;12:589–96; 2. Wolfe Z, et al. *J Thromb Haemost*. 2018;16:1296–306; 3. Christensen H, et al. *Eur Stroke J*. 2019;4:294–306.

# Several factors predict ICH risk in patients treated with DOACs

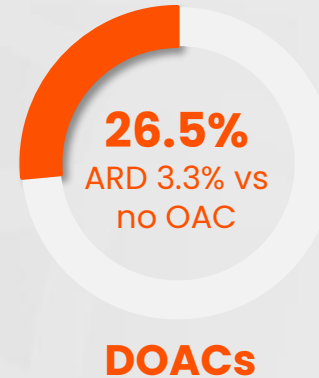
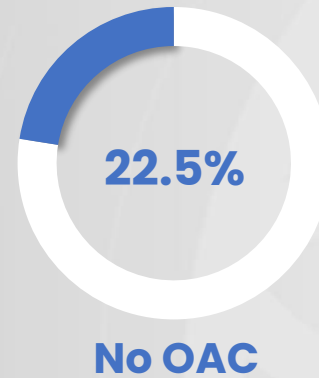


- Tools such as the HAS-BLED bleeding risk assessment evaluate some of these risk factors and may have value in predicting ICH risk<sup>2</sup>

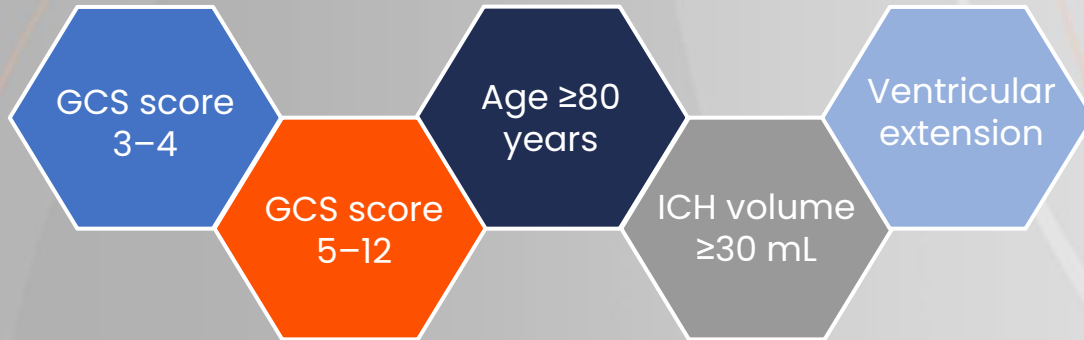
# Risk factors should be considered to reduce DOAC-ICH mortality

## In-hospital mortality following ICH is lower with DOACs vs warfarin but remains high<sup>1</sup>

- Registry-based retrospective cohort study
- Patients presenting with ICH (N=141,311)
- Analysis based on exposure to OACs within 7 days prior to presentation

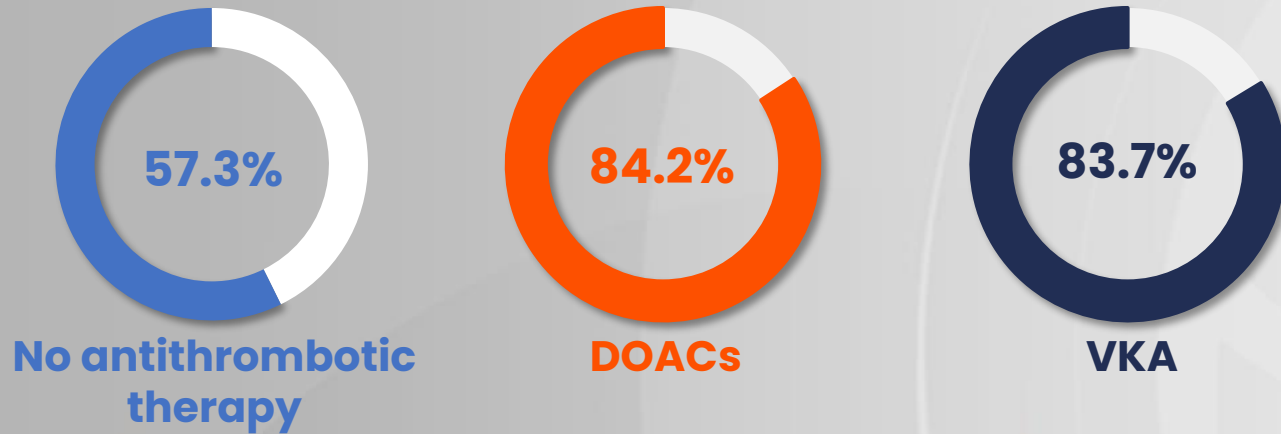


## Risk factors for 30-day mortality in patients with ICH using OACs have been identified<sup>2</sup>

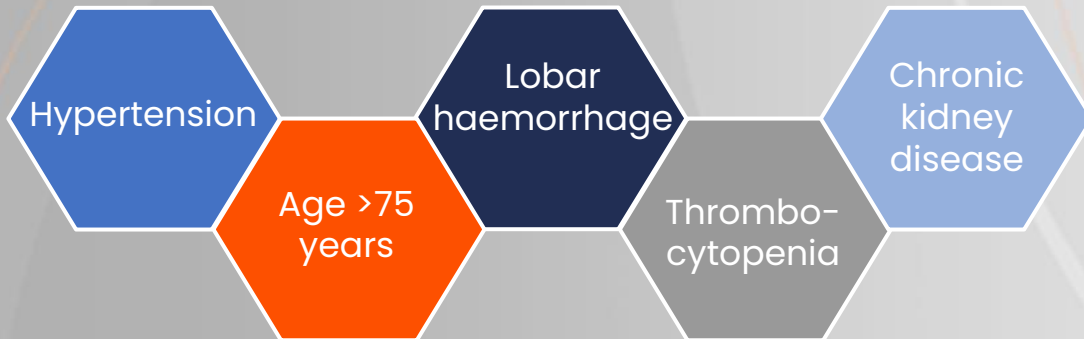


# Risk factors should be considered to reduce morbidity in DOAC-ICH

Proportion of patients with poor functional outcomes following ICH, by anticoagulant status (N=916)<sup>1\*</sup>



Risk factors for recurrence of ICH have been identified, including:<sup>2</sup>



\*Poor functional outcomes were defined as modified Rankin scale score 4–6<sup>1</sup> (moderately severe disability or greater, including death).

DOAC, direct oral anticoagulant; ICH, intracranial haemorrhage; VKA, vitamin K antagonist.

1. Baharoglu MI, et al. *Front Neurol.* 2021;12:684476; 2. Grainger BT, et al. *J Thromb Haemost.* 2024;22:594–603.

# **Evidence for DOAC reversal agents for the management of ICH**

# Case study in DOAC-ICH



- A 76-year-old man presents to the ED at 8 am with **suspected ischaemic stroke**, having **developed symptoms in the last 2.5 hours**. He was well and without symptoms the evening before
- He has a **history of AF** and **blood pressure upon arrival is 190/120 mmHg**



His wife explained to the paramedic that he is taking a **twice-daily anticoagulant tablet**; she is **not sure which one** and **he has not taken his morning dose**



