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

Practice aid for the management of intracranial haemorrhage related to direct oral anticoagulants

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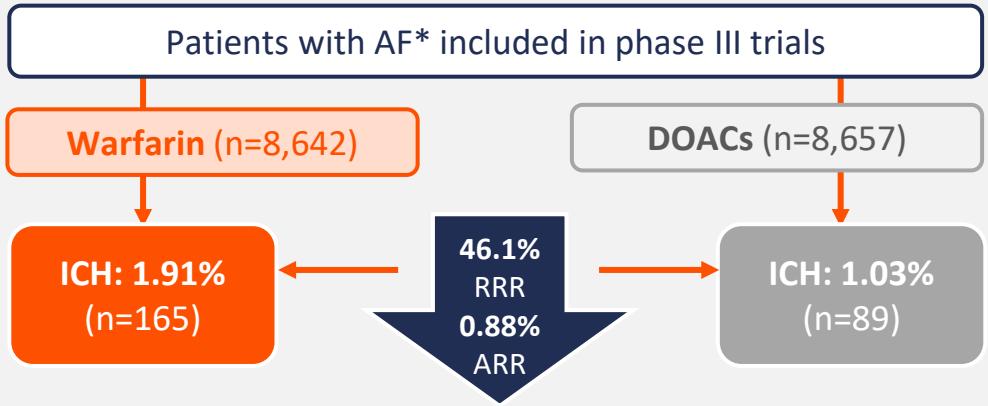
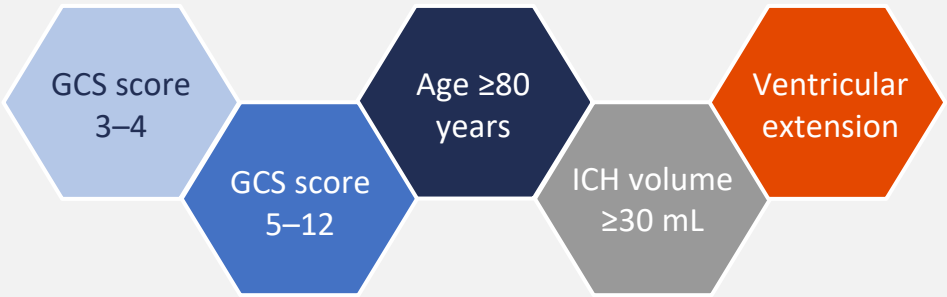
ICH is an important complication in patients treated with DOACs

- Although the risk of ICH is lower with DOACs vs warfarin therapy,[1] this remains an important potential complication
- ICH incidence is likely to increase given the rise in use of DOACs and the ageing population[2]

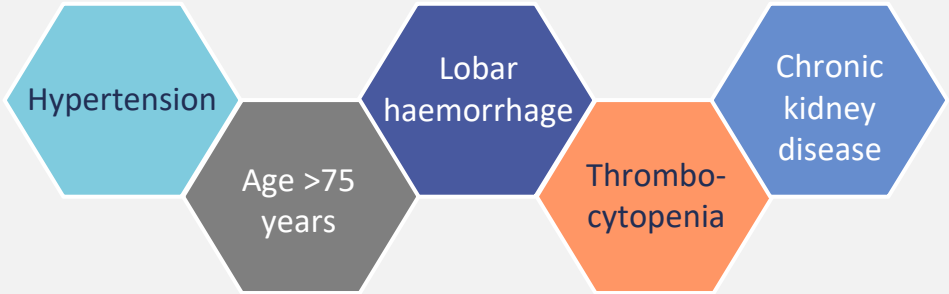
DOACs are associated with a lower incidence of ICH vs warfarin[3]



Key risk factors for 30-day mortality in patients with ICH using OACs are:[4]



Risk factors for recurrence of ICH include:[5]

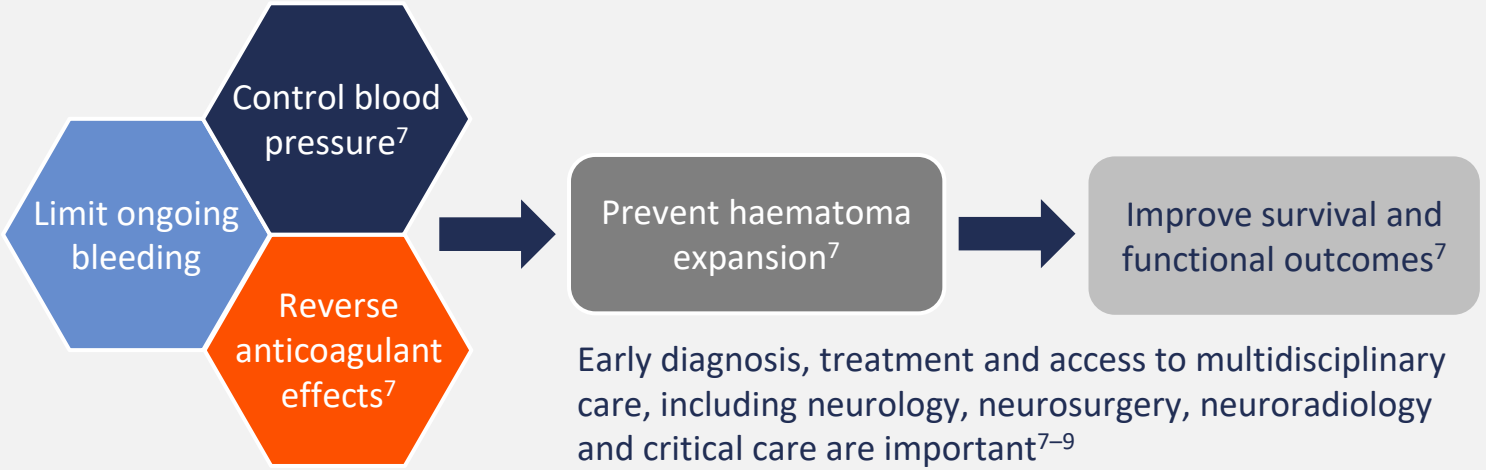


*Patients with AF and a history of stroke/transient ischaemic attack.

