Reversal bundle of care: è possibile cambiare outcome nel paziente emorragico

Emorragie da DOACs e Bundle of care

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XIII congresso nazionale
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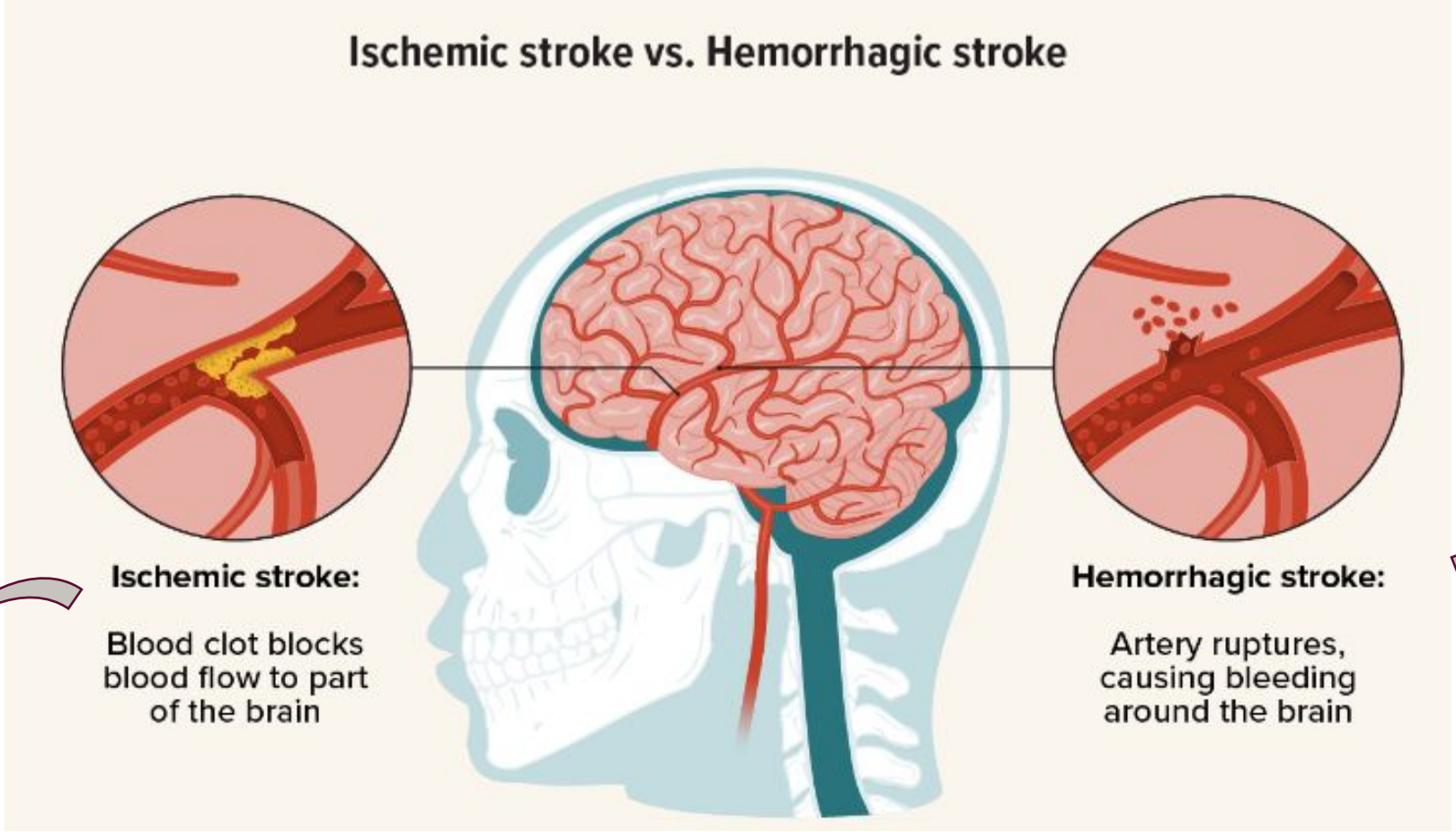
GENOVA 30 MAG - 1 GIU 2024

Strokes Aetiology and Epidemiology in Italy



68-83% ischemic

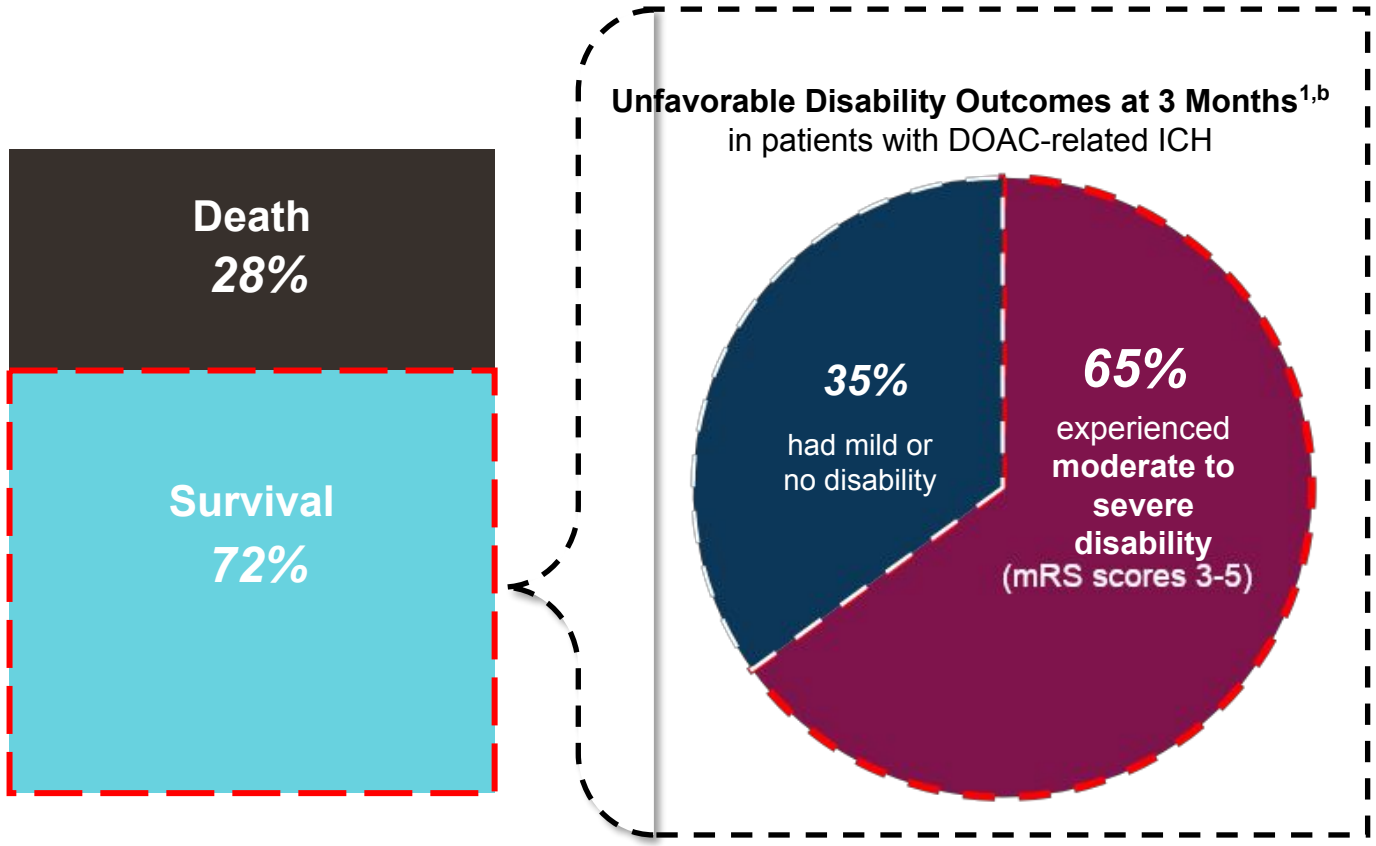
100K Hospitalized Patients (80% New Cases)[1]

10-20% as primary ICH
1.6-4.0% as sub-arachnoid haem.