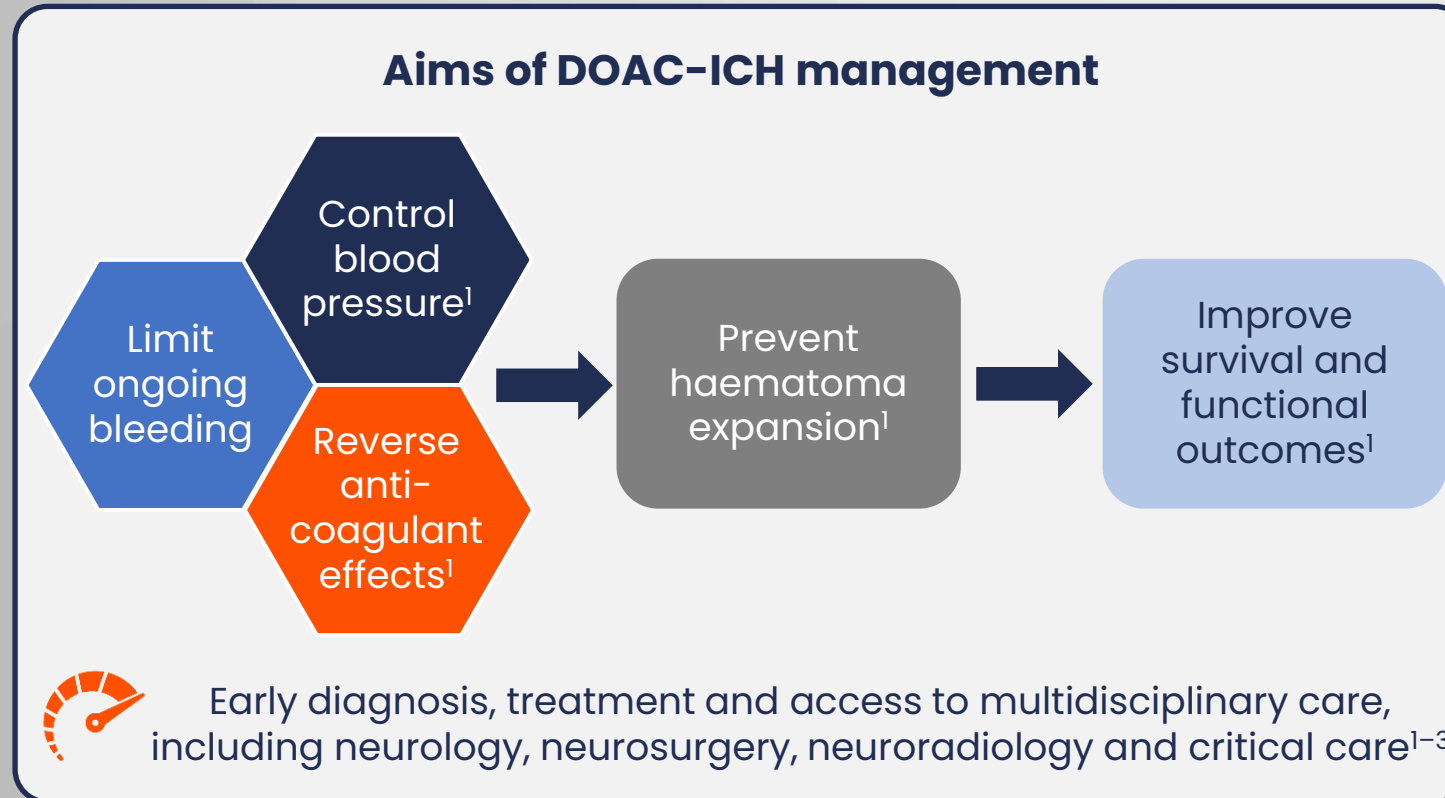
What next steps should the ED physician take?



## Consider the following:

- Lower blood pressure
- Verify anticoagulant taken
- CT scan
- Establish ischaemic vs haemorrhagic stroke

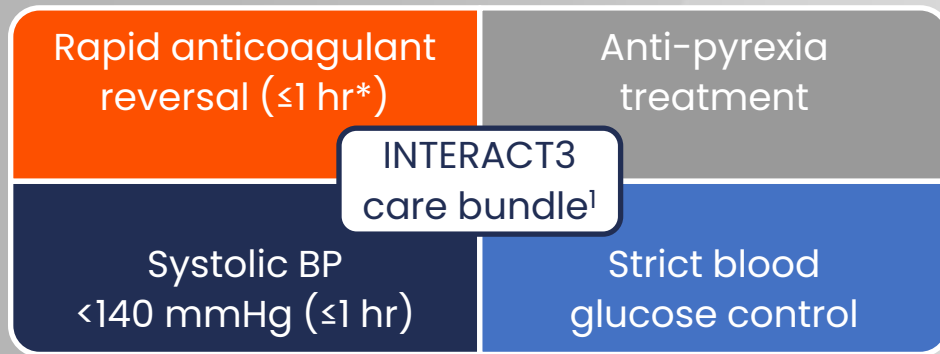
# A rapid response and early targeted therapy are crucial in DOAC-ICH



- Delays in identification and management of ICH are associated with poor prognosis<sup>4</sup>

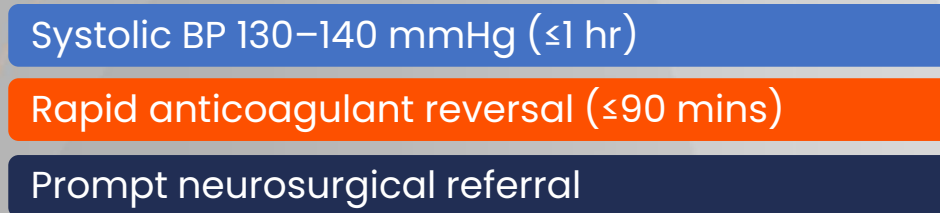
# Care bundles can reduce morbidity and mortality in DOAC-ICH

Care bundles combining treatment strategies can improve outcomes in ICH<sup>1,2</sup>



In a RCT that included **6,255 patients with ICH** in 121 hospitals, use of the **INTERACT3 care bundle** vs usual care led to a **14% reduction in poor functional outcomes** ( $p=0.015$ )<sup>1</sup>

ABC-ICH care bundle<sup>2</sup>



Implementation of **ABC-ICH** in **patients with ICH** led to a **38% reduction in 30-day mortality** vs pre-implementation levels ( $p=0.03$ )<sup>†2</sup>

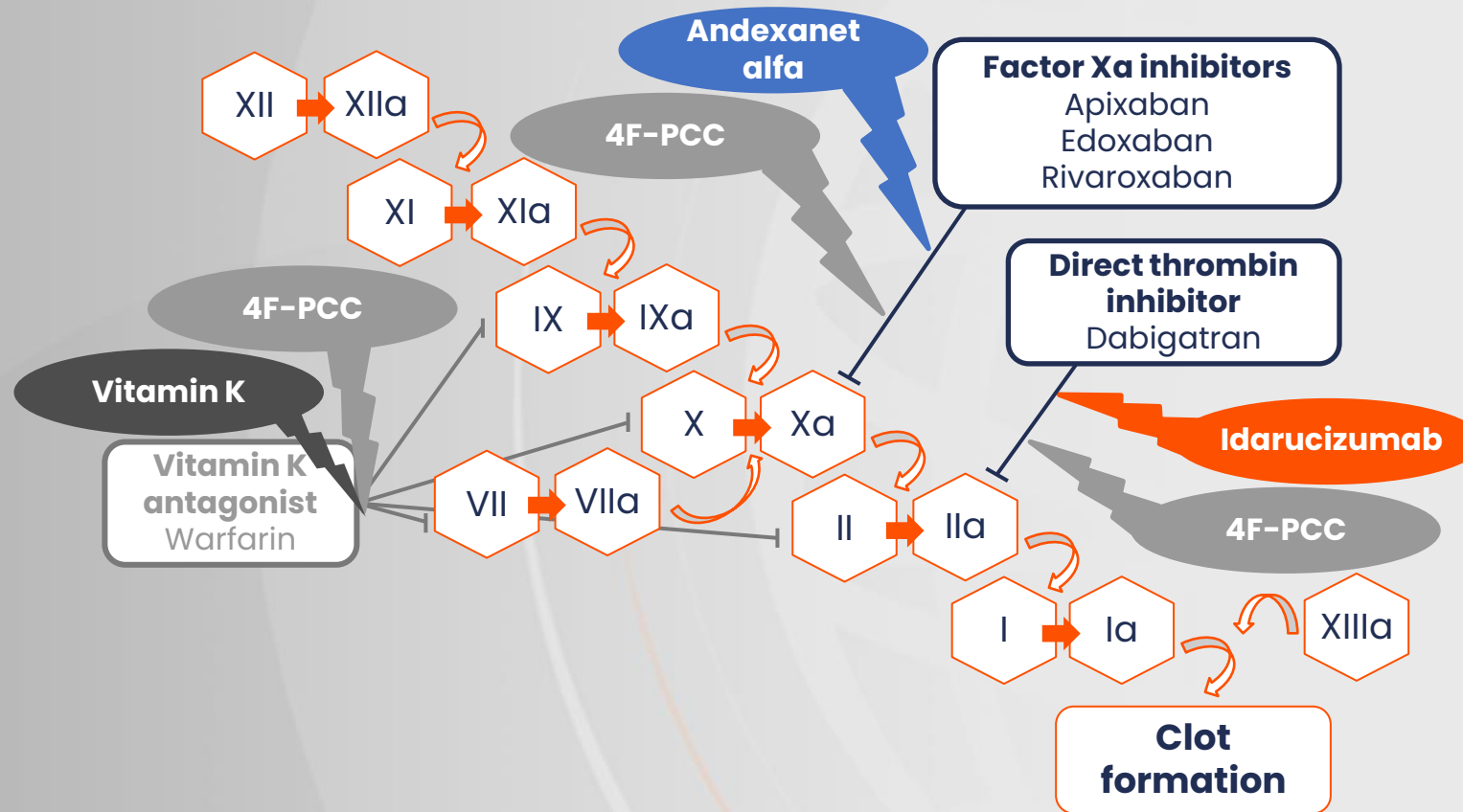
\*Target INR <1.5. †266 patients in the group admitted to hospital during the ABC-ICH implementation period; 353 patients in the group admitted before implementation.