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

- Delays in identification and management of ICH are associated with poor prognosis[6]

DOAC-ICH management aims to improve survival and functional outcomes



Early diagnosis, treatment and access to multidisciplinary care, including neurology, neurosurgery, neuroradiology and critical care are important[7–9]

Care bundles combining treatment strategies can improve outcomes in ICH[10,11]

INTERACT3 care bundle[10]

Rapid anticoagulant reversal (≤1 hour*)	Anti-pyrexia treatment
Systolic BP <140 mmHg (≤1 hour)	Strict blood glucose control

ABC-ICH care bundle[11]

- Rapid anticoagulant reversal (≤90 minutes)
- Systolic BP 130–140 mmHg (≤1 hour)
- Prompt neurosurgical referral

*Target INR <1.5.

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Reversal agents have been developed that target DOACs

DOAC-ICH reversal agents have unique characteristics

	DOACs targeted[12,13]	Approval status[12] (DOAC related)	Indications	Mechanism of action	Terminal half-life[13]
PCC	Non-specific	Not approved for DOAC reversal	Life-threatening or uncontrolled bleeding *(if specific reversal agents not available)*[12,14]	Non-specific; raises factor levels and 'overwhelms' DOAC[12,13]	Elevated clotting factors likely persist for ≥24 hours
Idarucizumab	Dabigatran	Approved	Life-threatening or uncontrolled bleeding; emergency surgery or urgent procedures[15]	Rapid, specific binding to dabigatran (<5 minutes)[13,16]	4–8 hours
Andexanet alfa	Apixaban Rivaroxaban Edoxaban*	Approved*	Life-threatening or uncontrolled bleeding[17]	Rapid, specific binding to factor Xa inhibitors (2–5 minutes)[13,18]	5–7 hours

Adverse events should be considered with DOAC-ICH reversal agents

	Meta-analysis data: Outcomes in patients with ICH[19†]		Serious adverse events include:
	All-cause mortality	TE event rate	
4F-PCC	**26%** (N=784)	**8%** (N=615)	Stroke, DVT, thrombosis, venous insufficiency[20]
Idarucizumab	**11%** (N=340)	**5%** (N=300)	Delirium, cardiac arrest, sepsis, septic shock[21]
Andexanet alfa	**24%** (N=506)	**14%** (N=445)	Thromboembolic events, ischaemic events, cardiac arrest, sudden death[18]

*Andexanet alfa is not approved for edoxaban-treated patients outside of Japan.[17,22,23] †Data based on meta-analysis; comparisons between agents are indirect.

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Guidelines for the management of DOAC-ICH share common principles

Use specific reversal agents for DOAC-ICH, when available[2,7,24,25]

Patient receiving DOAC presents with DOAC-ICH

↓

Discontinue DOAC immediately
Establish time since last dose

↓

ASA/AHA and ACC: Consider activated charcoal if DOAC taken <2 hr ago[7]/within 2–4 hr[25]

- Dabigatran
- Apixaban or rivaroxaban (or edoxaban*)

↓

Is the specific reversal agent available?

Yes	Idarucizumab	No	No	Andexanet alfa	Yes
↓	↓	↓	↓	↓	↓
Administer idarucizumab†		Initiate PCC therapy†§		Administer andexanet alfa†	

†Treatment recommendations are common across ASA/AHA 2022[7], APSC 2021[24], ACC 2020[25] and ESO 2019[2] guidelines

Anticoagulation after DOAC-ICH requires risk assessment

Based on the ASA/AHA,[7] APSC[24] and ACC[25] guidelines:

Balance benefits and risks,[7,24,25] involving MDT in discussion[24,25]

Risk of thrombosis[26]

Patients with AF
CHA_2DS_2-VASc score
Patients with VTE
Geneva score or Wells score

Risk of recurrent ICH[26]

Underlying cerebral disease/other comorbidities
Assess bleeding risk (e.g. HAS-BLED)

↓

Eligible for anticoagulation?

No	Yes
↓	↓
Consider left atrial appendage closure in patients with AF[7,24,25] Consider no anticoagulation[24]	**Resume anticoagulation** Regimen dependent on clinical scenario[7,24,25] MDT discussion is important[24,25]

In recent years, **data have become available which may not yet be incorporated into guidelines,** e.g. ANNEXA-I[27] and ANNEXA-4[28] trial data for andexanet alfa

*Andexanet alfa is not approved for edoxaban-treated patients outside of Japan.[17,22,23] §ASA/AHA 2022: RRT may be considered to reduce dabigatran concentration.[7]

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Abbreviations and references

Abbreviations

4F-PCC, four-factor PCC; ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; APSC, Asian Pacific Society of Cardiology; ARR, absolute risk reduction; ASA, American Stroke Association; BP, blood pressure; CHA_2DS_2-VASc, Congestive heart failure or left ventricular dysfunction, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex category; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ESO, European Stroke Association; GCS, Glasgow Coma Scale; HAS-BLED, Hypertension, Abnormal kidney and liver function, Stroke, Bleeding, Labile international; ICH, intracranial haemorrhage; MDT, multidisciplinary team; OAC, oral anticoagulant; PCC, prothrombin complex concentrate; RRR, relative risk reduction; RRT, renal replacement therapy; TE, thromboembolic; VTE, venous thromboembolism.

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