1. Codice BLU: Percorso Ictus 2018; 2. Sacco et al 2011 – Epidemiology of stroke in italy; Illustration by Jason Hoffman at https://www.healthline.com/

DOAC-Related ICH is Associated with Increased Disability Among Survivors[1]

RASUNOA: prospective, investigator-initiated, multicenter observational study evaluated 3-month survival and disability outcomes in patients with DOAC-related, nontraumatic ICH (N=60)[1,a]



Moderate disability[2]
mRS, 3: requiring some external help

Moderately severe disability[2]
mRS, 4: unable to walk/attend bodily needs without assistance

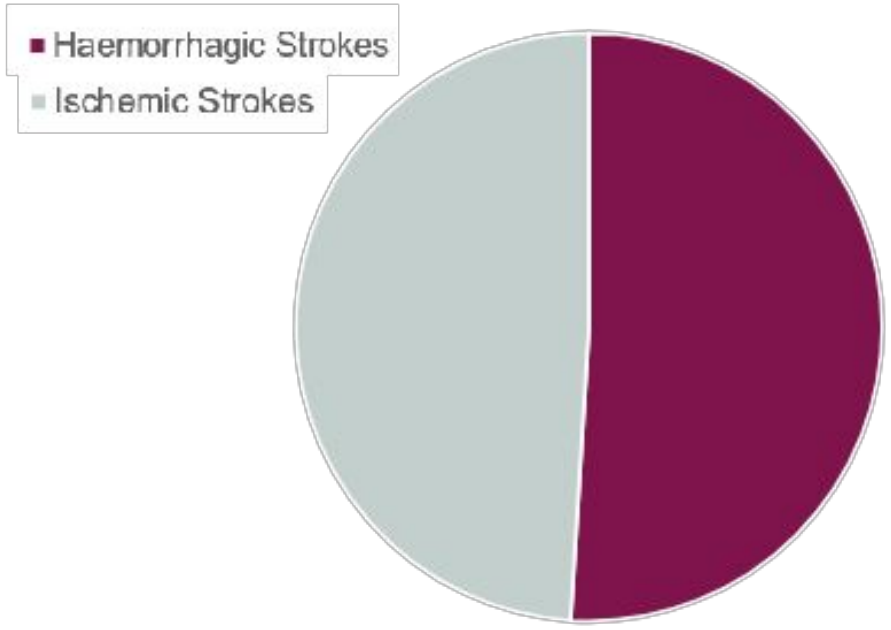
Severe disability[2]
mRS, 5: bedridden, requiring constant care

[a]DOAC therapies included apixaban, dabigatran, and rivaroxaban; [b]Unfavorable outcome defined as mRS score of 3-5 in survivors.
DOAC = direct oral anticoagulant; ICH = intracerebral hemorrhage; mRS = modified Rankin Scale.

1. Purrucker JC et al. *JAMA Neurol*. 2016;73(2):169-177; 2. Specifications Manual for Joint Commission National Quality Measures (v2018A). Modified Rankin Score (mRS). Accessed September 19, 2023. https://manual.jointcommission.org/releases/TJC2018A/DataElem0569.html.

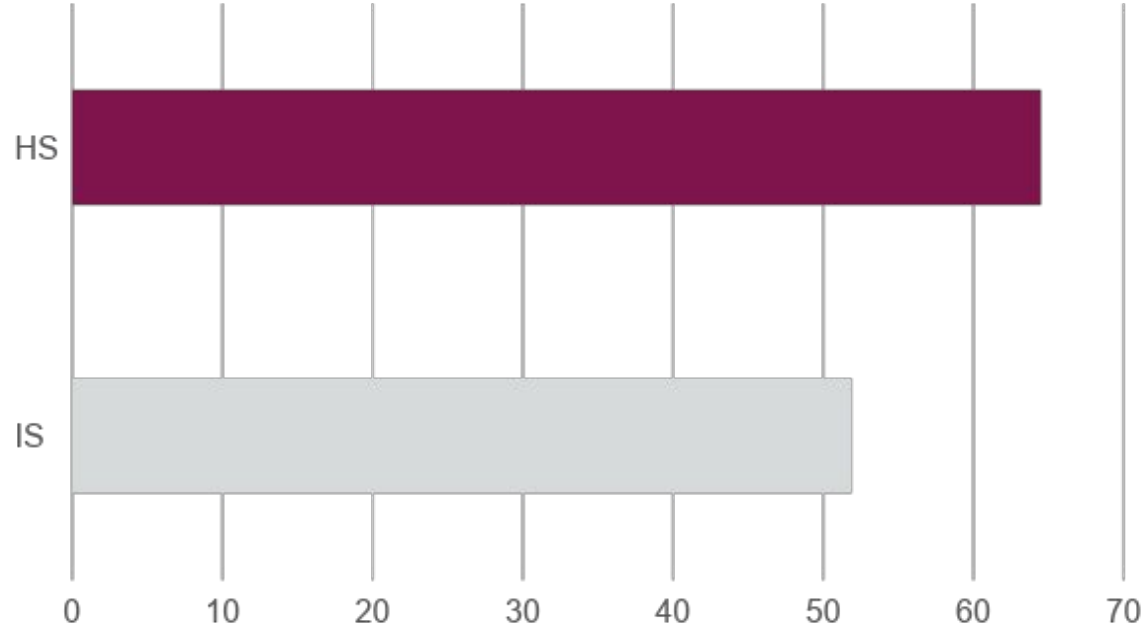
Haemorrhagic Strokes are less frequent but more severe

Deaths1



51% of all deaths are due to hemorrhagic stroke

Million DALYs1



more DALYs lost than ischaemic stroke

People <70yo Accounts for

60% of new hemorrhagic strokes

DALY=disability adjusted life-year

1. GBD 2019 Stroke Collaborators* (2021) Lancet Neurol 20: 795–820 2. Global stroke Fact Sheet 2019 (WSO);

Multiple Risk Factors for ICH

Non-modifiable

- Advanced age
- Gender/Race
- Cerebral amyloid Angiopathy
- Chronic Kidney disease

Modifiable

- Hypertension
- Anticoagulants/ antiplatelets drugs
- Hyperlipidemia
- Smoking/excessive alcohol consumption

CrCl = creatinine clearance; ICH = intracerebral hemorrhage; DOAC = direct oral anticoagulant; PAD = peripheral artery disease.