BP, blood pressure; DOAC, direct oral anticoagulant; hr, hour; ICH, intracranial haemorrhage; INR, international normalized ratio; RCT, randomized controlled trial.

1. Ma L, et al. *Lancet*. 2023;402:27–40; 2. Parry-Jones AR, et al. *Ann Neurol*. 2019;86:495–503.



# Reversal agents have been developed that target oral anticoagulants



# DOAC-ICH reversal agents show unique characteristics

	PCC	Idarucizumab	Andexanet alfa
<b>DOACs targeted<sup>1,2</sup></b>	Non-specific	Dabigatran	Apixaban Rivaroxaban Edoxaban*
<b>Approval status<sup>1</sup> (DOAC related)</b>	Not approved for DOAC reversal	Approved	Approved*
<b>Indications</b>	Life-threatening or uncontrolled bleeding (if specific reversal agents are not available) <sup>1,3</sup>	Life-threatening or uncontrolled bleeding; emergency surgery or urgent procedures <sup>4</sup>	Life-threatening or uncontrolled bleeding <sup>5</sup>
<b>Mechanism of action</b>	Non-specific; raises factor levels and 'overwhelms' DOAC <sup>1,2</sup>	Rapid, specific binding to dabigatran (<5 mins) <sup>2,6</sup>	Rapid, specific binding to factor Xa inhibitors (2-5 mins) <sup>2,7</sup>
<b>Terminal half-life<sup>2</sup></b>	Elevated clotting factors likely persist for at least 24 hr	4-8 hr	5-7 hr
<b>Contraindications</b>	Refer to local summary of product characteristics/prescribing information		

\*Andexanet alfa is not approved for edoxaban-treated patients outside of Japan.<sup>5,8,9</sup> DOAC, direct oral anticoagulant; FDA, US Food and Drug Administration; hr, hour; ICH, intracranial haemorrhage; PCC, prothrombin complex concentrate. 1. White K, et al. *Br J Cardiol*. 2022;29:1; 2. Cuker A, et al. *Am J Hematol*. 2019;94:697-709; 3. Hoffman M, et al. *Int J Emerg Med*. 2018;11:55; 4. FDA. Idarucizumab PI. 2015. Available at: [www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/7610251bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/7610251bl.pdf) (accessed 16 May 2024); 5. FDA. Coagulation factor Xa (recombinant) PI. 2024. Available at: [www.fda.gov/media/113279/download](http://www.fda.gov/media/113279/download) (accessed 16 May 2024); 6. Schiele F, et al. *Blood*. 2013;121:3554-62; 7. Heo YA. *Drugs Ther Perspect*. 2018;34:507-12; 8. Yajima T, et al. *Nihon Yakurigaku Zasshi*. 2023;158:89-100; 9. EMA. Andexanet alfa SmPC. 2023. Available at: <https://bit.ly/3WFrRjH> (accessed 16 May 2024).

# Meta-analysis data support use of PCCs in managing DOAC-ICH

## Meta-analysis of studies in 967 adults with DOAC-ICH



23 studies (21 retrospective, 2 prospective)



4F-PCC

77%

**Anticoagulation reversal rate**

# Idarucizumab effectively reverses dabigatran anticoagulation

## RE-VERSE AD trial<sup>1</sup>

### Multicentre, prospective, open-label study



- Patients on dabigatran with uncontrolled bleeding (n=301), or due an urgent procedure (n=202)
- In those with **uncontrolled bleeding, 33% presented with DOAC-ICH**

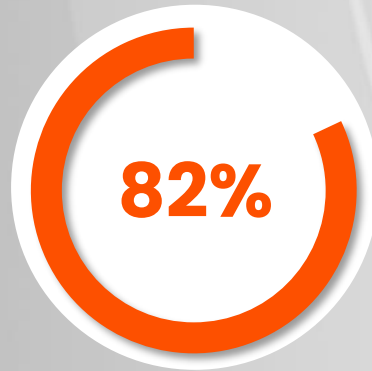


Idarucizumab 5 g IV



**100%** Median maximum percentage reversal of dabigatran within 4 hr\*

## Meta-analysis data in 340 patients with DOAC-ICH<sup>2</sup>



**Anticoagulation reversal rate**

\*Result for the 461 patients included in the primary efficacy analysis.

DOAC, direct oral anticoagulant; hr, hours; ICH, intracranial haemorrhage; IV, intravenous.

1. Pollack CV Jr, et al. *N Engl J Med.* 2017;377:431-41; 2. Chaudhary R, et al. *JAMA Netw Open.* 2022;5:e2240145.

# Andexanet alfa effectively reverses FXa inhibitor anticoagulation

## ANNEXA-4 trial<sup>1</sup>

### Multicentre, prospective, phase IIIb/IV cohort study



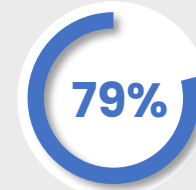
Patients with acute major bleeding within 18 hr of FXa inhibitor administration (n=349\*)



Low- or high-dose andexanet alfa



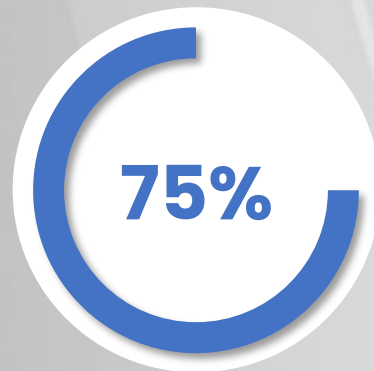
### ICH cohort (n=246)



Anticoagulation reversal rate

**ANNEXA-I trial** data support these findings in DOAC-ICH; at prespecified interim analysis after 450 patients had been randomized, the DSMB recommended termination of the study for superior efficacy<sup>2</sup>

## Meta-analysis data in 525 patients with DOAC-ICH<sup>3</sup>



Anticoagulation reversal rate

\*Efficacy population.

DOAC, direct oral anticoagulant; DSMB, Data and Safety Monitoring Board; FXa, factor Xa; hr, hours; ICH, intracranial haemorrhage.

1. Milling TJ Jr, et al. *Circulation*. 2023;147:1026-38; 2. Connolly S. *Int J Stroke*. 2023;18(Suppl. 3):422. LBO004/#2806; 3. Chaudhary R, et al. *JAMA Netw Open*. 2022;5:e2240145.