Paciaroni M et al. *Stroke*. 2021;52(4):1450-1454.; Wang S. et al. Front. Neurol., 16 September 2022; Joon an et al, *Journal of Stroke* 2017;19(1):3-10

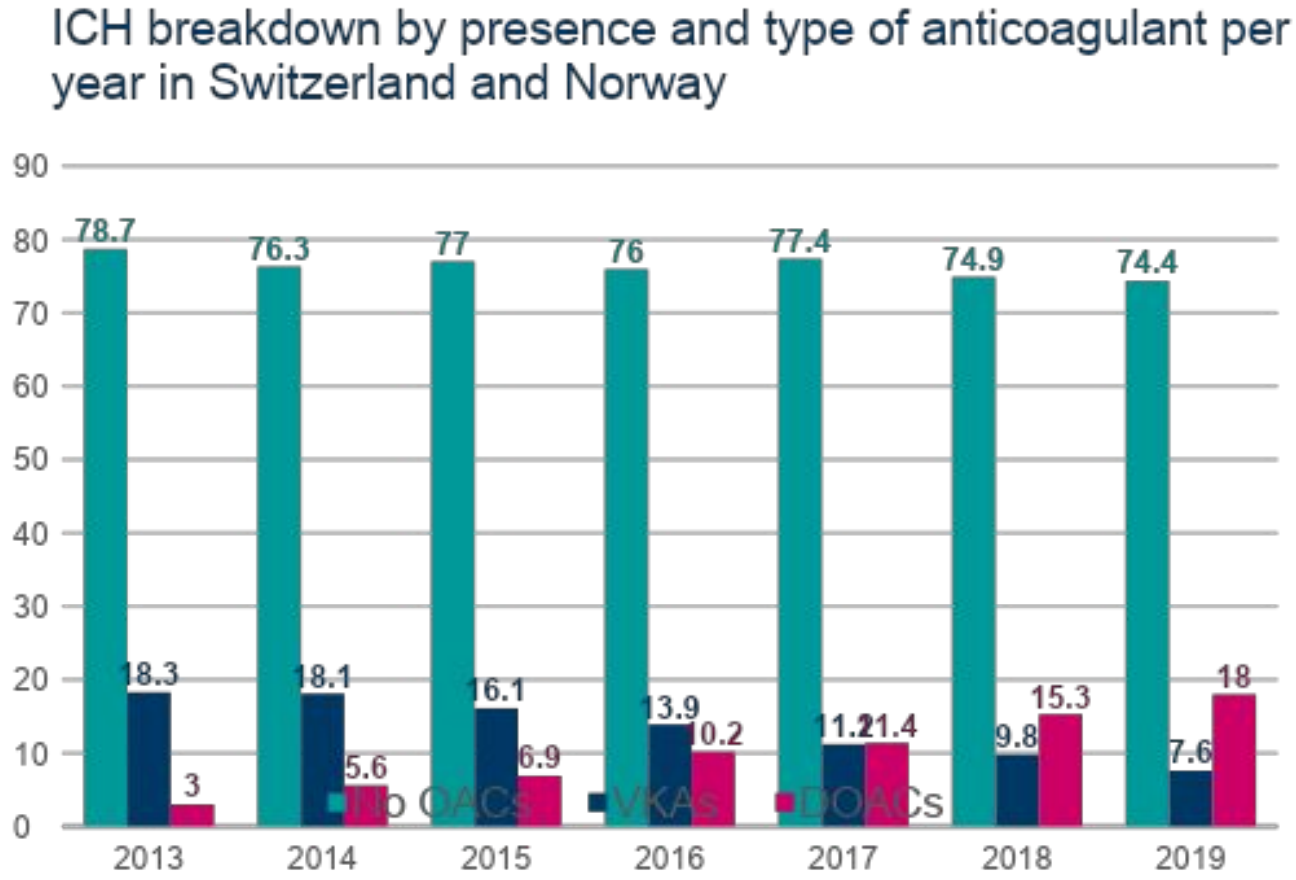
4

Anticoagulation-related ICH incidence is changing

Anticoagulant-related ICHs are steadily around 20-25% of all ICH

Due to their favourable safety profile, use of NOACs in Europe has increased significantly since their approval

European data show a higher prevalence of DOACs among OAC-related ICHs in recent years



DALY=disabilityadjusted life-year; OAC= Oral anticoagulant; DOAC= Direct oral anticoagulant

1 GBD 2019 Stroke Collaborators* (2021) Lancet Neurol 20: 795–820. 2 Feigin et al (2015) Neuroepidemiology 45:161-8. 3 Béjot et al (2013) BRAIN 136; 658–664. 4 Seiffge et al (2019) J Neurol 266:3126–3135. 5. Siepen BM, Forfang et al. Intracerebral haemorrhage in patients taking different types of oral anticoagulants: a pooled individual patient data analysis from two national stroke registries. Stroke & Vascular Neurology 2024;0. doi:10.1136/svn-2023-002813

L'uso di Doac è aumentanto in modo significativo dalla loro approvazione

Anticoagulanti, consumo (DDD / 1000 abitanti al giorno) in ITALIA: confronto 2014-2019[2]

Sottogruppi e sostanze	2014	2015	2016	2017	2018	2019	Δ % 19-18
DOAC	1,6	3,4	5,3	7,3	9,4	11,7	25,0
EBPM	9,7	9,7	9,5	9,2	8,9	8,7	-2,0
Antitrombotico	0,0	0,0	0,0	0,0	0,0	0,0	2,2
Fondaparinux	0,3	0,4	0,4	0,5	0,5	0,5	2,6
Eparina ed eparinoidi	0,6	0,4	0,5	0,4	0,4	0,4	-3,1
Antagonisti della vitamina K	6,5	6,1	5,6	5,1	4,6	4,1	-10,6
Anticoagulanti	**18,8**	**20,1**	**21,4**	**22,6**	**23,7**	**25,4**	**7,0**
enoxaparina	7,5	7,6	7,7	7,3	7,2	7,6	6,0
apixaban	0,2	0,8	1,6	2,3	3,0	3,6	22,2
rivaroxaban	0,6	1,5	2,3	2,8	3,2	4,1	28,9
dabigatran	0,8	1,1	1,4	1,8	2,2	2,4	10,2
edoxaban	0,0	0,0	0,0	0,4	1,0	1,6	51,7
nadroparina calcica	1,4	1,4	1,2	1,2	1,1	0,8	-27,1
fondaparinux	0,3	0,4	0,4	0,5	0,5	0,5	2,6
parnaparina	0,5	0,5	0,5	0,6	0,5	0,3	-50,9
alteplasi	0,0	0,0	0,0	0,0	0,0	0,0	5,2
eparina	0,6	0,4	0,4	0,4	0,4	0,4	-3,0

2. https://www.aifa.gov.it/it/rapporto-osmed-2019

Baseline Characteristics and Clinical Predictors of Hematoma Expansion and Prognosis

Non-modifiable baseline characteristics

Intracranial hemorrhage subtype	Spontaneous ICH and SAH were shown to have highest mortality in anticoagulated patients[1]
Hematoma volume	Volume of ICH was the most important predictor of 30-day survival[2]
Baseline NIHSS or GCS scores	Some observational studies found higher baseline scores associated with HE risk[4]
Age and gender	HE more likely in patients of older age ≥85 years and male gender[3-5]

Modifiable clinical characteristics

Prior use of anticoagulants is associated with larger initial hematoma volume as well as HE and worse outcomes[6-7]	**Prior use of anticoagulant agents**
Post-admission blood pressure variability and high mean arterial pressure are positively related to HE[8]	**Systolic blood pressure**
Admission hyperglycemia correlated with poor functional outcomes and high fatality rates[9]	**Blood glucose**
Temperature abnormalities can occur in >30% of ICH patients, with fever associated with and worse outcomes[9]	**Temperature**

1. Hart RG et al. *Stroke*. 2012;43(6):1511-1517. 2. Broderick et al. Stroke, 24(7), 987–993.3. Forti P et al. *Cerebrovasc Dis*. 2016;42(5-6):485-492. 4. Franco L et al. *Eur J Intern Med*. 2020;75:35-43. 5. Marini S et al. *J Neurol Sci*. 2017;379:112-116. 6. Gerner ST et al. *Stroke*. 2019;50(6):1392-1402. 7. Tsivgoulis G et al. *Neurology*. 2017;89(11):1142-1151 8. Buratti L et al. *J Neurol Sci*. 2014;339(1-2):164-1688. 9. Greenberg 2022 - Stroke. AHA/ASA Guidelines Stroke, 53(7), e282–e361.

HE is associated with early neurological deterioration, poor functional outcomes, and increased risk of mortality after ICH

10% increase in hematoma growth[2,b]

=

16% greater likelihood of 1 point reduction on the mRS

Cumulative OR, 0.84; 95% CI, 0.75-0.92; p <0.0001

5% increase in risk of death

HR, 1.05; 95% CI, 1.03-1.08; p <0.0001

10.7 mL increase in hematoma volume

=

72% greater likelihood of death or dependency[c,d]

OR, 1.72; 95% CI, 1.19-2.49; p=0.004

mL increase in hematoma volume

=

5% higher chance of death or dependency[d]

95% CI, 2-9%

[a]Early neurological deterioration defined as a decrease in the GCS score by ≥2 points or increase in NIHSS score by ≥4 points within 24 hours of admission; [b]HE diagnosed via CT within 3 hours of stroke onset and at 24-hour follow-up; [c]Increase in hematoma volume measured over 24 hours; [d]Dependency defined as mRS scores 3-5 at 90 days after randomization.

1. Kuohn LR et al. *Stroke*. 2022;53(8):2441-2448; 2. Davis SM et al. *Neurology*. 2006;66(8):1175-1181; 3. Delcourt C et al. *Neurology*. 2012;79(4):314-319; 4. Brott T et al. *Stroke*. 1997;28(1):1-5

Recommendations on Systolic Blood Pressure

Evidence-based Recommendation

In patients with hyperacute (<6 hours) intracerebral haemorrhage, we suggest **lowering blood pressure to below 140 mmHg** (and to keep it above 110 mmHg) to reduce haematoma expansion.

QoE: Moderate⊕⊕
SoR: Weak ↑

Expert Consensus Statement

In patients with acute intracerebral haemorrhage, we suggest initiating antihypertensive treatment as early as possible and ideally **within 2 hours** of symptom onset. The decrease of systolic blood pressure should not exceed 90mmHg from baseline values. Vote 10 of 10.

Vote 10 of 10

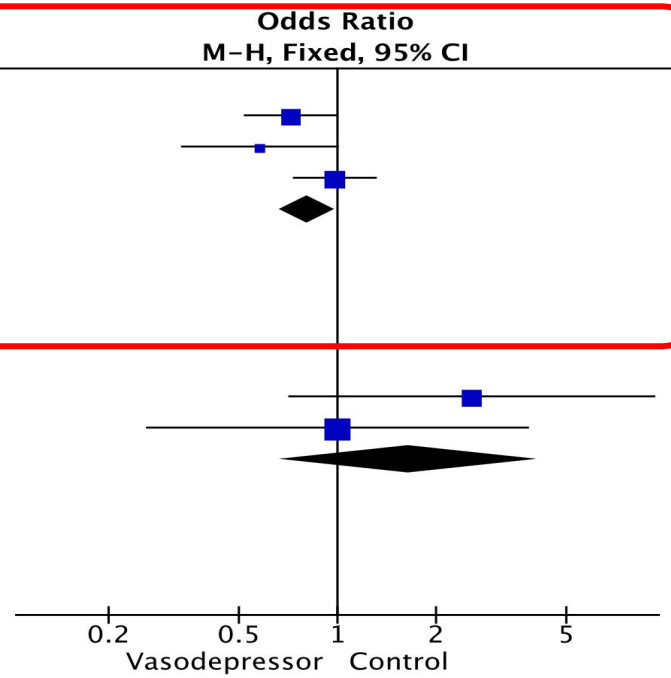
ESO EUROPEAN STROKE ORGANISATION

Control of Systolic Blood Pressure is associated with lower HE

Meta-analysis of studies on the effect of vasodepressors on HE

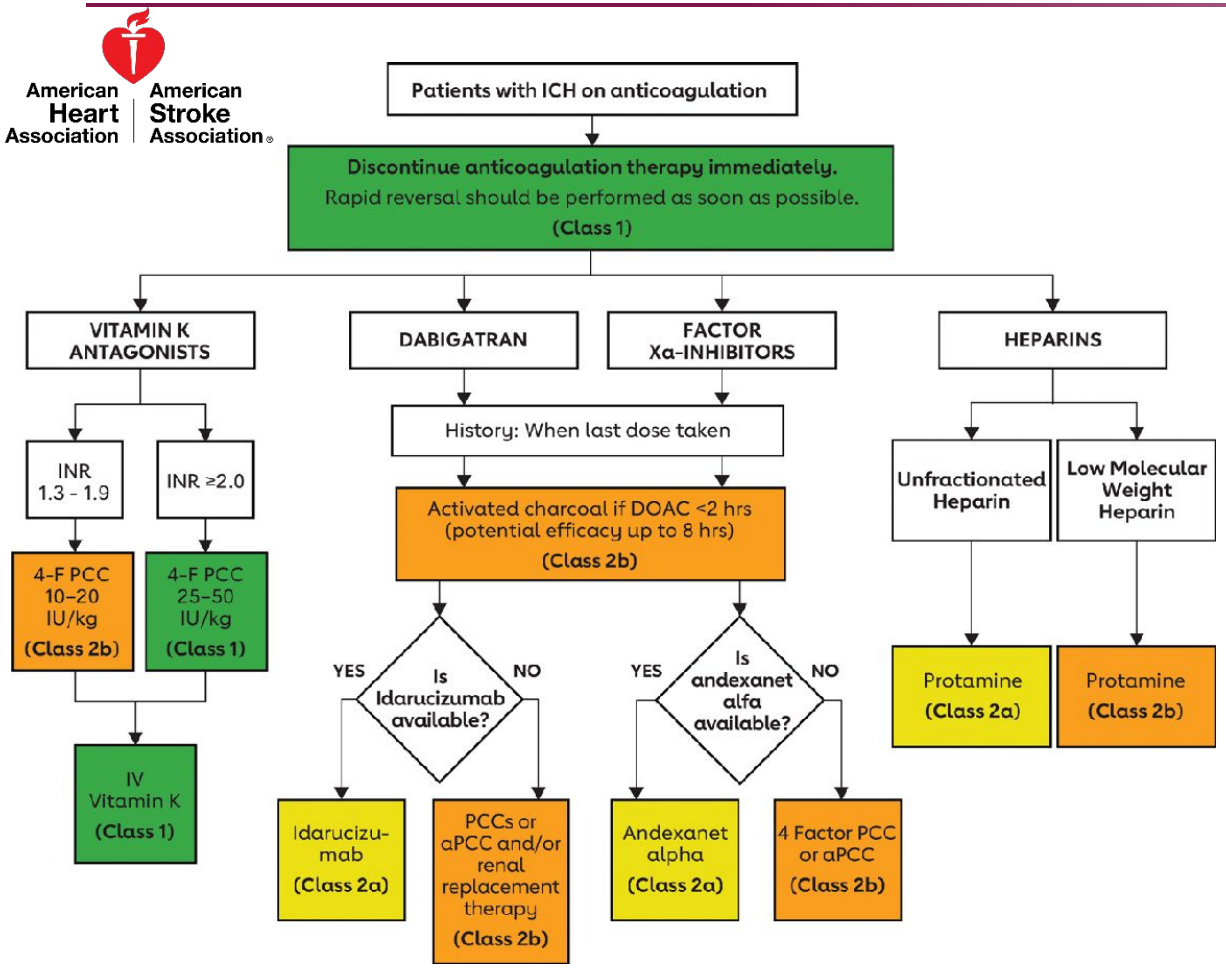
Study or Subgroup	Vasodepressor Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
5.10.1 < 6 hours						
ATACH-2 2016	85	450	104	426	40.3%	0.72 [0.52, 1.00]
INTERACT 2008	26	174	40	172	15.9%	0.58 [0.34, 1.00]
INTERACT2 2013	128	491	125	473	43.8%	0.98 [0.74, 1.31]
Subtotal (95% CI)		**1115**		**1071**	**100.0%**	**0.81 [0.67, 0.99]**
Total events	239		269			
Heterogeneity: $Chi^2 = 3.66$, df = 2 (P = 0.16); $I^2 = 45\%$						
Test for overall effect: Z = 2.04 (P = 0.04)						
5.10.2 < 24 hours						
ICH ADAPT 2013	9	37	4	36	41.7%	2.57 [0.71, 9.27]
Koch 2008	6	21	6	21	58.3%	1.00 [0.26, 3.81]
Subtotal (95% CI)		**58**		**57**	**100.0%**	**1.66 [0.67, 4.10]**
Total events	15		10			
Heterogeneity: $Chi^2 = 1.00$, df = 1 (P = 0.32); $I^2 = 0\%$						
Test for overall effect: Z = 1.09 (P = 0.28)						