# Adverse events should be considered with DOAC-ICH reversal agents

## Meta-analysis data: All-cause mortality and TE events<sup>1\*</sup>



## Serious adverse events include:

**4F-PCC<sup>2</sup>**  
Stroke, DVT, thrombosis, venous insufficiency

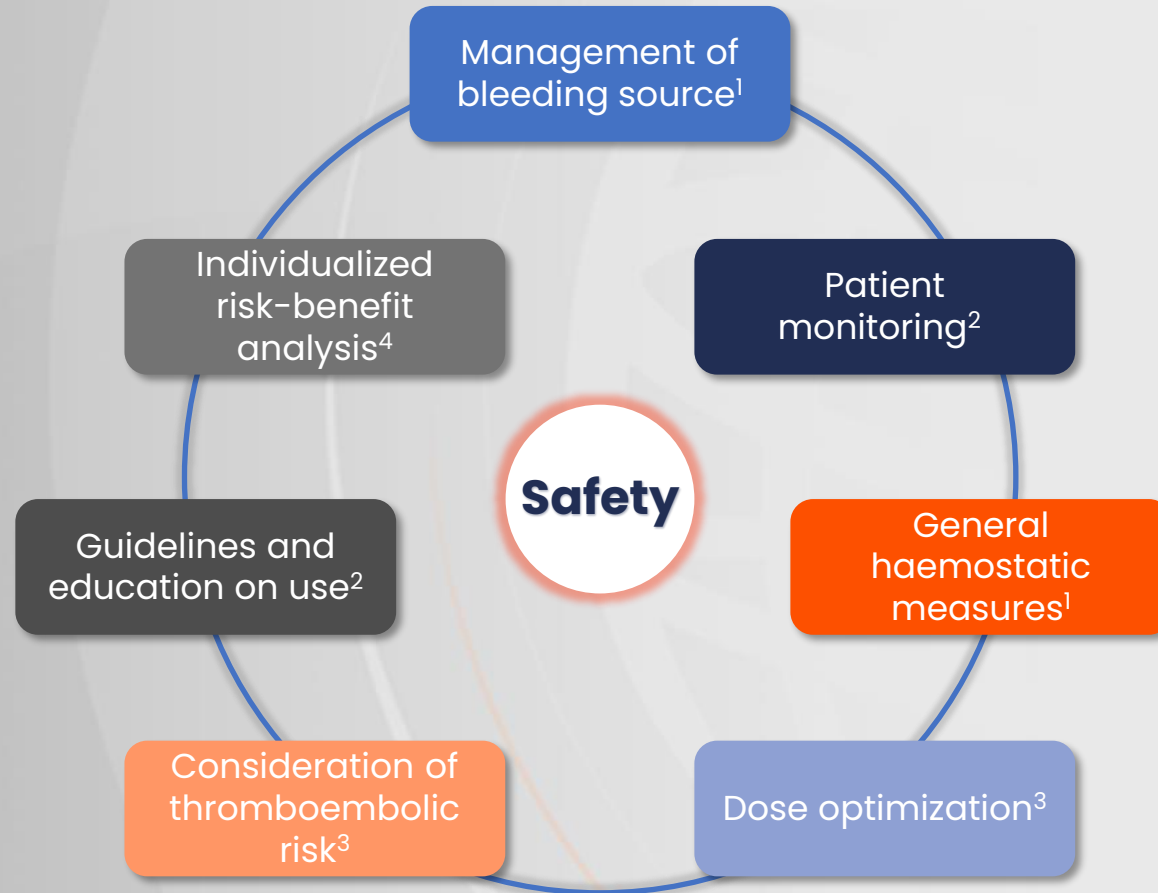
**Andexanet alfa<sup>3</sup>**  
Thromboembolic events, ischaemic events, cardiac arrest, sudden death

**Idarucizumab<sup>4</sup>**  
Delirium, cardiac arrest, sepsis, septic shock

\*Data based on meta-analysis, using different timeframes for outcome assessments; comparisons between agents are indirect and may be prone to bias due to differences in study designs and populations. 4F-PCC, four-factor prothrombin complex concentrate; DOAC, direct oral anticoagulant; DVT, deep-vein thrombosis; ICH, intracranial haemorrhage; pts, patients; TE, thromboembolic.

1. Chaudhary R, et al. *JAMA Netw Open*. 2022;5:e2240145; 2. FDA. Prothrombin complex concentrate (human) PI. 2023. Available at: [www.fda.gov/media/85512/download](http://www.fda.gov/media/85512/download) (accessed 7 April 2024); 3. Heo YA. *Drugs Ther Perspect*. 2018;34:507-12; 4. Pollack CV Jr, et al. *N Engl J Med*. 2017;377:431-41.

# Multiple factors influence the safe and effective use of DOAC reversal agents



DOAC, direct oral anticoagulant.

1. White K, et al. *Br J Cardiol.* 2022;29:1; 2. Cuker A, et al. *Am J Hematol.* 2019;94:697–709; 3. Greenberg SM, et al. *Stroke.* 2022;53:e282–361;

4. Milling TJ, Pollack CV. *Am J Emerg Med.* 2020;38:1890–903.

# Multiple factors influence the safe and effective use of DOAC reversal agents

- Patients experiencing DOAC-associated bleeding are also at **increased risk** of developing **subsequent thrombotic events**, with those experiencing ICH being most at risk<sup>1</sup>
- Reversing DOAC therapy exposes patients to the **thrombotic risk of their underlying disease**<sup>1-3</sup>



There is a need to implement strategies to reduce risk and identify patients at greatest risk of thromboembolism<sup>4</sup>

Consideration of thromboembolic risk<sup>3</sup>

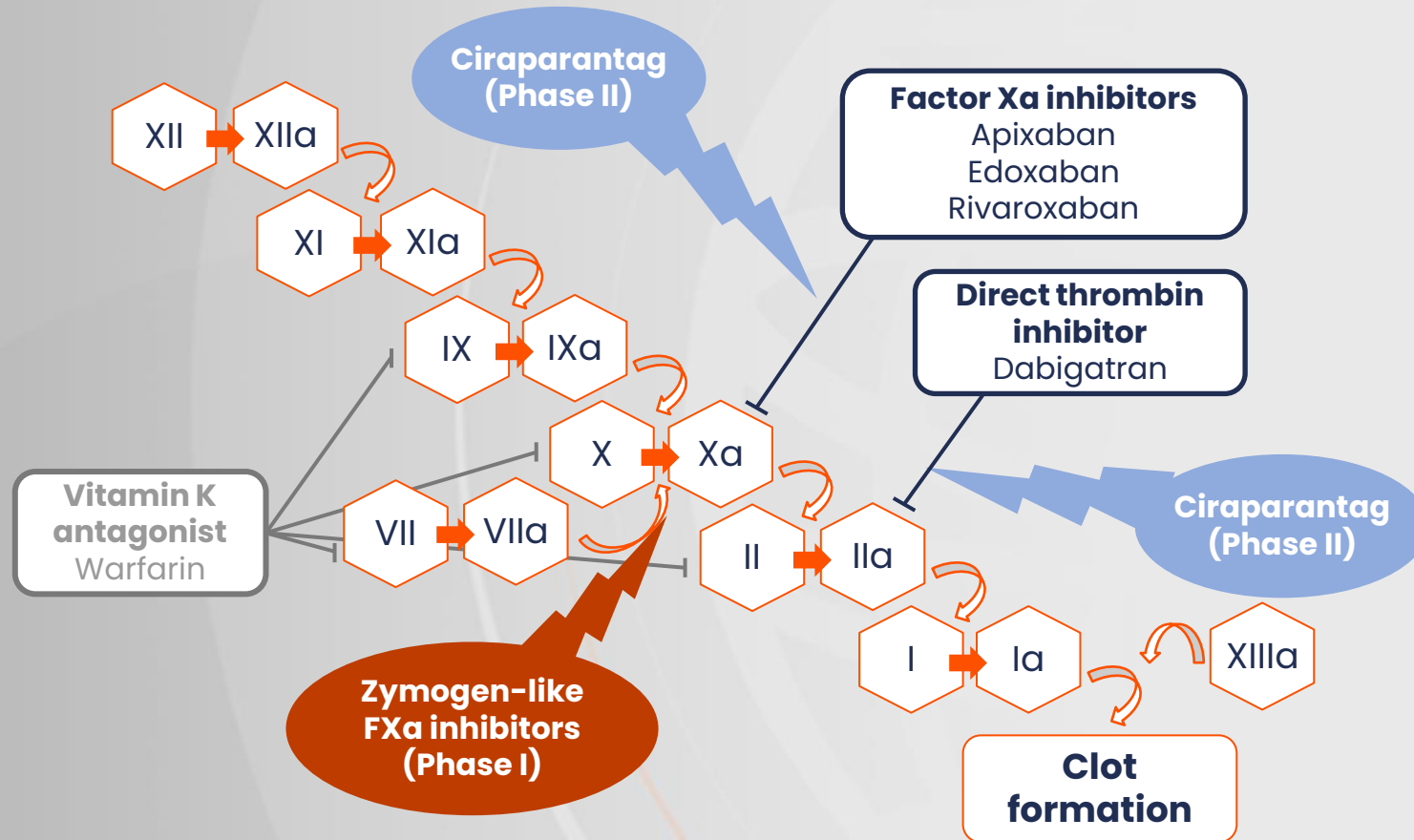
DOAC, direct oral anticoagulant; ICH, intracranial haemorrhage.