Test for subgroup differences: $Chi^2 = 2.25$, df = 1 (P = 0.13), $I^2 = 55.6\%$



EUROPEAN STROKE ORGANISATION

Recommendations on Management of Anticoagulant-Related Hemorrhage



VKA	fXa-inhibitors	dabigatran
Ultrafast INR testing	In some centres specific testing is available. To be used if results are ready in <20 min	In some centres specific testing is available. To be used if results are ready in <20 min
INR: reverse if >1.3	1. line andexanet alfa* (for apixaban, rivaroxaban) Last dose>7 hours: bolus 400 mg, infusion 480 mg over 120 minutes Last dose <7 hours:bolus 800 mg, infusion 960 mg over 120 minutes	Idarucizumab 2.5 g x 2 IV
1. line INR >1.3-1.9: PCC 10 IU/kg INR >1.9: PCC 30 IU/kg	Repeat specific testing after 3, 6, 12 and 24 hours because rebound might occur	Repat specific testing after 12 and 24h because rebound might occur
2.line FFP 20 mL/kg	2. line PCC 50 IU/kg (if andexanet is not available or for edoxaban-ICH)	
Always Vit K 10 mg IV		
Repeat INR at 12-24 hours		

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DOAC, direct oral anticoagulant; ESO, European Stroke Organization; FFP, fresh frozen plasma; Fxa, factor Xa; ICH, intracerebral hemorrhage; INR, international normalized ratio; IV, intravenous; PCC, prothrombin complex concentrate; 4F-PCC, four factor PCC; aPCC, activated PCC; VKA, vitamin k antagonist; ICH, intracerebral hemorrhage; and INR, international normalized ratio.

Christensen H et al. *Eur Stroke J*. 2019;4(4):294-306. *Greenberg 2022 - Stroke. AHA/ASA Guidelines - Management of Patients With Spontaneous Intracerebral Hemori*

Reversal of Vitamin K Antagonists in ICH patients

PICO	Table 1. Summary of recommendations.	Quality of evidence	Strength of recommendation
1	We recommend using PCC (30 IU/kg) in adults with ICH occurring during use of vitamin K antagonists (with an INR above normal) over no treatment to decrease mortality and normalise INR.	Very low	Strong
2	We recommend using PCC (30 IU/kg) in patients with ICH occurring during use of vitamin K antagonists (with an INR above normal) over FFP (20 mL/kg) to decrease mortality and normalise INR.	Moderate	Strong
3	In adult patients with ICH occurring during use of vitamin K antagonists (with an INR above normal) we recommend using vitamin K (10 mg IV) in addition to fast reversal strategies including PCC to prevent re-increase of INR to decrease haematoma expansion and decrease mortality	Very low	Strong

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No RCTs investigating **PCC vs placebo** are available.

Retrospective pooled analysis[2] of 1,547 patients treated with FFP (24%), PCC (38%), both (9%), or neither (29%) from 16 stroke registries from 9 countries

Primary endpoint: all-cause case fatality

Outcomes with PCC versus FFP were similar (HR = 1.075); 4F-PCC was associated with higher case fatality compared to 3F-PCC.

INCH trial: Phase 3b/4 Study[3]
multicentre, prospective, randomised, open-label, blinded-endpoint trial: PCC vs FFP

Primary endpoint: proportion of patients with INR 1.2 or lower <3 h of treatment initiation.

54 patients were randomly assigned (26 to FFP and 28 to PCC)

Christensen et al. - European Stroke Journal 2019, Vol. 4(4) 294–306; 2 Parry-Jones, A. R. et al (2015). *Annals of neurology*, *78*(1), 54–62. 3 Steiner T et all. (INCH) Lan

Reversal of Dabigatran in ICH patients

	Quality of evidence	Strength of recommendation
In adult patients with ICH occurring during use of dabigatran, idarucizumab is recommended to reverse effects of dabigatran.	Low	Strong

REVERSE-AD: Phase 3b/4 Study

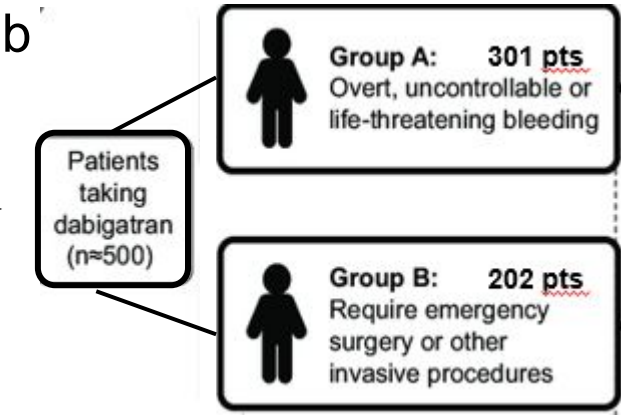
Multicenter, prospective, open-label, single-arm study with Idarucizumab

Primary efficacy end point:

- Maximum Reversal of Anticoagulant Effect of Dabigatran Based on dTT or ECT

Secondary outcome measure:

- Time to Cessation of Bleeding (for Group A Only)



100% **percentage reversal** on the basis of either the dTT or the EC

Only 98 pts with **ICrH**

Head imaging studies were not mandated

- The time to the cessation of bleeding could not be assessed.
- Hematoma expansion on early follow-up imaging studies was not analyze