1. White K, et al. *Br J Cardiol.* 2022;29:1; 2. FDA. Coagulation factor Xa (recombinant) PI. 2024. Available at: [www.fda.gov/media/113279/download](http://www.fda.gov/media/113279/download) (accessed 13 May 2024);

3. FDA. Idarucizumab PI. 2015. Available at: [www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/761025lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761025lbl.pdf) (accessed 16 May 2024); 4. Greenberg SM, et al. *Stroke.* 2022;53:e282-361.



# Emerging reversal agents are in clinical development<sup>1,2</sup>



FXa, factor Xa.

1. van Es N, et al. *Eur Heart J.* 2023;44:1795–806; 2. ClinicalTrials.gov. Available at: [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (accessed 14 May 2024).

# Trials are ongoing with current and new DOAC reversal agents

## Currently used agents



### 4F-PCC

- Evaluation in DOAC-ICH (NCT06096051)
- Phase III trial of low- and high-doses in patients with acute major bleeding on DOAC therapy (NCT04867837)

### Andexanet alfa

- ASTRO-DE: Non-interventional study of impact on ICH volume in patients taking apixaban or rivaroxaban (NCT05127941)
- Retrospective, real-world study of outcomes in hospitalized patients (NCT05898412)

### Idarucizumab

- No ongoing trials identified

## Emerging agents



### Ciraparantag

- Phase I/II data demonstrate restoration of coagulation in DOAC-treated healthy volunteers<sup>1,2</sup>
- Well tolerated in healthy elderly subjects<sup>2</sup>
- Phase II trial ongoing in healthy adults (NCT04593784)

### Others

- Most are in early clinical development<sup>3</sup>
- Data needed in DOAC reversal contexts

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

Trial information by NCT identifiers available at: [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (accessed 7 May 2024).

1. Ansell JE, *N Engl J Med.* 2014;371:2141–2; 2. Ansell J, et al. *Eur Heart J.* 2022;43:985–92; 3. van Es N, et al. *Eur Heart J.* 2023;44:1795–806.

**Managing DOAC-ICH:  
What do the guidelines say?**

# Guidelines on DOAC-ICH are diverse and potentially outdated

## ASA/AHA 2022<sup>1</sup>

### USA focus

Recommendations on the management of patients with spontaneous ICH

## APSC 2021<sup>2</sup>

### Asia-Pacific focus

Consensus recommendations on thrombotic and bleeding risk management in patients with AF on DOACs

## ACC 2020<sup>3</sup>

### USA focus

Expert consensus decision pathway on management of bleeding in patients on oral anticoagulants

## ESO 2019<sup>4</sup>

### European focus

Recommendations on reversal of VKA and DOACs in patients with acute ICH

## Guidelines from other regions and organizations are available, but are potentially outdated or lack a focus on DOAC-ICH:

- Japanese Circulation Society (2020)<sup>5</sup>
- National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (2018)<sup>6</sup>
- Brazilian Society of Cardiology (2016)<sup>7</sup>

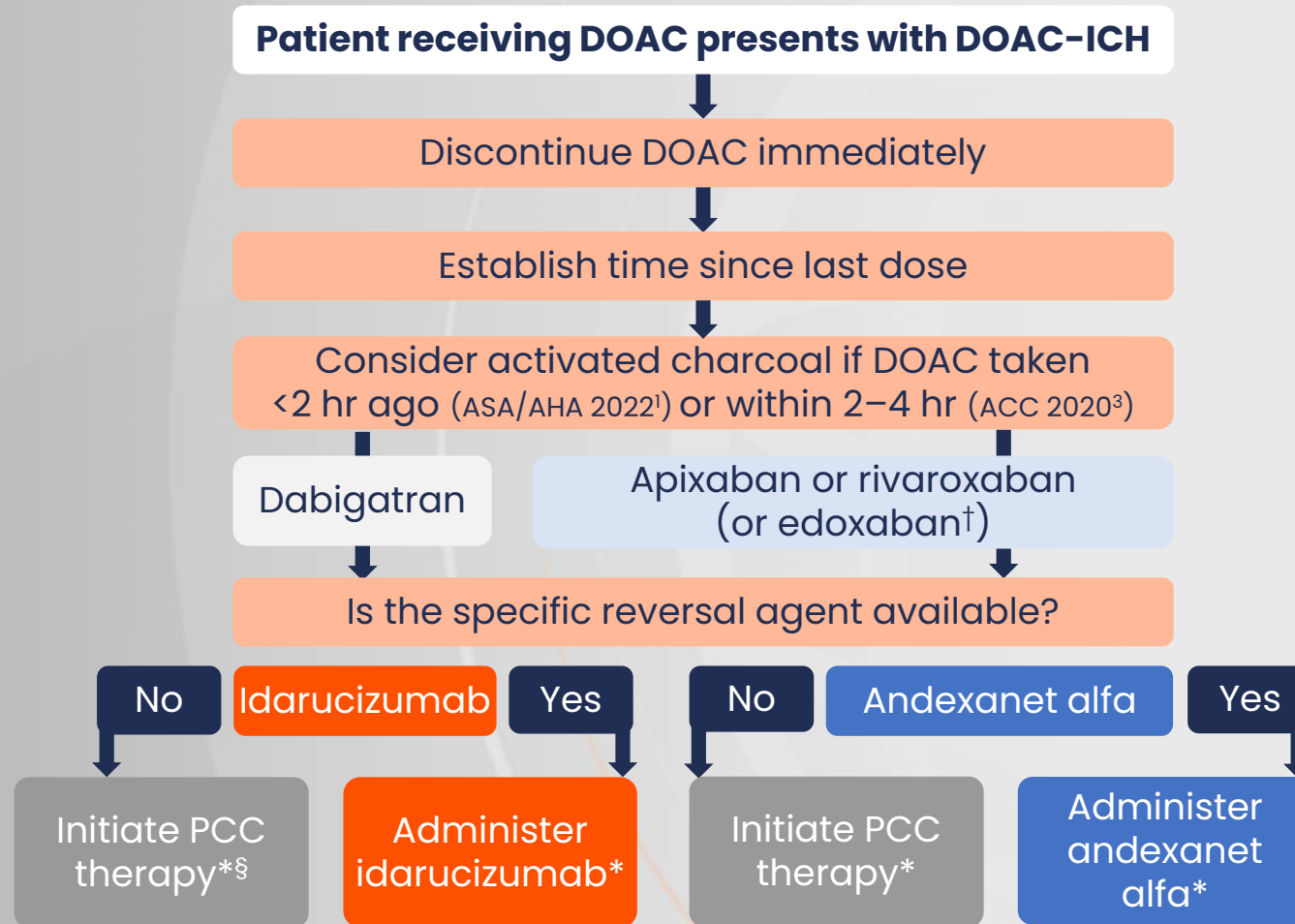
ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; APSC, Asian Pacific Society of Cardiology; ASA, American Stroke Association; DOAC, direct oral anticoagulant; ESO, European Stroke Association; ICH, intracranial haemorrhage; VKA, vitamin K antagonist.

1. Greenberg SM, et al. *Stroke*. 2022;53:e282–361; 2. Chong DT, et al. *Eur Cardiol*. 2021;16:e23; 3. Tomaselli GF, et al. *J Am Coll Cardiol*. 2020;76:594–622;

4. Christensen H, et al. *Eur Stroke J*. 2019;4:294–306; 5. Nakamura M, et al. *Circ J*. 2020;84:831–65; 6. Brieger D, et al. *Heart Lung Circ*. 2018;27:1209–66;

7. Magalhães LP, et al. *Arq Bras Cardiol*. 2016;107:501–8.

# Specific reversal agents are recommended in DOAC-ICH when available<sup>1-4</sup>



\*Treatment recommendations are common across ASA/AHA 2022<sup>1</sup>, APSC 2021<sup>2</sup>, ACC 2020<sup>3</sup> and ESO 2019<sup>4</sup> guidelines

<sup>†</sup>Andexanet alfa is not approved for edoxaban-treated patients outside of Japan.<sup>5,6,7</sup> §ASA/AHA 2022: renal replacement therapy may be considered to reduce dabigatran concentration.<sup>1</sup> ACC, American College of Cardiology; AHA, American Heart Association; APSC, Asian Pacific Society of Cardiology; ASA, American Stroke Association; DOAC, direct oral anticoagulant; ESO, European Stroke Association; hr; hours; ICH, intracranial haemorrhage; PCC, prothrombin complex concentrate. 1. Greenberg SM, et al. *Stroke*. 2022;53:e282-361; 2. Chong DT, et al. *Eur Cardiol*. 2021;16:e23; 3. Tomaselli GF, et al. *J Am Coll Cardiol*. 2020;76:594-622; 4. Christensen H, et al. *Eur Stroke J*. 2019;4:294-306; 5. Yajima T, et al. *Nihon Yakurigaku Zasshi*. 2023;158:89-100; 6. FDA. Coagulation factor Xa (recombinant) PI. 2024. Available at: [www.fda.gov/media/113279/download](https://www.fda.gov/media/113279/download) (accessed 13 May 2024); 7. EMA. Andexanet alfa SmPC. 2023. Available at: <https://bit.ly/3WFrRjH> (accessed 13 May 2024).

# There are key factors to consider when using guidelines on anticoagulant reversal in DOAC-ICH

1st

**Current guidelines** are consistent in advocating first-line use of andexanet alfa or idarucizumab, where available<sup>1-4</sup>



**Specific reversal agents** should be used promptly in patients with DOAC-ICH<sup>1</sup>



**The strength of recommendations varies** due to lack of inclusion of recent trials in some guidelines<sup>1-7</sup>



In recent years, **data have become available which may not yet be incorporated into guidelines**, e.g. ANNEXA-1<sup>8</sup> and ANNEXA-4<sup>9</sup> trial data for andexanet alfa

DOAC, direct oral anticoagulant; ICH, intracranial haemorrhage.

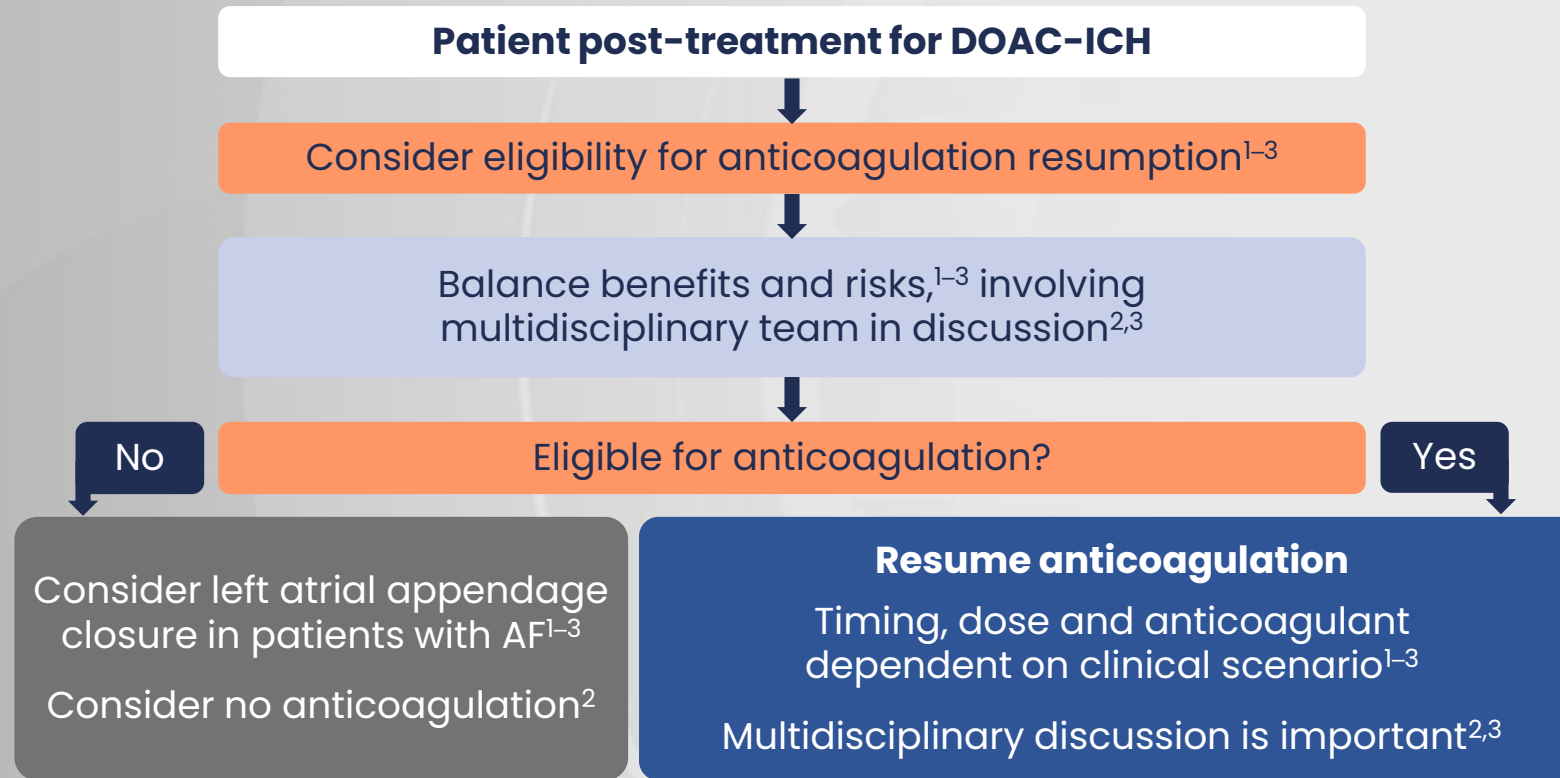
1. Greenberg SM, et al. *Stroke*. 2022;53:e282-361; 2. Chong DT, et al. *Eur Cardiol*. 2021;16:e23; 3. Tomaselli GF, et al. *J Am Coll Cardiol*. 2020;76:594-622;

4. Christensen H, et al. *Eur Stroke J*. 2019;4:294-306; 5. Nakamura M, et al. *Circ J*. 2020;84:831-65; 6. Brieger D, et al. *Heart Lung Circ*. 2018;27:1209-66;

7. Magalhães LP, et al. *Arq Bras Cardiol*. 2016;107:501-8; 8. Connolly S. *Int J Stroke*. 2023;18(Suppl. 3):422. LBO004/#2806; 9. Milling TJ Jr, et al. *Circulation*. 2023;147:1026-38.