Pollack et al. 2017 NEJM

dTT = diluted thrombin time ; ECT= ecarin clotting time; IcrH = Intracranial Haemorrhage

Reversal of Anti-FXa in ICH patients

	Quality of evidence	Strength of recommendation
In adult patients with ICH occurring during use of rivaroxaban or apixaban, andexanet alfa may be considered to reverse the anticoagulant effect.	Low	Weak

ANNEXA-A/R: Phase 3 study[1]

Two-part randomized, placebo-controlled studies
145 healthy volunteers dosed to steady state with apixaban or rivaroxaban

Primary efficacy endpoints:

- Percent change in anti-FXa activity from baseline to nadir

After a bolus plus 2-hour infusion, reversed anti-FXa activity by:

ANNEXA-A: **-92%**

ANNEXA-R: **-97%**

Median of **percent change in anti-FXa** from baseline to nadir

ANNEXA-4: Phase 3b/4 study[2]

Earliest report of **67 pts** with **major bleedings** enrolled the multicenter, prospective, open-label with andexanet alfa

Co-primary efficacy endpoints:

- % change in anti-FXa activity from baseline to nadir
- Excellent or good hemostatic efficacy 12h after andexanet alfa administration

-89% median of **percent change in anti-FXa** from baseline to nadir

79% **Excellent/good hemostatic efficacy** of Overall Patients 12 Hours After Treatment

1. Siegal DM et al. N Engl J Med 2015;373(25):2413-2424; 2. Connolly et al. N Engl J Med. 2016;375:1131-1141;

Andexanet alfa: Latest evidence became available after 2019

ANNEXA-4: Phase 3b/4 Study

Multicenter, prospective, open-label, single-arm

246 pts with IntraCranial Haemorrhages
treated with Andexanet alfa assessed on CT-Imaging

Co-primary efficacy endpoints:

- % change in anti-FXa activity from baseline to nadir
- Excellent or good hemostatic efficacy 12h after andexanet alfa administration

-92% median of **percent change in anti-FXa** from baseline to nadir

80% **Excellent/good hemostatic efficacy** (in 195/246) of Overall Patients 12 Hours After Treatment

Full paper published in March 2023

ANNEXA-I: Phase 4 study

multicenter, prospective, randomized, open-label

530 pts with **IntraCerebral Haemorrhages**
treated with Andexanet alfa vs Usual care

Primary Efficacy Endpoint:
Effective Hemostasis[1,b]

Defined as meeting **all 3** of the following criteria:

1. ≤35% hematoma volume expansion at 12 hours
2. NIHSS score increase of <7 at 12 hours
3. No rescue therapy administered between 3 and 12 hours after randomization

11%
95% CI, 2.8-19.3
p=0.008

adjusted absolute increase in **Effective Hemostasis** with **andexanet alfa** vs **usual care**[1,b]

Presented at WSC in october 2023

1. Milling TJ et al. Circulation. 2023.; 2. Connolly SJ. Presented at: WSC; October 10-12, 2023; Toronto, Canada;

ABC-ICH: an Acute Bundle of Care study in ICH

A **Anticoagulant reversal:** Reversal agents delivered as quickly as possible (**<90 min**)

B **Blood pressure :** using IV antihypertensives for rapid, intensive BP lowering (**<60 min**)

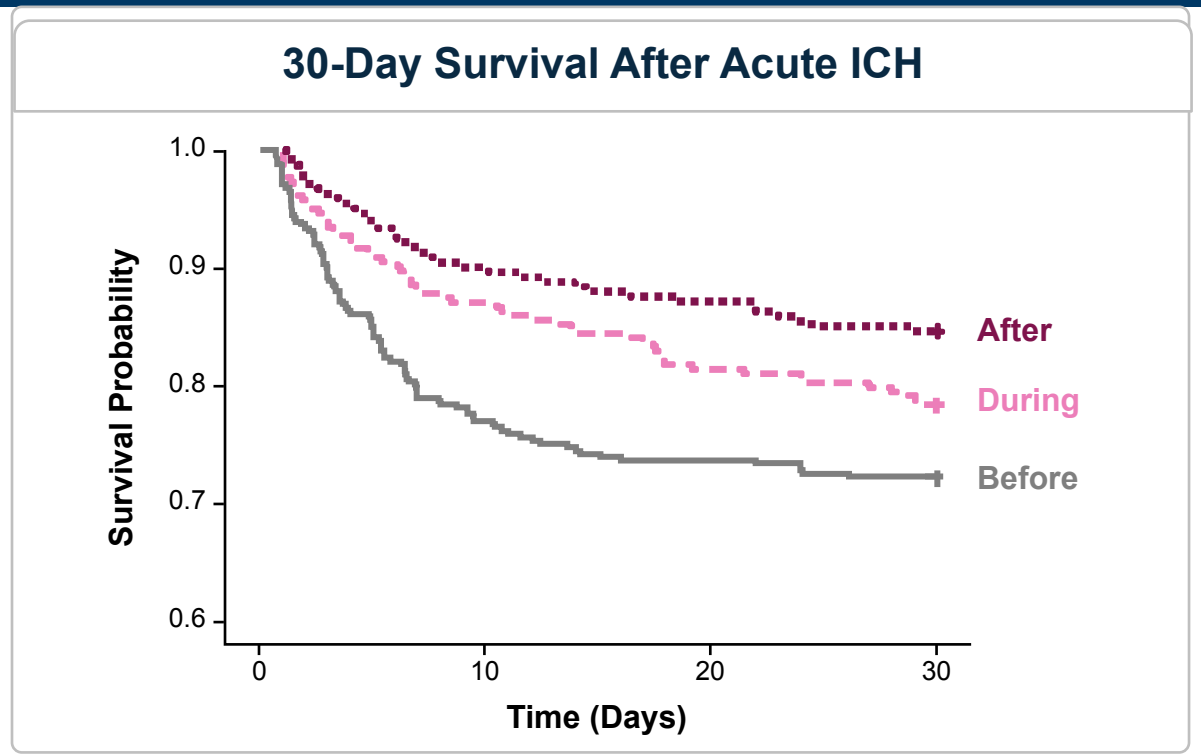
C **Care pathway:** Prompt referral of appropriate patients to neurosurgery of all patients with mRS score ≤2 and any of the following:

- GCS <9,
- posterior fossa ICH,
- an obstructed 3rd/4th ventricle,
- or hematoma volume >30ml

Parry-Jones AR et al. *Ann Neurol*. 2019;86(4):495-503.

Acute Bundle of Care Implementation for ICH Management was Associated with Reduced 30-Day Mortality

An **ABC-ICH project** was implemented at a large comprehensive stroke center and regional neurological center; the study compared 30-day case mortality **before**, **during**, and **after bundle implementation** in patients with spontaneous ICH (N=860)



Pre QI	
Salford	35.5%
SSNAP	31.6%

QI / Post-QI	
Salford	24.2%
SSNAP	31.1%

Lower odds of 30-day case mortality[a]

During implementation period:[b] OR 0.62; 95% CI: 0.38-0.97, p=0.003

After implementation period:[c] OR 0.40; 95% CI: 0.24-0.61, p <0.0001

[a]Adjusted for premorbid mRS, GCS on arrival, age, IVH, ICH volume, and anticoagulant use; [b]From June 1, 2015-May 31, 2016; [c]From June 1, 2016-May 31, 2017.
ABC = Acute Bundle of Care; ICH = intracerebral hemorrhage; OR = odds ratio
Parry-Jones AR et al. *Ann Neurol*. 2019;86(4):495-503. SSNAP = Sentinel Stroke National Audit Programme

The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3): an international, stepped wedge cluster randomised controlled trial

Lu Ma, Xin Hu*, Lili Song*, Xiaoying Chen*, Menglu Ouyang, Laurent Billot, Qiang Li, Alejandra Malavera, Xi Li, Paula Muñoz-Venturelli, Asita de Silva, Nguyen Huy Thang, Kolawole W Wahab, Jeyaraj D Pandian, Mohammad Wasay, Octavio M Pontes-Neto, Carlos Abanto, Antonio Arauz, Haiping Shi, Guanghai Tang, Sheng Zhu, Xiaochun She, Leibo Liu, Yuki Sakamoto, Shoujiang You, Qiao Han, Bernard Crutzen, Emily Cheung, Yunke Li, Xia Wang, Chen Chen, Feifeng Liu, Yang Zhao, Hao Li, Yi Liu, Yan Jiang, Lei Chen, Bo Wu, Ming Liu, Jianguo Xu, Chao You, Craig S Anderson, for the INTERACT3 Investigators†*

Summary

Background Early control of elevated blood pressure is the most promising treatment for acute intracerebral

BUNDLE OF CARE approach in INTERACT-3, an RCT

INTERACT-3 Trial: an international, stepped wedge cluster randomised controlled trial

Background

- INTERACT3 was designed to determine the effectiveness of a goal-directed care bundle of active management vs. usual care in ICH.
- **121 Hospitals from 10 countries** were enrolled, totalling 7067 patients ≥18 years within six hours of experiencing ICH that received either SOC or the care bundle protocol.

Start Date: December 2017
Completion Date: November 2022

N=7067

R
Sequential Assignment

Care bundle protocol

- Intensive **BP lowering** to systolic target of <140mmHg within 1 h
- **Glucose control** target 6.1-7.8 mmol/l (non-diabetic); 7.8-10.0 mmol/l (diabetic) - as soon as possible
- Treatment of **Pyrexia** to a target body t ≤37.5 ℃ within 1h
- **Reversal of anticoagulation to target INR <1.5** involving use of vitamin K and prothrombin complex concentrate (**PCC**) or alternatively, fresh frozen plasma (**FFP**) – within 1 h.
- All target were **to be maintained in patients for 7 days** (or until discharge or death, should these events occur earlier).

Usual care

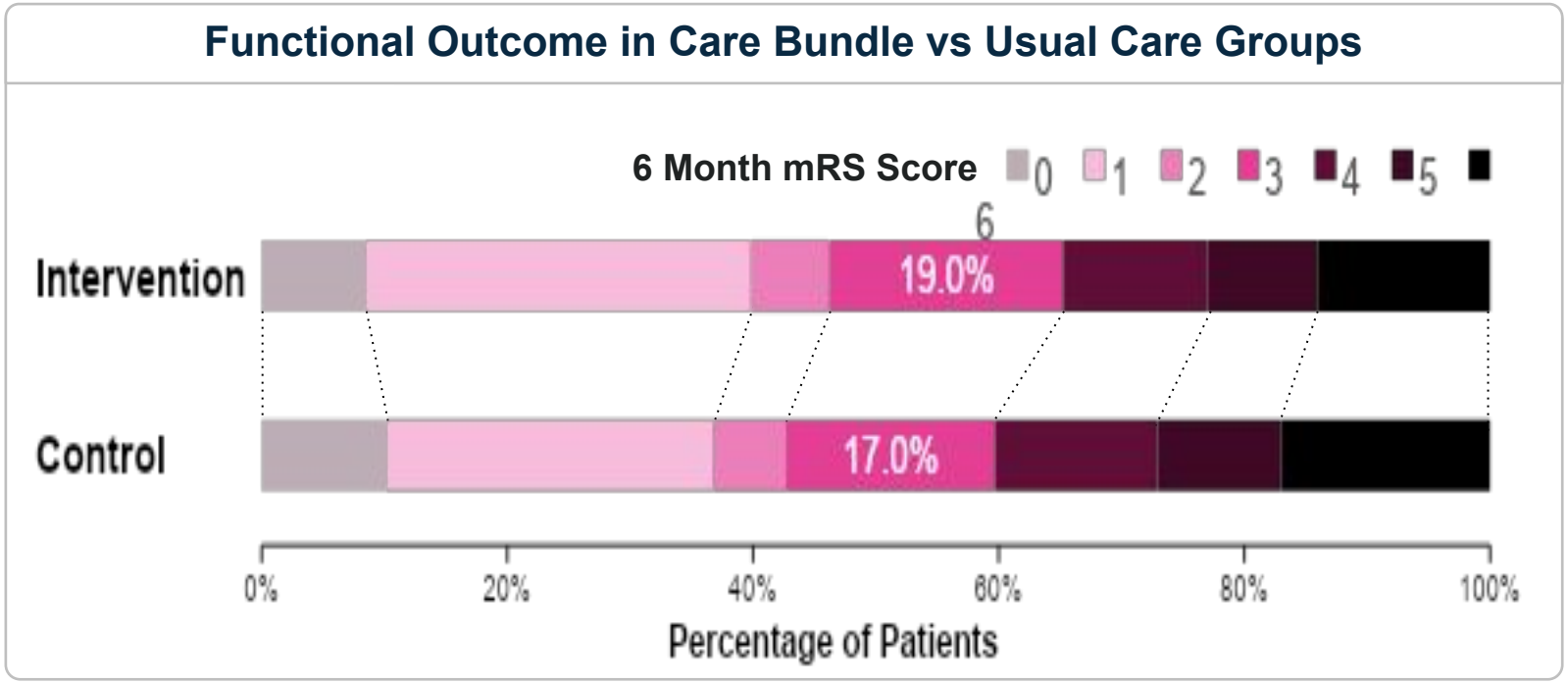
Patients receive the usual management based on local guidelines and hospital's individual policy

Primary endpoint

- Functional recovery at 6 m (mRS; range 0 [no symptoms] to 6 [death])

Ma L et al. *Lancet*. 2023;402(10395):27-40.

Implementation of a CARE BUNDLE for active management of ICH can improve outcomes



Compared to usual care, implementation of a **time-sensitive care bundle** was associated with:

Favorable mRS scores[d,e]
OR, 0.86; 95% CI, 0.76-0.97; p=0.015

Lower odds of mortality[d,e]
OR, 0.77; 95% CI, 0.63-0.95; p=0.015

Increased odds of hospital discharge by day 7
OR, 0.72; 95% CI, 0.53-0.98; p=0.034

Fewer serious AE
16·0% vs 20·1%; p=0·0098

[a]Intensive BP lowering to systolic target of <140mmHg within 1 hr of treatment initiation; [b]Glucose control target 6.1-7.8 mmol/L (non-diabetic); 7.8-10.0 mmol/L (diabetic); [c]Reversal of warfarin-related anticoagulation with PCC or FFP; [d]Analyzed as an ordinal outcome (shift across all categories); [e]Outcomes measured at 6 months; [f]HRQoL measured by the EQ-5D-3L.
BP = blood pressure; CI = confidence interval; EQ-5D-3L = European Quality of Life 5 Dimensions 3 Level Version; FFP = fresh frozen plasma; hr = hour; HRQoL = health-related quality of life; ICH = intracranial hemorrhage; INR = international normalized ratio; mRS = modified Rankin Scale; OR = odds ratio; PCC= prothrombin complex concentrate; QoL = quality of life; SAE = serious adverse events.
Ma L et al. *Lancet*. 2023;402(10395):27-40.

Bundle of Care: An International Expert Consensus

Review Article

EUROPEAN STROKE JOURNAL

Acute care bundles should be used for patients with intracerebral haemorrhage: An expert consensus statement

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EUROPEAN STROKE JOURNAL

Acute care bundles should be used for patients with intracerebral haemorrhage: an expert consensus statement

ICH care bundles reduce morbidity and mortality.
We review current evidence and make practical recommendations for implementation.

Methods


Neurology


Neurosurgery


Critical Care


Emergency Medicine

Consensus Meeting May 2023


Consensus statement agreed

Results

We recommend:

Door	Stabilise patient, rapid imaging Coagulation tests
< 30 min	Reverse anticoagulant Start intensive BP lowering
< 60 min	SBP < 140, Consult Neurosurgery Achieve T < 37.5°C
7 days	Maintain SBP < 140; T < 37.5°C Maintain normoglycaemia

Conclusion

Multiple simultaneous interventions improve functional outcome

Rapid bundled care should be introduced

Quality improvement will help achieve **ambitious process targets**

Parry-Jones, A., et al. European Stroke Journal, 2023 adrian.parry-jones@manchester.ac.uk doi.org/10.1177_23969873231220235

"Parry-Jones AR, Järhult SJ, Kreitzer N, et al. Acute care bundles should be used for patients with intracerebral haemorrhage: An expert consensus statement. European Stroke Journal. 2023;0(0). doi:10.1177/23969873231220235

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Table 1. Individual interventions for possible inclusion in an acute, ICH-specific bundle of care.

Intervention	Criteria for treatment	Recommended process targets	Supporting guidelines/key evidence
Anticoagulant reversal	PCC and vitamin K (VKA antagonist): INR ⩾ 1.3 Andexanet alfa: currently taking apixaban or rivaroxaban and last dose taken ⩽18 h Idarucizumab: currently taking dabigatran PCC (DOACs): taking a DOAC and specific reversal agent unavailable or unlicenced for specific agent	Door-to-needle time ⩽ 30 min	1. ESO anticoagulant-associated ICH guideline (2019)[11] 2. AHA/ASA ICH guideline (2022)[5] 3. REVERSE-AD[14] 4. ANNEXA-4[15]
Intensive blood pressure reduction	⩽6 h after symptom onset: SBP ⩾ 150 mmHg ⩾6 h after symptom onset or unknown onset: uncertain, consider if SBP ⩾ 150 mmHg	Treatment target ⩽ 140 mmHg, maintained for 7 days Avoid large (>90 mmHg) initial drops on SBP Door-to-first antihypertensive: ⩽30 min Door-to-target: ⩽60 min	1. ESO BP guideline (2021)[21] 2. AHA/ASA ICH guideline (2022)[5] 3. INTERACT2[47] & 3[3]

AHA/ASA: American Heart Association/American Stroke Association; DOAC: direct oral anticoagulant; ESO: European Stroke Organisation; GCS: Glasgow Coma Scale; ICH: intracerebral haemorrhage; INR: international normalised ratio; PCC: prothrombin complex concentrate; SBP: systolic blood pressure; VKA: vitamin-K antagonist; mRS: modified Rankin Scale.


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Surgical evacuation of haematoma and/or external ventricular drainage	Decision to operate on a case-by-case basis by a multi-disciplinary team. Local criteria should be established to identify patients where a consultation with neurosurgery must occur, for example: Patients with a pre-morbid mRS of ⩽2, reasonable prognosis and one or more of: 1. GCS ⩽ 13 2. Supratentorial ICH volume ⩾ 20 mL 3. Posterior fossa ICH 4. Obstruction of third and fourth ventricle(s)	100% of patients meeting consultation criteria are discussed with neurosurgery ⩽50% of patients not meeting consultation criteria are discussed with neurosurgery within 60 min of arrival.	1. ESO ICH guideline (2014)[33] 2. AHA/ASA ICH guideline (2022)[5]


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Control of glucose	Non-diabetic patients: Blood glucose > 7.8 mmol/L in first 7 days Diabetic patients: Blood glucose > 10 mmol/L in first 7 days	Non-diabetic patients: maintain blood glucose between 6.1 and 7.8 mmol/L for ⩾90% of measurements in first 7 days Diabetic patients: maintain blood glucose between 7.8 and 10 mmol/L for ⩾90% of measurements in first 7 days For both groups, optimise protocols to avoid hypoglycaemia	1. INTERACT3[3] 2. QASC[37] AHA/ASA guideline (2022)[5]
Control of temperature	Monitor body temperature every 4 h for 7 days and initiate anti-pyretic treatment if temperature ⩾ 37.5°C	Achieve normothermia (<37.5°C) within 1 h of starting treatment	1. INTERACT3[3] 2. QASC[37] 3. AHA/ASA guideline (2022)[5]


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Early Anti-FXa reversal was associated with lower mortality risk

In an observational cohort study, a subgroup analysis of patients treated for DOAC-related ICrH (n=1,283) found an association between in-hospital mortality and multiple clinical factors

Longer door-to-reversal administration time
(≥30 min) was associated with

higher mortality risk in ICrH subgroup

aOR, 2.46; 95% CI, 1.12-6.22[a]

Take-home messages

- **L'ictus emorragico è meno frequente dell'ictus ischemico ma è associato a tassi di mortalità e disabilità più elevati**
- **Il 20% dei pazienti con Stroke emorragico è in terapia anticoagulante, con la percentuale di pazienti in terapia con DOAC in costante aumento. Gli anticoagulanti sono associati ad un aumento della mortalità e della disabilità**
- **Sebbene le prove sui benefici della gestione isolata della temperatura, della glicemia, della pressione arteriosa e della coagulazione siano modeste, l'approccio "bundle" sembra aumentare i tassi di sopravvivenza di questi pazienti**
- **Per quanto riguarda l'ictus ischemico TIME IS BRAIN: un intervento precoce sulla pressione arteriosa (<60 min) e sulla coagulazione (<60-90 min) sembra essenziale per ridurre la mortalità e disabilità per Stroke emorragico**
- **I pazienti con ICH richiedono una precoce ed intensiva terapia a causa dell'alto rischio di compromissione neurologica e mortalità**

Conclusioni

Annexa

- **Andexanet alfa è l'agente di inversione specifico approvato per apixaban o rivaroxaban in pazienti con sanguinamento incontrollato o potenzialmente fatale correlato inbitori Fxa**

- **quasi l'80% dei pazienti ha raggiunto i risultati desiderati di efficacia emostatica, ma il 10% aveva un evento trombotico.**

SCALA MRS *(Modified Rankin Scale)*

0	Nessun sintomo
1	Nessuna disabilità significativa malgrado i sintomi: è in grado di svolgere tutte le attività e i compiti abituali
2	Disabilità lieve: non riesce più di svolgere tutte le attività precedenti, ma è autonomo/a nel camminare e nelle attività della vita quotidiana
3	Disabilità moderata: richiede qualche aiuto nelle attività della vita quotidiana, ma cammina senza assistenza
4	Disabilità moderatamente grave: non è più in grado di camminare senza aiuto né di badare ai propri bisogni corporali
5	Disabilità grave: costretto/a a letto, incontinente e bisognoso/a di assistenza infermieristica e di attenzione costante
	TOTALE