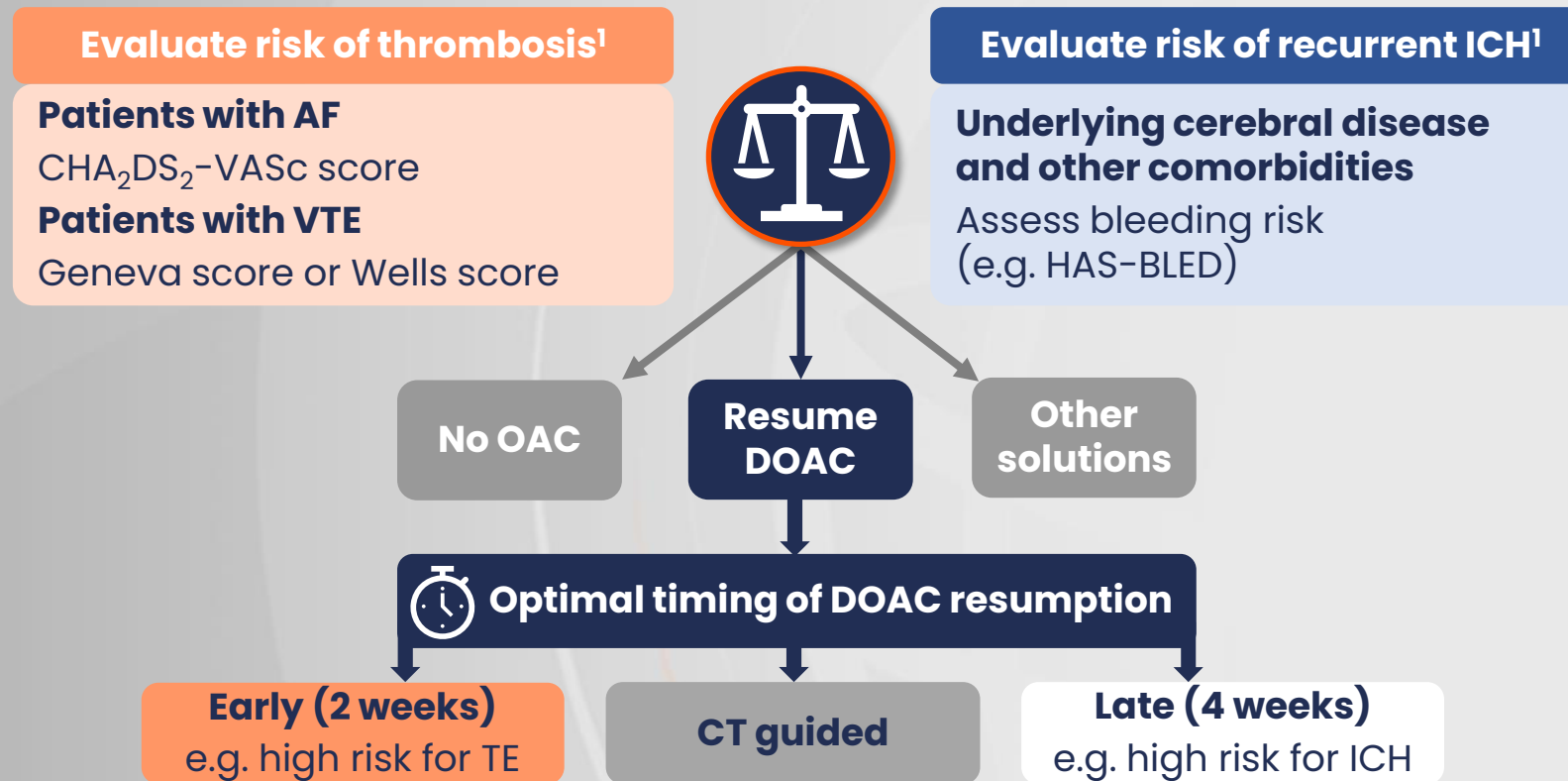
# Guidelines vary for anticoagulation resumption following DOAC-ICH, but have some common principles

Based on recommendations in the **ASA/AHA**,<sup>1</sup> **APSC**<sup>2</sup> and **ACC**<sup>3</sup> guidelines:



There are no recommendations on resuming anticoagulation in the 2019 ESO guidelines<sup>4</sup>

# Anticoagulation resumption after DOAC-ICH requires risk assessment



- Address modifiable risk factors at every patient contact<sup>1,2</sup>
- Schedule more regular review and follow-up for high-risk patients<sup>1</sup>



# Case study in DOAC-ICH



- A 76-year-old man presents to the ED at 8 am with **suspected ischaemic stroke**, having **developed symptoms in the last 2.5 hours**. He was well and without symptoms the evening before
- He has a **history of AF** and **blood pressure upon arrival is 190/120 mmHg**



His wife explained to the paramedic that he is taking a **twice-daily anticoagulant tablet**; she is **not sure which one** and **he has not taken his morning dose**



- CT **confirmed ICH**
- **Apixaban identified** as the anticoagulant (twice-daily tablet)
- **Anti-factor Xa** level was **112 ng/mL**



- Low-dose **andexanet alfa** commenced
- Blood pressure lowered
- **After 7 days, discharged** to neurorehabilitation unit for management of residual impairments
- **Decision** to be made **on whether to restart anticoagulation**

# Summary



Although DOACs are generally associated with lower bleeding rates and are increasingly used in preference to VKA therapy, they are also associated with a risk of ICH



Specific reversal agents are effective, with an acceptable safety profile, in DOAC-ICH management



Guidelines agree on the use of specific reversal agents, where available

# Data updates

# Latest evidence for the efficacy of andexanet alfa in DOAC-ICH

## Andexanet alfa resulted in better control of haematoma expansion than usual care in DOAC-ICH

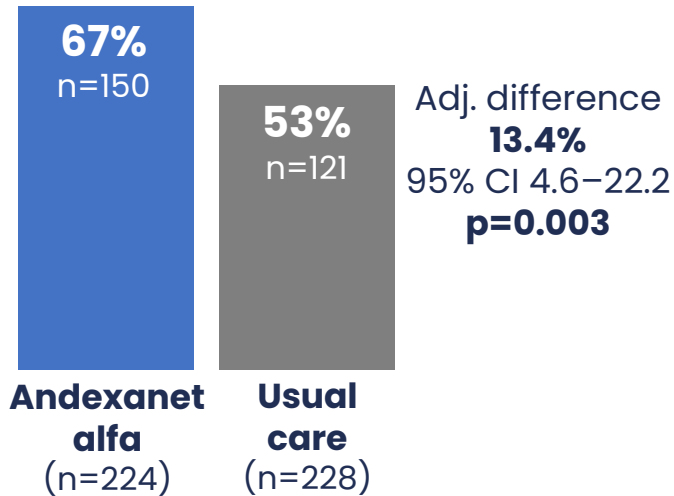
### ANNEXA-I<sup>1</sup>



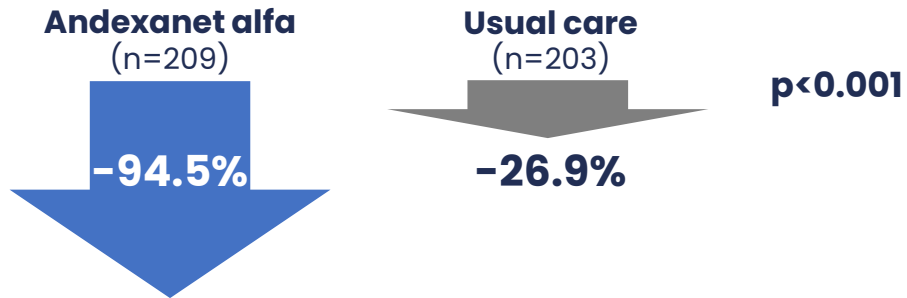
- Patients who had taken FXa inhibitors within 15 hrs before acute ICH
- Randomized to andexanet alfa (n=263) or usual care (n=267; of whom 230 received PCC)



### Haemostatic efficacy\*



### Change in anti-FXa activity (BL to 1-2 hr nadir)<sup>†</sup>



### TE and ischaemic stroke

- **TE:** andexanet alfa, 10.3%; UC, 5.6% (**p=0.048**)
- **Ischaemic stroke:** andexanet alfa, 6.5%; UC, 1.5%<sup>‡</sup>

## In ANNEXA-I patients, various factors predict haematoma expansion

### ANNEXA-I subanalysis<sup>2</sup>



- Aimed to identify patients in ANNEXA-I at greatest risk for haematoma expansion and most likely to benefit from andexanet alfa

### Risk of haematoma expansion at 12 hrs

Parameter	OR (95% CI)	P
Andexanet vs UC	0.45 (0.30–0.71)	<0.001
Symptom onset to treatment, hrs	0.72 (0.62–0.83)	<0.001
Anti-FXa activity, per 100 ng/mL	1.19 (1.00–1.43)	0.056
Haematoma volume, mL	1.01 (1.00–1.02)	0.025

- Overall decrease in rate of haematoma expansion with andexanet alfa vs UC per 100 patients: **-13.7%\*\***

\*Primary endpoint. Haemostatic efficacy was achieved if all the following criteria were met: a change in the haematoma volume of 20% or less (excellent) or 35% or less (good) within 12 hours after baseline, an increase in the NIHSS score of <7 points at 12 hours, and receipt of no rescue therapies or surgery to decompress the haematoma within 3–12 hours after randomization. †Secondary endpoint. ‡Difference, 5.0%; 95% CI 1.5–8.8; \*\*95% CI -22.2 to -5.2. The decrease with andexanet per 100 patients is estimated from the proportion difference, and the 95% CIs are Wald CIs. Adj., adjusted; BL, baseline; CI, confidence interval; DOAC, direct oral anticoagulant; FXa, Factor Xa; hr, hour; ICH, intracranial haemorrhage; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PCC, prothrombin complex concentrate; TE, thrombotic events; UC, usual care.

1. Connolly SJ, et al. *N Engl J Med.* 2024;390:1745–55; 2. Shoamanesh A, et al. Presented at the International Stroke Conference; 7–9 February 2024; Phoenix, AZ, USA. Abstr. LB19.

# Latest evidence for the importance of early blood pressure control in ICH

## Prehospital reduction of blood pressure can reduce the risk of poor functional outcomes in ICH

### INTERACT4: Multicentre, ambulance-delivered, PROBE study<sup>1</sup>



- 2,404 patients in China with suspected acute stroke (causing motor deficit) and SBP  $\geq$ 150 mmHg, **assessed in the ambulance  $\leq$ 2 hours after symptom onset**



- Randomized 1:1 to immediate SBP-lowering therapy (**target: 130–140 mmHg within 30 mins**) or usual BP management
- Haemorrhagic stroke confirmed in 1,041\* patients; of these **1,029 (99%) had an ICH**

- Symptom onset to randomization: median **61 mins**
- Symptom onset to hospital arrival: median **75–80 mins**

#### Mean SBP:

- At randomization: **178 mmHg** (both groups)
- At hospital arrival:
  - Early intervention, **159 mmHg**; Usual care, **170 mmHg**
- At 24 hours: **140 mmHg** (both groups)

**Prehospital BP reduction associated with reduced risk of poor functional outcome<sup>†</sup> in patients with haemorrhagic stroke (COR 0.75; 95% CI 0.60–0.92)<sup>‡</sup>**

**No reduced risk of poor functional outcome overall (COR 1.00; 95% CI 0.87–1.15) and increased risk in patients with cerebral ischaemia (COR 1.30; 95% CI 1.06–1.60)<sup>‡</sup>**

## Early initiation of blood pressure-lowering treatment can reduce the likelihood of haematoma growth in ICH

### Pooled analysis of four INTERACT trials<sup>2</sup>



- Effects of BP lowering in reducing haematoma growth according to timing of therapy in 2,921 patients with ICH
- Outcomes: haematoma growth at 24 hours; absolute ( $\geq$ 6 mL) and relative ( $\geq$ 33%)

- Interaction between time to initiation of BP-lowering therapy and relative haematoma growth: **p=0.007\*\***
- Effect only significant when ICH score was 0 (p=0.007)
- **Earlier treatment associated with lower likelihood of haematoma growth** (up to a cut-off of 2.5 hours)
- **Early treatment most effective in milder acute ICH**

\*Including 12 patients with sub-arachnoid haemorrhage; <sup>†</sup>Modified Rankin scale score at 90 days; <sup>‡</sup>This subgroup analysis was not part of a hierarchical statistical plan, therefore causal inferences about these associations cannot be drawn; \*\*Interaction for absolute haematoma growth, p=0.77.

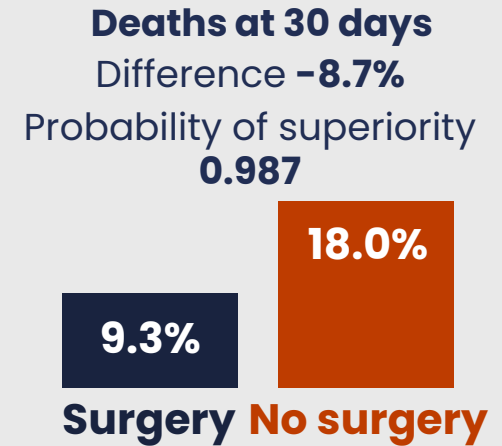
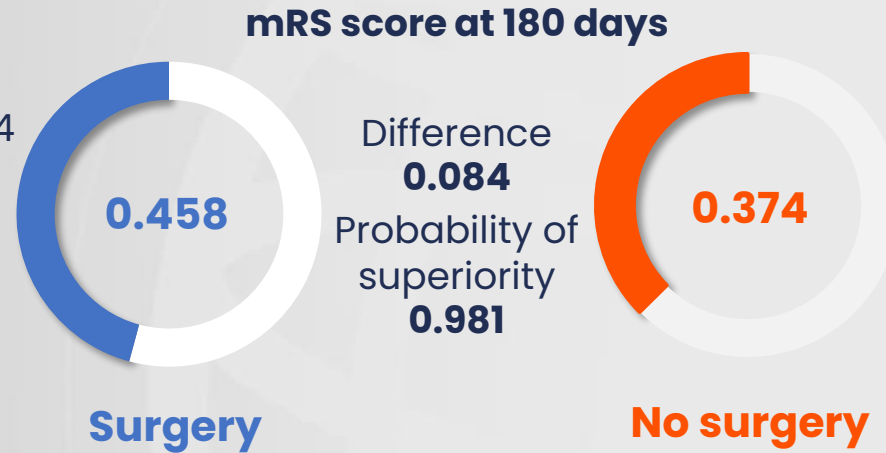
BP, blood pressure; CI, confidence interval; COR, common odds ratio; ICH, intracranial haemorrhage; PROBE, prospective, randomized, open-label, blinded endpoint; SBP, systolic blood pressure.

1. Li G, et al. *N Engl J Med.* 2024;390:1862–72; 2. Wang X, et al. Presented at the European Stroke Organisation Conference; 15–17 May 2024; Basel, Switzerland. Abstr. 519.

# Latest evidence for the utility of surgery alongside medical management in ICH

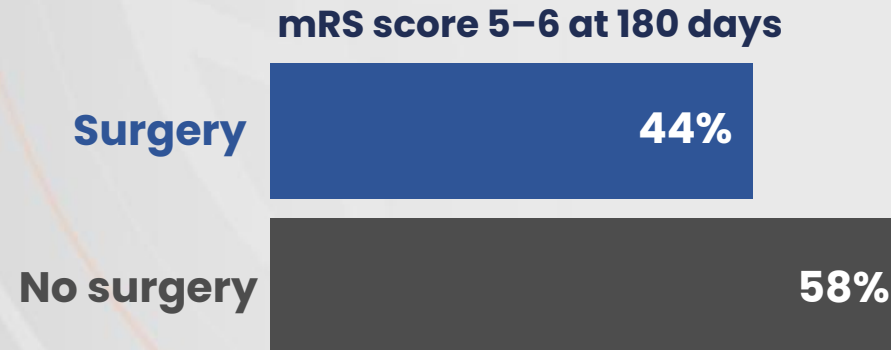
## Haematoma evacuation can result in better functional outcomes than medical management alone in ICH<sup>1</sup>

- **ENRICH:** Multicentre RCT in 300 patients with acute ICH
- Assessed surgical removal\* of haematoma within 24 hrs plus guideline-directed medical management (GDMM) (n=150) vs GDMM alone (n=150)
- Primary endpoint: mean score on utility-weighted modified Rankin scale at 180 days
- Prespecified threshold for posterior probability of superiority  $\geq 0.975$



## Decompressive craniectomy might be superior to medical management alone in severe deep ICH<sup>2</sup>

- **SWITCH:** Multicentre, randomized, open-label trial in 197 patients with severe ICH
- Assessed whether decompressive craniectomy plus best medical treatment (BMT) (n=96) improves outcome at 6 months vs BMT alone (n=101)
- Primary endpoint: a score of 5–6 on the modified Rankin Scale at 180 days



aRR **0.77**  
95% CI **0.59–1.01**  
p=**0.057**

\*Minimally invasive surgery.

aRR, adjusted risk ratio; BMT, best medical treatment; CI, confidence interval; GDMM, guideline-directed medical management; hr, hour; ICH, intracranial haemorrhage; mRS, modified Rankin scale; RCT, randomized controlled trial.

1. Pradilla G, et al. *N Engl J Med.* 2024;390:1277–89; 2. Beck J, et al. *Lancet.* 2024;403:2395–404.

# The ESO–EANS guideline on ICH is due to be published in 2024

Guidelines aim to include the latest evidence, including from:

Study	Reference
<b>ANNEXA-I</b>	Connolly SJ, et al. <i>N Engl J Med.</i> 2024;390:1745–55.
<b>ENRICH</b>	Pradilla G, et al. <i>N Engl J Med.</i> 2024;390:1277–89.
<b>INTERACT-4</b>	Li G, et al. <i>N Engl J Med.</i> 2024;390:1862–72.
<b>RICH-2</b>	Zhao W, et al. <i>Eur Stroke J.</i> 2024;9(Suppl. 1):648–705. Abstr. 4001.
<b>STOP-MSU</b>	Yassi N, et al. <i>Lancet Neurol.</i> 2024;23:577–87.
<b>SWITCH</b>	Beck J, et al. <i>Lancet.</i> 2024;403:2395–404.

Guidelines will cover:

