University of Nottingham
UK | CHINA | MALAYSIA

TICH-3

Nottingham University Hospital NHS Trust


# State of the art in ICH management – and impact on global health

07 Oct 2024

Instituto de Salud Carlos III
Plan de Recuperación, Transformación y Resiliencia
ISCBFM International Society for Cerebral Blood Flow & Metabolism
Funded by the European Union NextGenerationEU
RICORS - ICTUS
Vall d'Hebron Institut de Recerca

III Stroke Congress

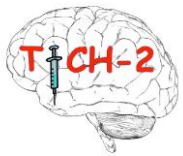
NEW INSIGHTS AND PERSPECTIVES ON INTRACEREBRAL HEMORRHAGE:
A COMPREHENSIVE UPDATE

**Prof. Nikola Sprigg**

# Financial disclosures

•Chief investigator for the TICH-2 and TICH-3 funded by National Institute of Health Research Health Technology Assessment (NIHR HTA project code 11_129_109) and Assessment (NIHR HTA project code 129917)

•Chief investigator for DASH funded by National Institute of Health Research for Patient Benefit (RfPB)






FUNDED BY
NIHR | National Institute for Health and Care Research

# Overview: State of the art treatment for ICH

- Global burden of ICH
  Primary prevention and public awareness

- ICH care now: ABC **bundles** of care
  **A**nticoagulation reversal
  **B**P lowering
  **C**are pathway for prompt neurosurgical referral

- Secondary prevention:
  Anti-thrombotics, Blood pressure lowering, statins

- Measuring quality of care for ICH indicators

# ‘State of the art’ treatment

## Core components

- Evidence based treatments
- Highly trained team
- Multi-disciplinary, across organisations
- Research to develop evidence based treatments
- Audit and quality improvement

- Technology – imaging
- Environment – stroke unit, surgery, critical care

- Patient/family involvement throughout the pathway

# Healthcare needs to be for all....

**Robin Hood**

‘robar a los ricos y dar a los pobres’

## sICH or IVH and hydrocephalus which is contributing to decreased level of consciousness or GCS <8:

Ventricular drainage should be performed to reduce mortality (1)

ICP monitoring and treatment to reduce mortality and improve outcomes (2b)

Corticosteroids should not be administered for treatment of elevated ICP (3: No Benefit)

Early prophylactic hyperosmolar therapy for improving outcomes is not well established (2b)

Bolus hyperosmolar therapy may be considered for transiently reducing ICP (2b)

**Abbreviation:** ICP indicates intracranial pressure; IVH, intraventricular hemorrhage; and sICH, spontaneous intracerebral hemorrhage.



Greenberg, S. M. 2022 AHA/ASA . Guideline for the Management of Patients with Spontaneous Intracerebral Hemorrhage. *Circulation.*

# All strokes need state of the art care – many overlaps

## Ischaemic stroke

1. Pre-hospital alert
2. Immediate imaging
3. Pathways of care
4. Thrombolysis
5. Thrombectomy
6. Stroke Unit Care
7. VTE prevention
8. Hemicraniectomy
9. Secondary prevention
10. Rehabilitation therapy
11. Carotid surgery/stenting

## Intracerebral haemorrhage

1. Pre-hospital alert
2. Immediate imaging
3. Pathways of care
4. Anticoag. reversal, BP lowering
5. Neurosurgery
6. Stroke Unit Care
7. VTE prevention
8. Hemicraniectomy
9. Secondary prevention
10. Rehabilitation therapy
11. Follow up imaging/MRI/MRA

# Overview: State of the art treatment for ICH

- Outstanding questions: How best to organise ICH care
  Can we identifty patients in the pre-hospital setting?
  Should ICH patients go to specialist centres?

- Possible future treatment targets:
  ? Stop the bleeding – haemostatic agents
  rFactor VIIa, Tranexamic acid, Desmopressin
  ? Reduce damage caused by the blood
  Anti-odema agents
  Inflammation
  ? Improve recovery with non drug interventions
  Transcranial magnetic stimulation/

# SPANISH STROKE RESEARCH NETWORK MEETING

## October 9th

| Time | Event |
|---|---|
| **08:30 - 08:45** | **Welcome and Opening Remarks.**<br>Ignacio Lizasoain, Hospital 12 de Octubre, UCM, Madrid (Spain) |
| **08:45 – 09:05** | **2022 Seed Fund:** "Study of the role of RhoA and XDH proteins in mid intracerebral haemorrhage through the development of an in vitro model".<br>***IdIPAZ**, IDIS and IRYCIS groups. María Gutierrez* |
| **09:05 - 09:25** | **2023 Seed Fund:** "Neuromodulation of executive dysfunction by transcranial direct current stimulation in a rat model of cerebral infarction".<br>***FIBAO**, IdIPAZ and IBIS groups. Patricia Martinez* |
| **09:25 - 09:45** | **2024 Seed Fund:** "Effect of TLR4-mediated modulation of inflammation on the reduction of brain damage after paediatric ischaemic stroke".<br>***Imas12**, HCUV, IGTP and IIS La Fe groups. Macarena Hernández* |
| **09:45 – 10:05** | **RESEARCH LINE 1. BIOMARKERS**<br>**Summary** of the main results of the "collaborative projects"<br>*Anna Rosell, Joan Montaner* |
| **10:05 - 10:35** | **Coffee break** |
| **10:35 - 10:55** | **RESEARCH LINE 2. ACUTE-PHASE TREATMENT**<br>**Summary** of the main results of the "collaborative projects"<br>*Joan Martí, Natalia Pérez de Ossa,* |
| **10:55 – 11:15** | **RESEARCH LINE 3. CEREBROPOTECTION**<br>**Summary** of the main results of the "collaborative projects"<br>*Angeles Almeida, Francisco Campos* |
| **11:15 - 11:35** | **RESEARCH LINE 4. BRAIN REPAIR AND FUNCTIONAL RECOVERY.**<br>**Summary** of the main results of the "collaborative projects"<br>*Exuperio Diez-Tejedor, Mar Freijó* |
| **11:35 - 11:55** | **RESEARCH LINE 5. SECONDARY PREVENTION.**<br>**Summary** of the main results of the "collaborative projects"<br>*Mar Castellanos, Tomás Segura* |

# Background – intracerebral haemorrhage

## Global burden of ICH

- Devastating disease – high early mortality, long term disability
- Incidence set to rise as age and high blood pressure are main risk factors
- GBD Study 2019: 3 million ICH, 1.5 million deaths due to ICH
- Despite causing 25% of stoke – ICH accounts 45% mortality
- Leading risk factor - hypertension
- Increased with lower economic class, lower level education, higher BM, older age

## Haematoma expansion

- Up to a third of ICH patients have continued bleeding (haematoma expansion) which occurs early (mostly < 6 hours)
- Even 1ml of blood in brain linked with worse outcome

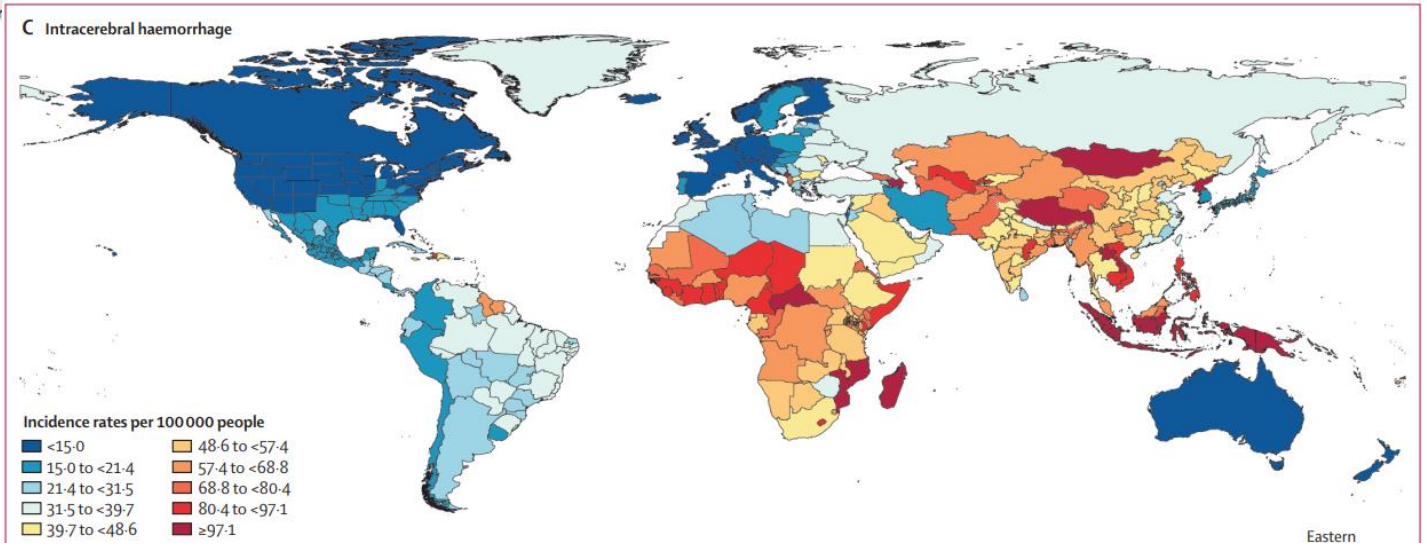
# Global burden of ICH

# Global burden of disease

| | Incidence (95% UI) | | Deaths (95% UI) | | Prevalence (95% UI) | | DALYs (95% UI) | |
|---|---|---|---|---|---|---|---|---|
| | 2019 | Percentage change, 1990–2019 | 2019 | Percentage change, 1990–2019 | 2019 | Percentage change, 1990–2019 | 2019 | Percentage change, 1990–2019 |
| **Ischaemic stroke** | | | | | | | | |
| Absolute number, millions | 7·63 (6·57 to 8·96) | 88·0% (83·0 to 92·0) | 3·29 (2·97 to 3·54) | 61·0% (46·0 to 75·0) | 77·19 (68·86 to 86·46) | 95·0% (92·0 to 99·0) | 63·48 (57·83 to 68·99) | 57·0% (43·0 to 68·0) |
| Age-standardised rate, per 100 000 people | 94·51 (81·9 to 110·76) | −10·0% (−12·0 to −8·0) | 43·50 (39·08 to 46·77) | −34·0% (−39·0 to −28·0) | 951·0 (849·2 to 1064·1) | −2·0% (−3·0 to 0·0) | 798·8 (727·5 to 866·9) | −29·0% (−35·0 to −23·0) |
| **Intracerebral haemorrhage** | | | | | | | | |
| Absolute number, millions | 3·41 (2·97 to 3·91) | 43·0% (41·0 to 45·0) | 2·89 (2·64 to 3·10) | 37·0% (22·0 to 51·0) | 20·66 (18·02 to 23·42) | 58·0% (56·0 to 60·0) | 68·57 (63·27 to 73·68) | 25·0% (12·0 to 36·0) |
| Age-standardised rate, per 100 000 people | 41·81 (36·53 to 47·88) | −29·0% (−30·0 to −28·0) | 36·04 (32·98 to 38·67) | −36·0% (−43·0 to −29·0) | 248·8 (217·1 to 281·4) | −17·0% (−18·0 to −15·0) | 823·8 (769·2 to 894·7) | −37·0% (−43·0 to −31·0) |

Absolute numbers in millions and age-standardised rates per 100 000 people are presented to two decimal places and percentage change is shown to one decimal place. UI=uncertainty interval. DALY=disability-adjusted life-year.

***Table 1:*** **Absolute number and age-standardised rates per year of incident and prevalent strokes, deaths from stroke and DALYs due to stroke in 2019, and percentage change globally for 1990–2019, by path**

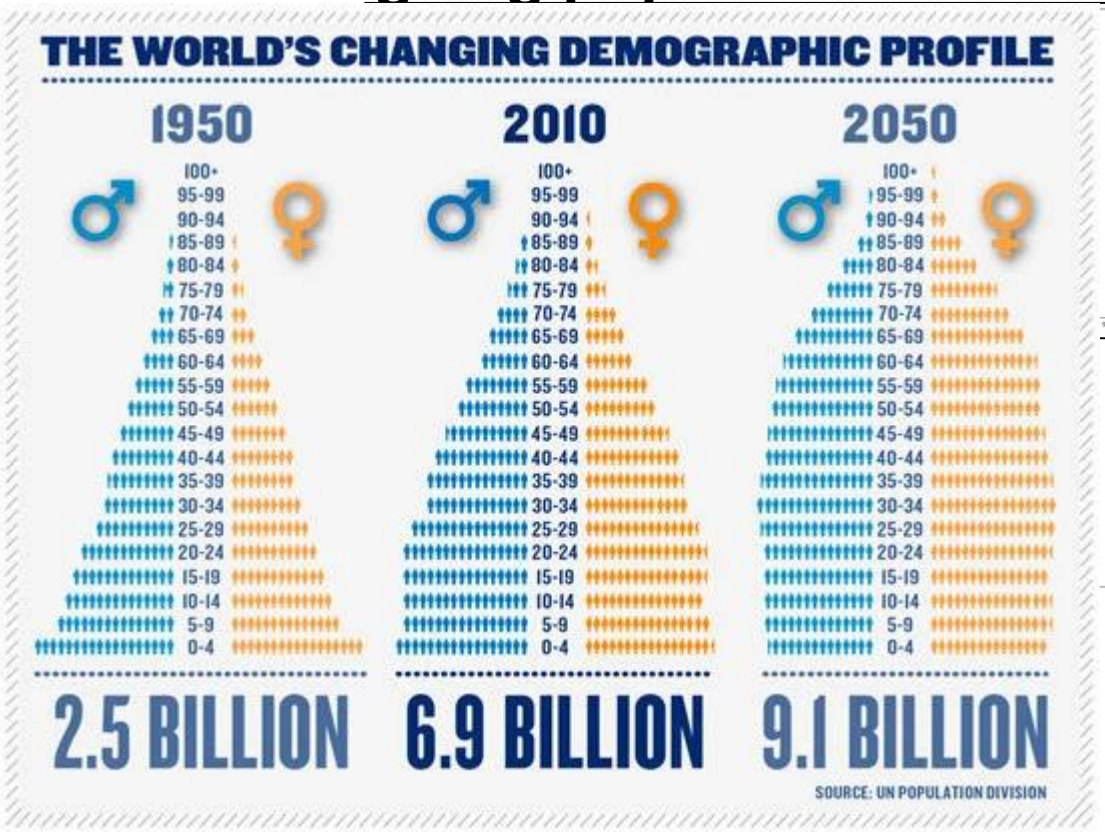





- Lancet Neurol 2021; 20: 795–820

# ICH – increasing burden due to ageing population

- Incidence related to ag
- Leading risk factor - hy
- Increased with lower e
  lower level education,



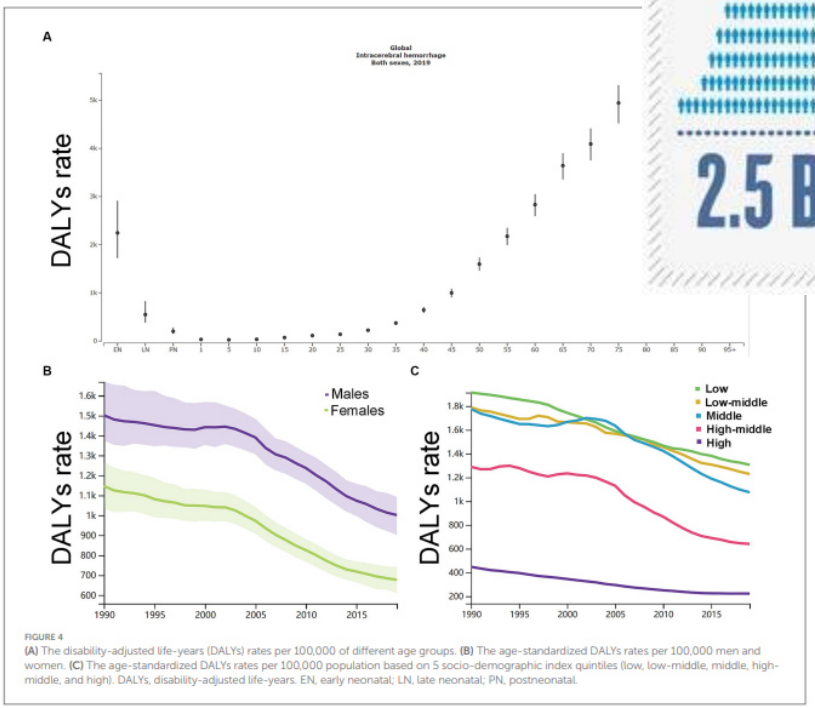




FIGURE 4
**(A)** The disability-adjusted life-years (DALYs) rates per 100,000 of different age groups. **(B)** The age-standardized DALYs rates per 100,000 men and women. **(C)** The age-standardized DALYs rates per 100,000 population based on 5 socio-demographic index quintiles (low, low-middle, middle, high-middle, and high). DALYs, disability-adjusted life-years. EN, early neonatal; LN, late neonatal; PN, postneonatal.

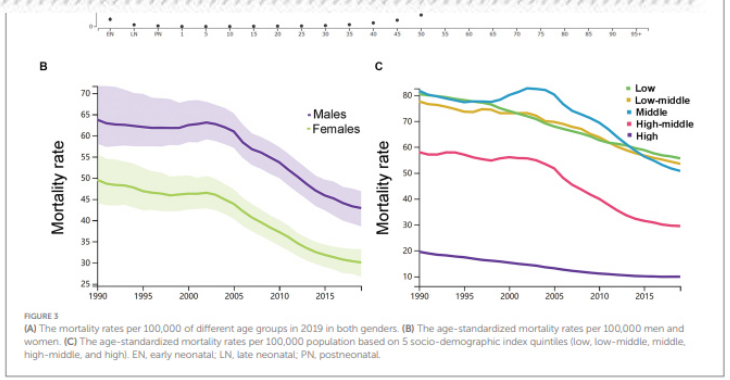



FIGURE 3
**(A)** The mortality rates per 100,000 of different age groups in 2019 in both genders. **(B)** The age-standardized mortality rates per 100,000 men and women. **(C)** The age-standardized mortality rates per 100,000 population based on 5 socio-demographic index quintiles (low, low-middle, middle, high-middle, and high). EN, early neonatal; LN, late neonatal; PN, postneonatal.

https://doi.org/10.3389/fneur.2023.1241158

Xu et al. BMC Public Health (2024) 24:2426
https://doi.org/10.1186/s12889-024-19923-7

BMC Public Health

RESEARCH Open Access

# Global, regional, and national burden of intracerebral hemorrhage and its attributable risk factors from 1990 to 2021: results from the 2021 Global Burden of Disease Study

Libo Xu[1], Zhenhao Wang[1], Wenchao Wu[1], Mao Li[2] and Qingsong Li[1*]

- Despite overall decrease in incidence there remains very high global burden

- Regionally, Central Asia, Oceania, Southeast Asia had the highest ag standardized prevalence rates of I whereas Australasia, high-income North America, and Western Euro had the lowest rates.

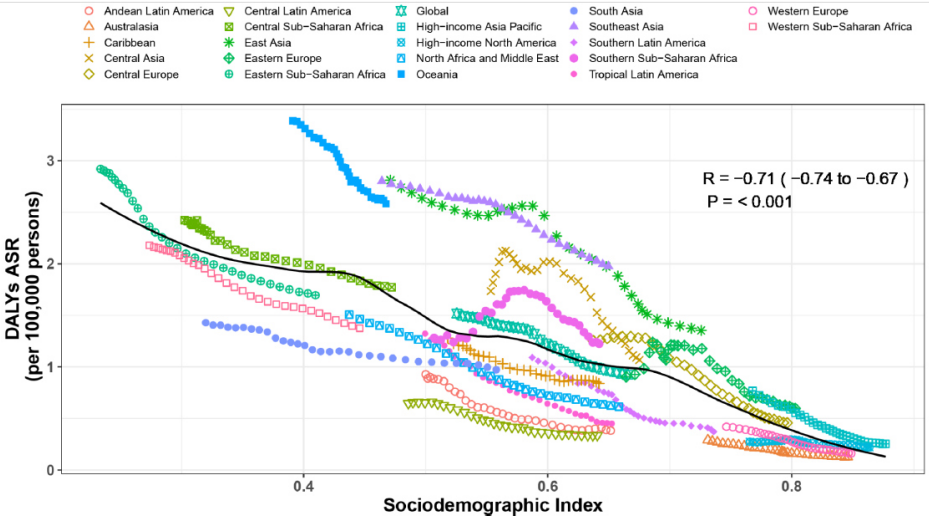



**Fig. 4** Age-standardised disability adjusted life year (DALY) rates of intracerebral hemorrhage for the 21 Global Burden of Disease regions by sociodemographic index, 1990–2021. Thirty-two points are plotted for each region and show the observed age standardised DALY rates from 1990 to 2021 for that region. Expected values, based on sociodemographic index and disease rates in all locations, are shown as a solid line. Regions above the solid line represent a higher than expected burden

# The Burden of Stroke in Spain

Based on the findings of *The Burden of Stroke in Europe* report conducted by King's College London for the Stroke Alliance for Europe

S·A·F·E
Stroke Alliance For Europe
THE STROKE PATIENT VOICE IN EUROPE

**Population: 46,777,373**

**Healthcare cost of stroke in Spain = €1,244.8 million (€27 per capita)**

## Stroke in Spain:

**Incidence:**
**40,214** strokes per year
**46.2** strokes per **100,000** inhabitants annually

**Prevalence:**
**273,971** strokes
**357.3** strokes per **100,000** inhabitants

**Mortality:**
**36,302** deaths due to stroke per year
**34.5** deaths per **100,000** inhabitants annually

## Estimated increase 2015–2035:

| Incidence: | Prevalence: | Deaths: | DALYs Lost: |
|---|---|---|---|
| 35% | 31% | 39% | 35% |

## Risk factor prevalence:

| High blood pressure | High cholesteroll | Smoking | Raised glucose | Atrial fibrillation (AF) |
|---|---|---|---|---|
| 24.8% | 56.1% | 30.3% | 9.4% | 4.4%* |

**There is a National Stroke Day, held annually since 1999, with several mass media activities to raise stroke awareness.**

# Stroke prevention – Spanish strategy

- Stroke 2nd ranked cause of death in Spain
- Leading cause of death in females
- Leading cause of disability in Spain

Stroke Strategy of the Spanish National Health System

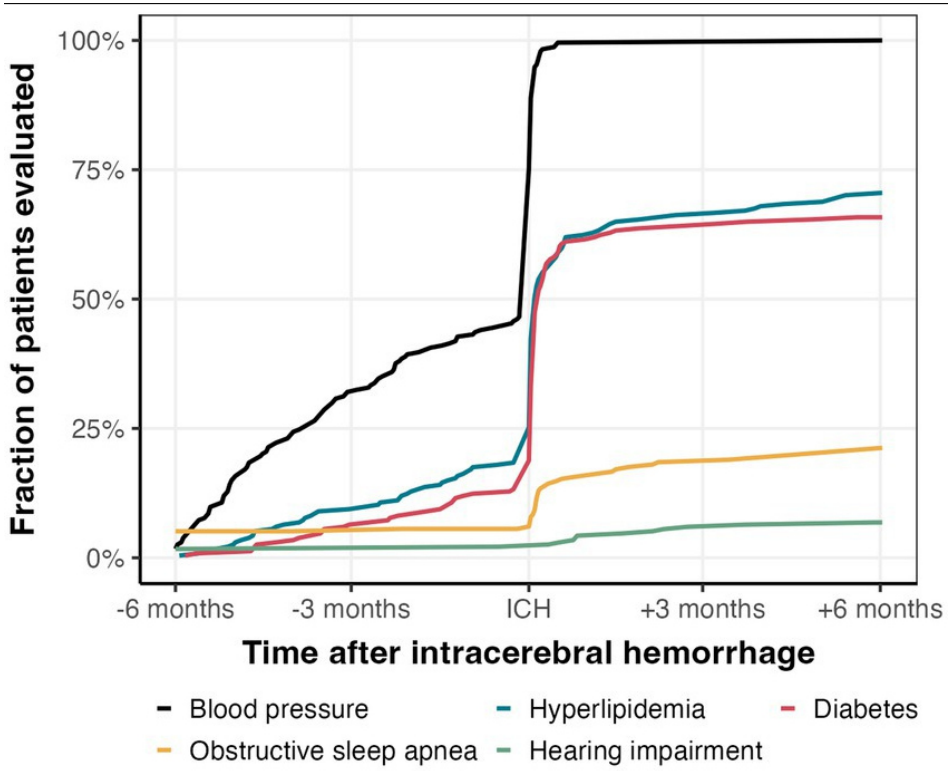
- Prevention
- Informing citizens – recognise stroke
- Stroke code
- Specialist stroke unit care for all
- Tackle health inequalities

http://www.msssi.gob.es/

CONSENSUS STATEMENT

# Recommendations of the Spanish Society of Neurology for the prevention of stroke. Interventions on lifestyle and air pollution

Volume 14 - 2023 | https://doi.org/10.3389/fneur.2023.1194810




## Lifestyle modification

Smoking

Alcohol

Stress

Obesity

Exercise

Mediterranean diet

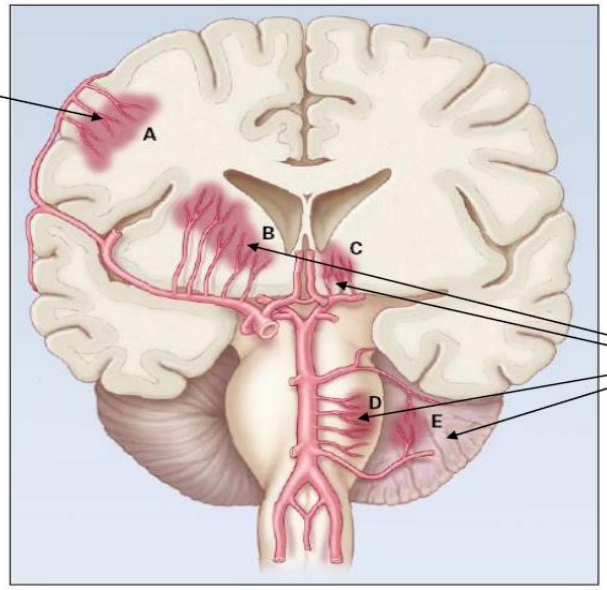
Air pollution

Recomendaciones de la Sociedad Española de Neurología para la prevención del ictus. Actuación sobre los hábitos de vida y la contaminación atmosférica

# Location, Location, Location …

Lobar ICH

Mostly due to cerebral amyloid angiopathy (75%)

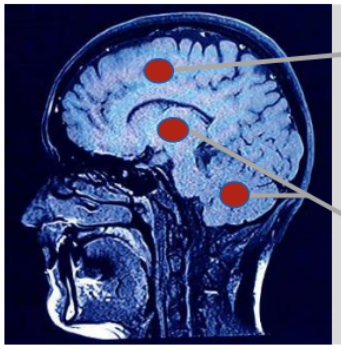



Deep ICH

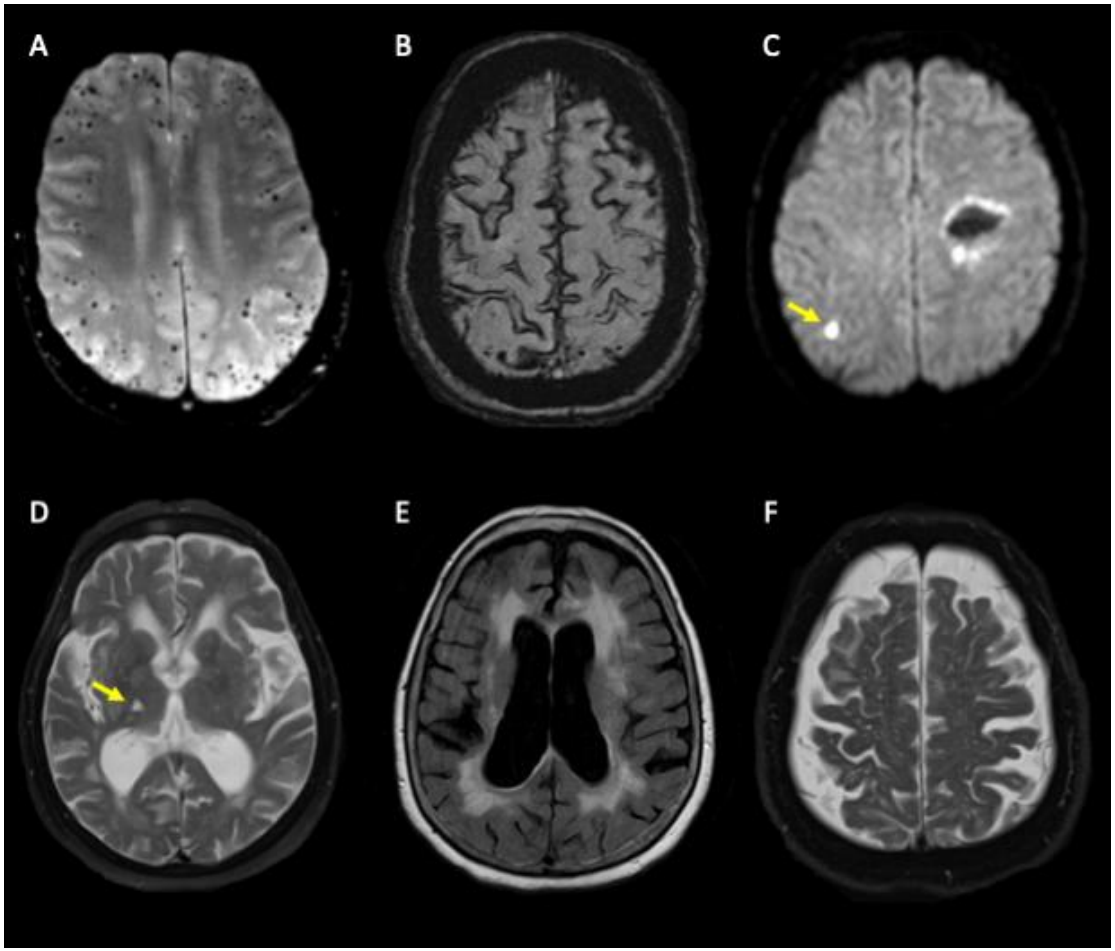
Mostly due to hypertensive vasculopathy (>80%)

Figure from Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. N Engl J Med. 2001;344:1450-1460.

# Diagnosis & Assessment | Strategy to Determine ICH Etiology

| For Patients With... | Utilize This Diagnostic Strategy... |
| --- | --- |
|  **Lobar ICH**<br>• Age <70 yrs<br>**- OR -**<br>**Deep/Posterior Fossa ICH**<br>• Age <45<br>• Age 45-70 yrs, NO HTN | **CT Angiogram/Venogram Recommended (1)**<br>**- AND -**<br>**MRI + MR Angiogram Reasonable (2a)**<br>**- AND -**<br>**Cerebral Angiogram Reasonable (2a)** |
| **Spontaneous IVH with NO parenchymal hemorrhage (any age)**<br>**- OR -**<br>**CTA/MRA suggestive of macrovascular ICH etiology (any age)** | **Cerebral Angiogram Recommended (1)** |

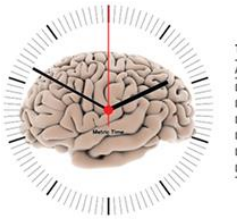
# MRI Markers of CSVD

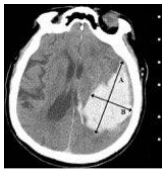



T2*-gradient echo (A) and susceptibility weighted imaging (B) sequences demonstrating multiple strictly lobar microbleeds and disseminated cortical superficial siderosis, respectively. Both are indicative of advanced cerebral amyloid angiopathy. Diffusion-weighted imaging showing a punctate region of restricted diffusion remote from an acute intracerebral hemorrhage (C; arrow). T2-weighted (D, F) and T2-FLAIR sequences (E) showing an occult subcortical infarct (D; arrow), severe periventricular white matter disease (E) and centrum semiovale dilated perivascular spaces (F; suggestive of cerebral amyloid angiopathy).

# Pre-hospital recognition of stroke symptoms:


# Treatment for ICH needs an emergency pathway

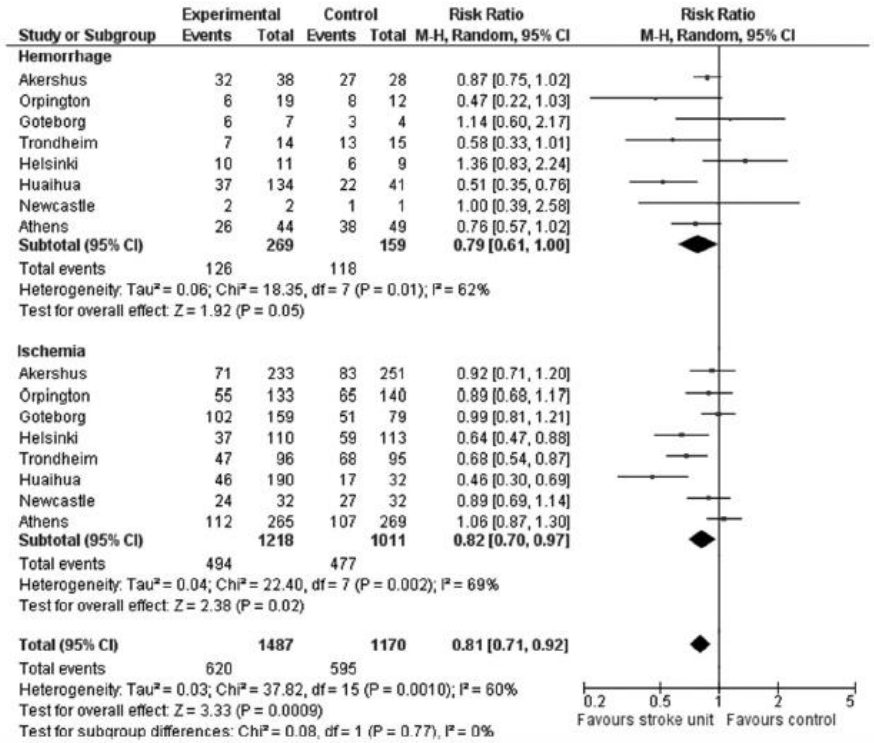




Stabilize the patient → Stop the bleeding → Reduce the brain damage → Increase recovery

# Stroke Unit Care

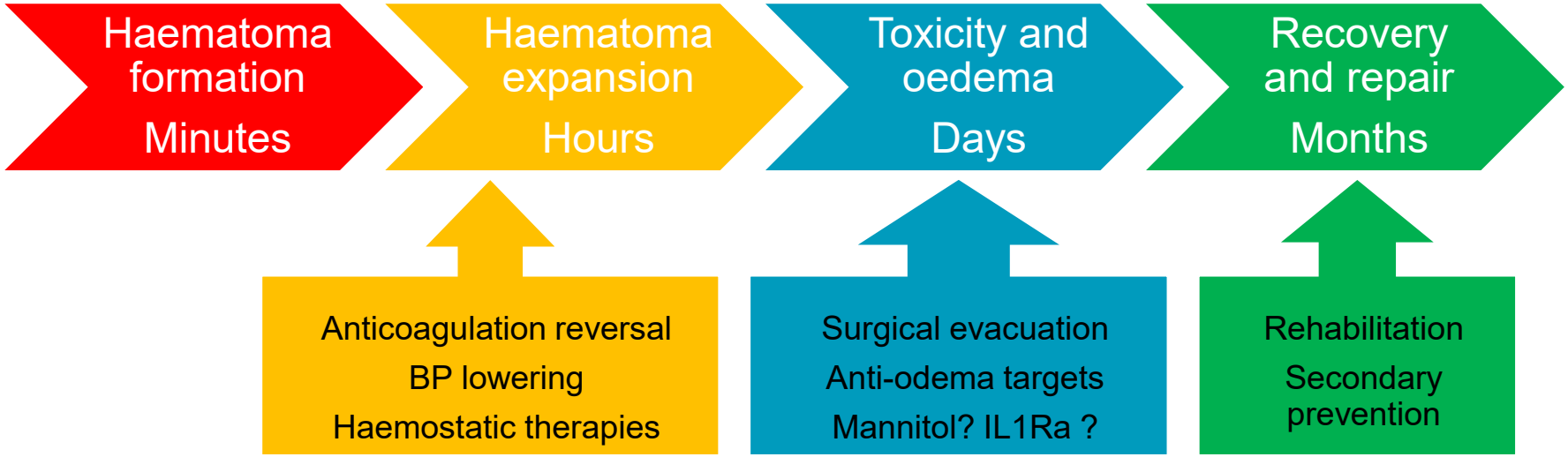
- ICH patients may benefit more than IS patients
- Greater mortality benefit in ICH
- Despite this not all ICH patients get to a stroke unit




Langhorne, Stroke 2013

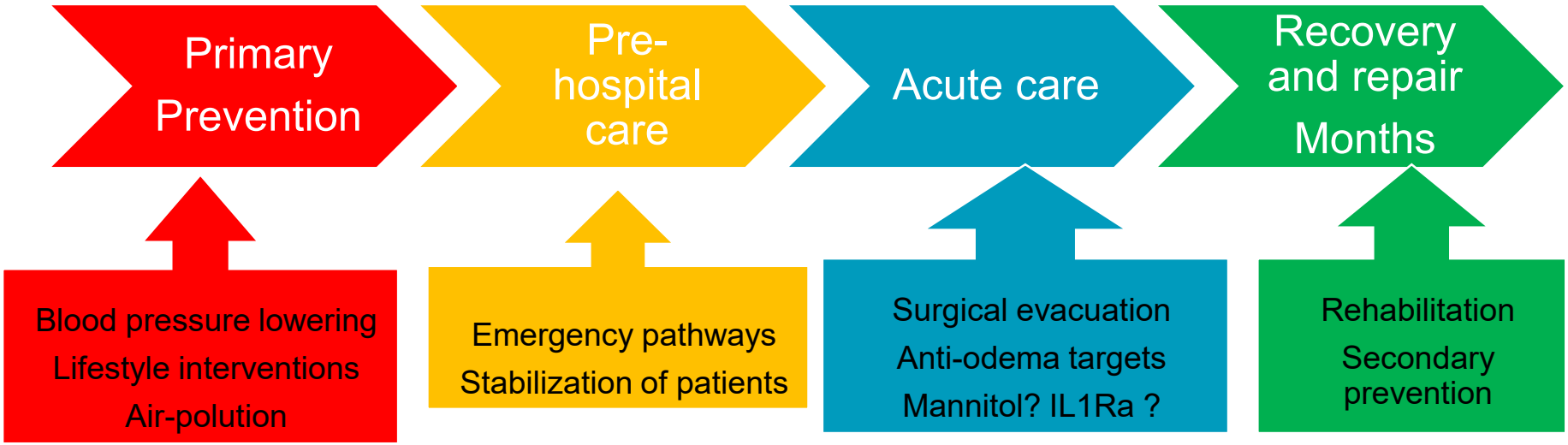
# Treatment targets vary by time

## Timeline after ICH for possible interventions



# State of the art ICH care

## Timeline for possible interventions



# What's new in ICH ?

HOT OFF THE PRESS

Update...

- **BP lowering**
  INTERACT-4
- **Anticoagulation reversal**

ANNEX A-I RCT - reversal of DOAC Factor Xa ICH

- **Care bundles**
  INTERACT-3 study
  ABC ICH care bundle
- **Neurosurgery**
  ENRICH study – minimally invasive surgery
  SWITCH – decompression surgery

## Evidence based guidelines

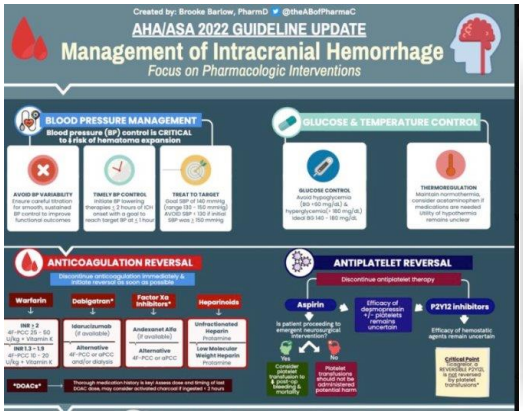
## AHA ICH 2022

## Audit Data

- Need to increase ICH metrics

## Brain imaging

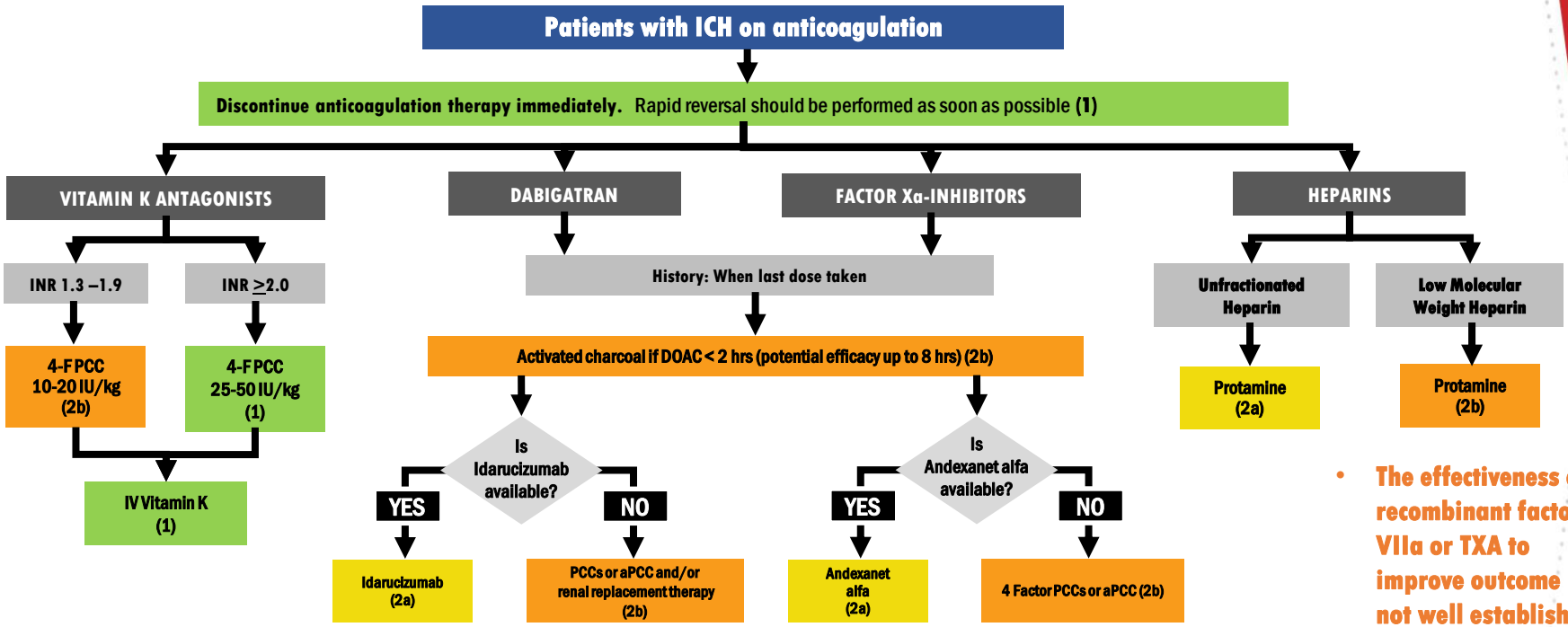
- Artificial Intelligence for detection of ICH – may help rapid access for treatments and trials



# Anticoagulation reversal

# Reversal of Coagulopathy

## Management of Anticoagulant-Associated Hemorrhage




- **The effectiveness of recombinant factor VIIa or TXA to improve outcome is not well established (2b)**

**Abbreviations:** 4-F PCC indicates four-factor prothrombin complex concentrate; aPCC, activated prothrombin complex concentrate; DOAC, direct oral anticoagulant; ICH, intracerebral hemorrhage; and INR, international normalized ratio.

American Heart Association.

Greenberg, S. M. 2022 AHA/ASA . Guideline for the Management of Patients with Spontaneous Intracerebral Hemorrhage. *Circulation.*

# Anticoagulation Reversal is an emergency


**Introduce a protocol of care for rapid administration:**

1.Point of care testing device in the emergency department

2.Drug storage in emergency department –

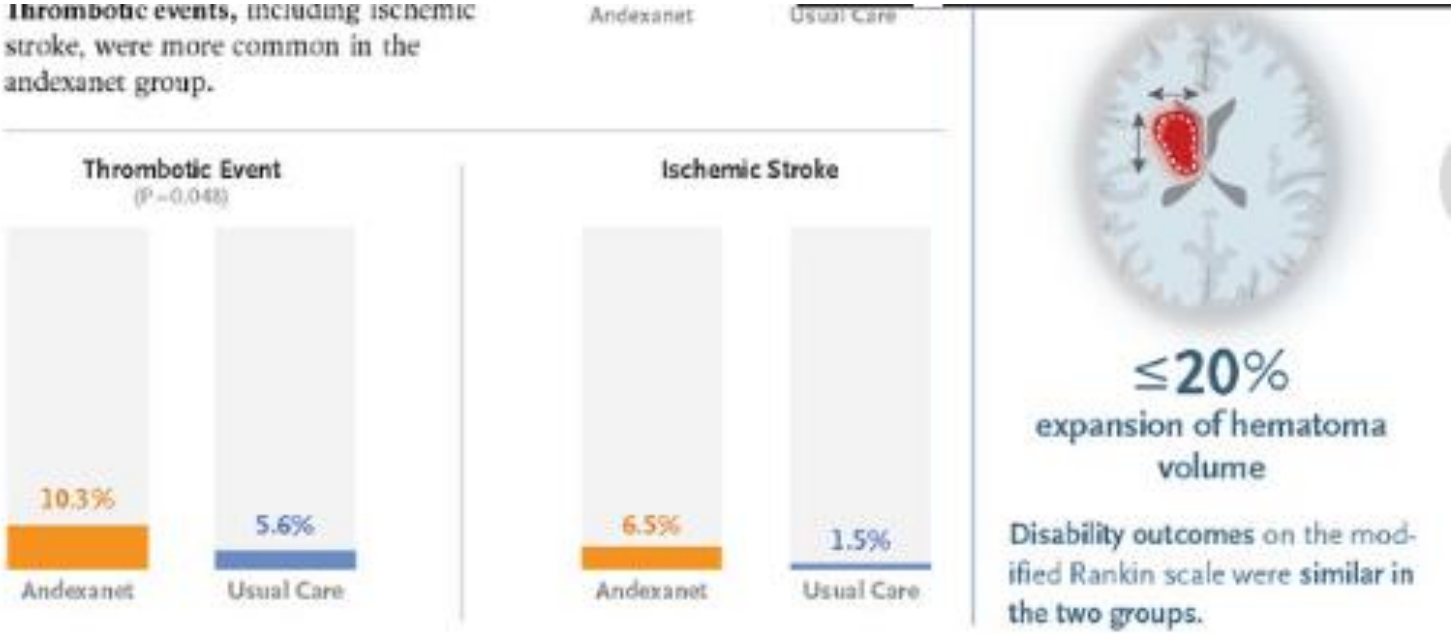
This can reduce door to needle time [1]

- Vitamin K antagonist - Warfarin
  4 factor Prothrombin Complex Concentrate and Vitamin K
- Direct Thrombin Inhibitors:
  Dabigitran – use Idarucizumab antidote if available
- Factor Xa inhibitors -
  Andexenat alfa reverses anticoag. effect – v. rapidly
  Prothrombin Complex Concentrate may have some benefit

1. A Parry-Jones BMJ Qual Improv 2015

# Andexanet alpha for DOAC ICH

- N Engl J Med 2024;390:1745-1755 DOI: 10.1056/NEJMoa2313040



# Blood pressure lowering

# BP Lowering in the Ambulance

## Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based, randomised, sham-controlled, blinded, phase 3 trial

*The RIGHT-2 Investigators**


### Summary

**Background** High blood pressure is common in acute stroke and is a predictor of poor outcome; however, large trials of lowering blood pressure have given variable results, and the management of high blood pressure in ultra-acute stroke remains unclear. We investigated whether transdermal glyceryl trinitrate (GTN; also known as nitroglycerin), a nitric oxide donor, might improve outcome when administered very early after stroke onset.

**Methods** We did a multicentre, paramedic-delivered, ambulance-based, prospective, randomised, sham-controlled, blinded-endpoint, phase 3 trial in adults with presumed stroke within 4 h of onset, face-arm-speech-time score of 2 or 3, and systolic blood pressure 120 mm Hg or higher. Participants were randomly assigned (1:1) to receive transdermal GTN (5 mg once daily for 4 days; the GTN group) or a similar sham dressing (the sham group) in UK-based ambulances by paramedics, with treatment continued in hospital. Paramedics were unmasked to treatment, whereas participants were masked. The primary outcome was the 7-level modified Rankin Scale (mRS; a measure of functional outcome) at 90 days, assessed by central telephone follow-up with masking to treatment. Analysis was hierarchical, first in participants with a confirmed stroke or transient ischaemic attack (cohort 1), and then in all participants who were randomly assigned (intention to treat, cohort 2) according to the statistical analysis plan. This trial is registered with ISRCTN, number ISRCTN26986053.

**Findings** Between Oct 22, 2015, and May 23, 2018, 516 paramedics from eight UK ambulance services recruited 1149 participants (n=568 in the GTN group, n=581 in the sham group). The median time to randomisation was 71 min (IQR 45–116). 597 (52%) patients had ischaemic stroke, 145 (13%) had intracerebral haemorrhage, 109 (9%) had transient ischaemic attack, and 297 (26%) had a non-stroke mimic at the final diagnosis of the index event. In the GTN group, participants' systolic blood pressure was lowered by 5·8 mm Hg compared with the sham group (p<0·0001), and diastolic blood pressure was lowered by 2·6 mm Hg (p=0·0026) at hospital admission. We found no difference in mRS between the groups in participants with a final diagnosis of stroke or transient ischaemic stroke (cohort 1): 3 (IQR 2–5; n=420) in the GTN group versus 3 (2–5; n=408) in the sham group, adjusted common odds ratio for poor outcome 1·25 (95% CI 0·97–1·60; p=0·083); we also found no difference in mRS between all patients (cohort 2: 3 [2–5]; n=544, in the GTN group *vs* 3 [2–5]; n=558, in the sham group; 1·04 [0·84–1·29]; p=0·69). We found no difference in secondary outcomes, death (treatment-related deaths: 36 in the GTN group *vs* 23 in the sham group [p=0·091]), or serious adverse events (188 in the GTN group *vs* 170 in the sham group [p=0·16]) between treatment groups.

**Interpretation** Prehospital treatment with transdermal GTN does not seem to improve functional outcome in patients with presumed stroke. It is feasible for UK paramedics to obtain consent and treat patients with stroke in the ultra-acute prehospital setting.


*Lancet* 2019; 393: 1009–20
Published Online
February 6, 2019
http://dx.doi.org/10.1016/S0140-6736(19)30194-1

See Comment page 963

*Members listed in the appendix
Correspondence to:
Prof Philip M Bath, Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham City Hospital Campus, Nottingham NG5 1PB, UK
philip.bath@nottingham.ac.uk

See Online for appendix

## Prehospital transdermal glyceryl trinitrate in patients with presumed acute stroke (MR ASAP): an ambulance-based, multicentre, randomised, open-label, blinded endpoint, phase 3 trial

*Sophie A van den Berg*, Simone M Uniken Venema*, Hendrik Reinink, Jeannette Hofmeijer, Wouter J Schonewille, Irene Miedema, Puck S S Fransen, D Martijn O Pruissen, Theodora W M Raaijmakers, Gert W van Dijk, Frank-Erik de Leeuw, Jorine A van Vliet, Vincent I H Kwa, Henk Kerkhoff, Alex van 't Net, Rene Boomars, Arjen Siegers, Tycho Lok, Klaartje Caminada, Laura M Esteve Cuevas, Marieke C Visser, Casper P Zwetsloot, Jooske M F Boomsma, Mirjam H Schipper, Roeland P J van Eijkelenburg, Olvert A Berkhemer, Daan Nieboer, Hester F Lingsma, Bart J Emmer, Robert J van Oostenbrugge, Aad van der Lugt, Yvo B W E M Roos, Charles B L M Majoie, Diederik W J Dippel, Paul J Nederkoorn†, H Bart van der Worp†, for the MR ASAP Investigators‡*


### Summary

**Background** Pooled analyses of previous randomised studies have suggested that very early treatment with glyceryl trinitrate (also known as nitroglycerin) improves functional outcome in patients with acute ischaemic stroke or intracerebral haemorrhage, but this finding was not confirmed in a more recent trial (RIGHT-2). We aimed to assess whether patients with presumed acute stroke benefit from glyceryl tr initrate started within 3 h after symptom onset.

**Methods** MR ASAP was a phase 3, randomised, open-label, blinded endpoint trial done at six ambulance services serving 18 hospitals in the Netherlands. Eligible participants (aged ≥18 years) had a probable diagnosis of acute stroke (as assessed by a paramedic), a face-arm-speech-time test score of 2 or 3, systolic blood pressure of at least 140 mm Hg, and could start treatment within 3 h of symptom onset. Participants were randomly assigned (1:1) by ambulance personnel, using a secure web-based electronic application with random block sizes stratified by ambulance service, to receive either transdermal glyceryl trinitrate 5 mg/day for 24 h plus standard care (glyceryl trinitrate group) or to standard care alone (control group) in the prehospital setting. Informed consent was deferred until after arrival at the hospital. The primary outcome was functional outcome assessed with the modified Rankin Scale (mRS) at 90 days. Safety outcomes included death within 7 days, death within 90 days, and serious adverse events. Analyses were based on modified intention to treat, and treatment effects were expressed as odds ratios (ORs) or common ORs, with adjustment for baseline prognostic factors. We separately analysed the total population and the target population (ie, patients with intracerebral haemorrhage, ischaemic stroke, or transient ischaemic attack). The target sample size was 1400 patients. The trial is registered as ISRCTN99503308.

**Findings** On June 24, 2021, the MR ASAP trial was prematurely terminated on the advice of the data and safety monitoring board, with recruitment stopped because of safety concerns in patients with intracerebral haemorrhage. Between April 4, 2018, and Feb 12, 2021, 380 patients were randomly allocated to a study group. 325 provided informed consent or died before consent could be obtained, of whom 170 were assigned to the glyceryl trinitrate group and 155 to the control group. These patients were included in the total population. 201 patients (62%) had ischaemic stroke, 34 (10%) transient ischaemic attack, 56 (17%) intracerebral haemorrhage, and 34 (10%) a stroke-mimicking condition. In the total population (n=325), the median mRS score at 90 days was 2 (IQR 1–4) in both the glyceryl trinitrate and control groups (adjusted common OR 0·97 [95% CI 0·65–1·47]). In the target population (n=291), the 90-day mRS score was 2 (2–4) in the glyceryl trinitrate group and 3 (1–4) in the control group (0·92 [0·59–1·43]). In the total population, there were no differences between the two study groups with respect to death within 90 days (adjusted OR 1·07 [0·53–2·14]) or serious adverse events (unadjusted OR 1·23 [0·76–1·99]). In patients with intracerebral haemorrhage, 12 (34%) of 35 patients allocated to glyceryl trinitrate versus two (10%) of 21 allocated to the control group died within 7 days (adjusted OR 5·91 [0·78–44·81]); death within 90 days occurred in 16 (46%) of 35 in the glyceryl trinitrate group and 11 (55%) of 20 in the control group (adjusted OR 0·87 [0·18–4·17]).

**Interpretation** We found no sign of benefit of transdermal glyceryl trinitrate started within 3 h of symptom onset in the prehospital setting in patients with presumed acute stroke. The signal of potential early harm of glyceryl trinitrate in patients with intracerebral haemorrhage suggests that glyceryl trinitrate should be avoided in this setting.


**Funding** The Collaboration for New Treatments of Acute Stroke consortium, the Brain Foundation Netherlands, the Ministry of Economic Affairs, Stryker, Medtronic, Cerenovus, and the Dutch Heart Foundation.

*Lancet Neurol* 2022; 21: 971–81
Published Online
September 1, 2022
https://doi.org/10.1016/S1474-4422(22)00333-7

See Comment page 948

*Joint first authors
†Contributed equally
‡Listed in the appendix (pp 3-5)
**Department of Neurology** (S A van den Berg MD, Prof Y B W E M Roos PhD, P J Nederkoorn PhD), **Department of Anesthesiology** (A Siegers MD), **and Department of Radiology & Nuclear Medicine** (O A Berkhemer PhD, B J Emmer PhD, Prof C B L M Majoie PhD), **Amsterdam UMC location University of Amsterdam, Amsterdam, Netherlands; Department of Neurology & Neurosurgery, Brain Center, University Medical Center Utrecht, Utrecht, Netherlands** (S M Uniken Venema MD, H Reinink MD, Prof H B van der Worp PhD); **Department of Neurology, Rijnstate, Arnhem, and Department of Clinical Neurophysiology, University of Twente, Enschede, Netherlands** (Prof J Hofmeijer PhD); **Department of Neurology, Sint Antonius Hospital, Nieuwegein, Netherlands** (W J Schonewille PhD); **Department of Neurology, Gelderse Vallei Hospital, Ede, Netherlands** (I Miedema PhD); **Department of Neurology** (P S S Fransen PhD) **and Department of Emergency Medicine** (K Caminada MD), **Isala, Zwolle, Netherlands; Department of Neurology,**

# Blood pressure lowering improves outcome: INTERACT 4


For patients with hemorrhagic stroke (Panel C), including 12 with subarachnoid hemorrhage, the distribution of scores indicates a significant decrease in the odds of a poor functional outcome (common odds ratio, 0.75; 95% CI, 0.60 to 0.92).

Drug used:
*Urapidil (Alpha-1 antagonist & 5-$HT_{1A}$ agonist) 25 mg IV bolus, repeated only once after 5 min);*

https://www.nejm.org/doi/full/10.1056/NEJMoa2314741

ORIGINAL ARTICLE

# Intensive Ambulance-Delivered Blood-Pressure Reduction in Hyperacute Stroke

G. Li, Y. Lin, J. Yang, C.S. Anderson, C. Chen, F. Liu, L. Billot, Q. Li, X. Chen, X. Liu, X. Ren, C. Zhang, P. Xu, L. Wu, F. Wang, D. Qiu, M. Jiang, Y. Peng, C. Li, Y. Huang, X. Zhao, J. Liang, Y. Wang, X. Wu, Xiaoyun Xu, G. Chen, D. Huang, Y. Zhang, L. Zuo, G. Ma, Y. Yang, J. Hao, Xiahong Xu, X. Xiong, Y. Tang, Y. Guo, J. Yu, S. Li, S. He, F. Mao, Q. Tan, S. Tan, N. Yu, R. Xu, M. Sun, B. Li, J. Guo, L. Liu, H. Liu, M. Ouyang, L. Si, H. Arima, P.M. Bath, G.A. Ford, T. Robinson, E.C. Sandset, J.L. Saver, N. Sprigg, H.B. van der Worp, and L. Song, for the INTERACT4 investigators*

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Song can be contacted at lsong@georgeinstitute.org.cn or at the George Institute for Global Health China, Rm. 052A, Unit 1, Tayuan Diplomatic Office Bldg., No. 14 Liangmahe Nan Lu, Chaoyang District, Beijing 100600, China. Dr. G. Li can be contacted at ligang@tongji.edu.cn or at Shanghai East Hospital, School of Medicine, Tongji University, 1800 Yuntai Rd., Shanghai 200120, China. Dr. J. Yang can be contacted at yangjie1126@163.com or at Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, 32# W. Sect. 2, 1st Ring Rd., Chengdu 610072, China.

*A complete list of trial sites, investigators, and coordinators in the INTERACT4 trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. G. Li, Lin, J. Yang, and Anderson contributed equally to this article.

This article was published on May 16, 2024, and updated on May 23, 2024, at NEJM.org.

This is the *New England Journal of Medicine* version of record, which includes all *Journal* editing and enhancements. The Author Accepted Manuscript, which is the author's version after external peer review and before publication in the *Journal*, is available at PubMed Central.

N Engl J Med 2024;390:1862-72.
DOI: 10.1056/NEJMoa2314741


CME

ABSTRACT

**BACKGROUND**

Treatment of acute stroke, before a distinction can be made between ischemic and hemorrhagic types, is challenging. Whether very early blood-pressure control in the ambulance improves outcomes among patients with undifferentiated acute stroke is uncertain.

**METHODS**

We randomly assigned patients with suspected acute stroke that caused a motor deficit and with elevated systolic blood pressure (≥150 mm Hg), who were assessed in the ambulance within 2 hours after the onset of symptoms, to receive immediate treatment to lower the systolic blood pressure (target range, 130 to 140 mm Hg) (intervention group) or usual blood-pressure management (usual-care group). The primary efficacy outcome was functional status as assessed by the score on the modified Rankin scale (range, 0 [no symptoms] to 6 [death]) at 90 days after randomization. The primary safety outcome was any serious adverse event.

**RESULTS**

A total of 2404 patients (mean age, 70 years) in China underwent randomization and provided consent for the trial: 1205 in the intervention group and 1199 in the usual-care group. The median time between symptom onset and randomization was 61 minutes (interquartile range, 41 to 93), and the mean blood pressure at randomization was 178/98 mm Hg. Stroke was subsequently confirmed by imaging in 2240 patients, of whom 1041 (46.5%) had a hemorrhagic stroke. At the time of patients' arrival at the hospital, the mean systolic blood pressure in the intervention group was 159 mm Hg, as compared with 170 mm Hg in the usual-care group. Overall, there was no difference in functional outcome between the two groups (common odds ratio, 1.00; 95% confidence interval [CI], 0.87 to 1.15), and the incidence of serious adverse events was similar in the two groups. Prehospital reduction of blood pressure was associated with a decrease in the odds of a poor functional outcome among patients with hemorrhagic stroke (common odds ratio, 0.75; 95% CI, 0.60 to 0.92) but an increase among patients with cerebral ischemia (common odds ratio, 1.30; 95% CI, 1.06 to 1.60).

**CONCLUSIONS**

In this trial, prehospital blood-pressure reduction did not improve functional outcomes in a cohort of patients with undifferentiated acute stroke, of whom 46.5% subsequently received a diagnosis of hemorrhagic stroke. (Funded by the National Health and Medical Research Council of Australia and others; INTERACT4 ClinicalTrials.gov number, NCT03790800; Chinese Trial Registry number, ChiCTR1900020534.)

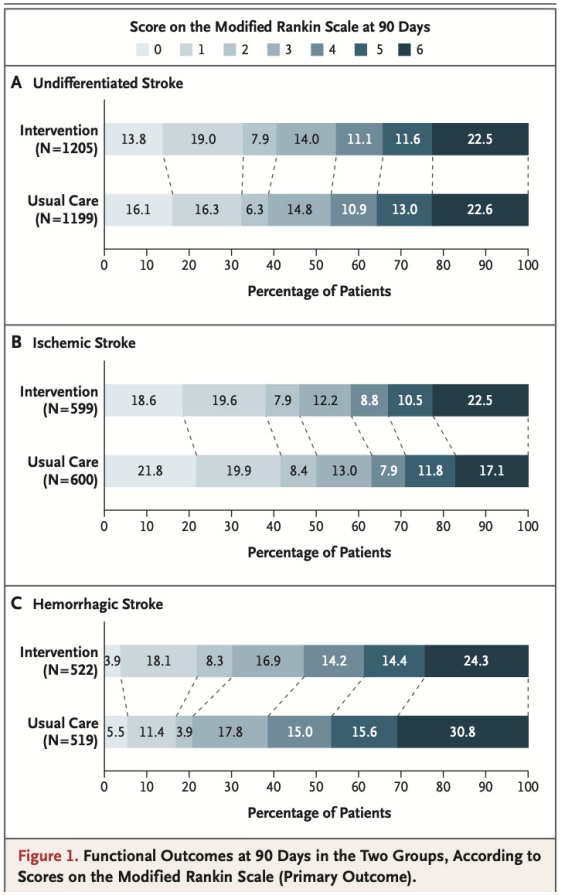



**Figure 1. Functional Outcomes at 90 Days in the Two Groups, According to Scores on the Modified Rankin Scale (Primary Outcome).**

# Pre-hospital GTN treatment : RIGHT-2, MR ASAP

## RIGHT-2 2019

- ICH patients n=145

## MR ASAP 2022

- ICH patients n=56
- 2 hours from onset time
- No imaging pre-treatment
- Larger ICH and more early deaths
- Increased bad outcome in ICH patients

Stroke
Volume 50, Issue 11, November 2019, Pages 3064-3071
https://doi.org/10.1161/STROKEAHA.119.026389

RIGHT-2

American Heart Association.

CLINICAL SCIENCES

**Prehospital Transdermal Glyceryl Trinitrate for Ultra-Acute Intracerebral Hemorrhage**

**Data From the RIGHT-2 Trial**

Prehospital transdermal glyceryl trinitrate in patients with presumed acute stroke (MR ASAP): an ambulance-based, multicentre, randomised, open-label, blinded endpoint, phase 3 trial

Sophie A van den Berg*, Simone M Uniken Venema*, Hendrik Reinink, Jeannette Hofmeijer, Wouter J Schonewille, Irene Miedema, Puck S S Fransen, D Martijn O Pruissen, Theodora W M Raaijmakers, Gert W van Dijk, Frank-Erik de Leeuw, Jorine A van Vliet, Vincent I H Kwa, Henk Kerkhoff, Alex van 't Net, Rene Boomars, Arjen Siegers, Tycho Lok, Klaartje Caminada, Laura M Esteve Cuevas, Marieke C Visser, Casper P Zwetsloot, Jaaske M F Boomsma, Mirjam H Schipper, Roeland P J van Eijkelenburg, Olvert A Berkhemer, Daan Nieboer, Hester F Lingsma, Bart J Emmer, Robert J van Oostenbrugge, Aad van der Lugt, Yvo B W E M Roos, Charles B L M Majoie, Diederik W J Dippel, Paul J Nederkoorn†, H Bart van der Worp†, for the MR ASAP Investigators‡

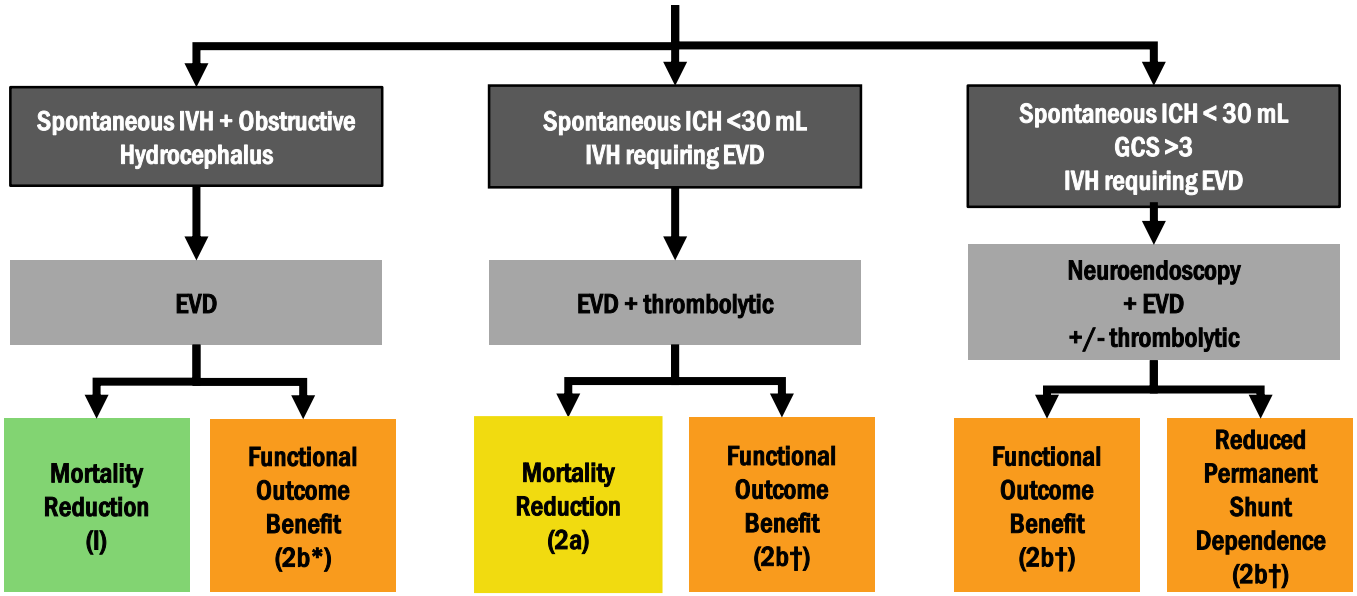
? avoid GTN in first few hours after ICH

https://www.MRASAPLancetNov2022

https://doi.org/10.1161/STROKEAHA.RIGHT2ICH

# Care pathway for prompt **neurosurgical** referral

# Minimally Invasive Surgical Evacuation of Intraventricular Hemorrhage




Dose: 1 mg every 8h up to 12 doses was the dose used in CLEAR III

American Heart Association.

Greenberg, S. M. 2022 AHA/ASA . Guideline for the Management of Patients with Spontaneous Intracerebral Hemorrhage. *Circulation.*

## Recommendations for Minimally Invasive Surgical Evacuation of ICH

Referenced studies that support recommendations are summarized in online data supplements X & Y.

| COR | LOE | Recommendations |
|---|---|---|
| 2a | B-R | 1. For patients with supratentorial intracerebral hemorrhage of >20 mL volume, with GCS in the moderate range (5–12), minimally invasive hematoma evacuation with endoscopic or stereotactic aspiration with or without thrombolytic usage can be useful to reduce mortality compared to medical management alone. [Akhigbe, T 2015;Guo, G 2020;Hanley, DF 2019;Li, M 2020;Scaggiante, J 2018;Sondag, L 2020;Tang, Y 2018;Yao, Z 2018;Zhou, X 2012;Zhou, X 2020] |
| 2b | B-R | 2. For patients with supratentorial intracerebral hemorrhage of >20 mL volume, with GCS in the moderate range (5–12) and being considered for hematoma evacuation, it may be reasonable to select minimally invasive hematoma evacuation over conventional craniotomy to improve functional outcomes. [Li, M 2020;Scaggiante, J 2018;Sun, S 2020;Tang, Y 2018;Xia, Z 2018;Yao, Z 2018;Zhou, X 2012] |
| 2b | B-R | 3. For patients with supratentorial intracerebral hemorrhage of >20 mL volume, with GCS in the moderate range (5–12), minimally invasive hematoma evacuation with endoscopic or stereotactic aspiration with or without thrombolytic usage may be considered to improve functional outcomes. [Akhigbe, T 2015;Guo, G 2020;Hanley, DF 2019;Li, M 2020;Scaggiante, J 2018;Sondag, L 2020;Tang, Y 2018;Zhou, X 2012;Zhou, X 2020] |

American Heart Association.

- 20mls
  GCS 5-12
- Can be useful to reduce mortality
- Maybe reasonable to improve functional outcome

**NO COMMENT ON SUBCORTICAL ICH**

https://doi.org/10.1161/STR.0000000000000407Stroke. 2022;53:e282–e361

## Recommendations for Craniotomy for Supratentorial Hemorrhage

Referenced studies that support recommendations are summarized in online data supplements X & Y.

| COR | LOE | Recommendations |
|---|---|---|
| 2b | A | 1. For most patients with spontaneous supratentorial intracerebral hemorrhage of moderate or greater severity, the usefulness of craniotomy for hemorrhage evacuation to improve functional outcomes or mortality is uncertain [Gregson, BA 2012;Guo, G 2020;Li, M 2020;Mendelow, AD 2015;Mendelow, AD 2013;Pantazis, G 2006;Sondag, L 2020]. |
| 2b | C-LD | 2. In patients with supratentorial intracerebral hemorrhage who are deteriorating, craniotomy for hematoma evacuation might be considered as a life-saving measure [Bhaskar, MK 2017;Li, M 2020;Mendelow, AD 2013;Sondag, L 2020]. |

https://doi.org/10.1161/STR.0000000000000407Stroke. 2022;53:e282–e361

# Trial Design — ENRICH RCT

- Multicenter, randomized, adaptive clinical trial
- 1:1 block randomization
  - Index GCS, and
  - ICH location
    - Anterior Basal Ganglia [ABG], or
    - Lobar
- Planned sample size: 150-300
- Interim analyses starting at 150, then every 25 thereafter

## Key Inclusion / Exclusion Criteria

### Inclusion Criteria

- Age 18 – 80
- Head CT showing acute, spontaneous, **primary ICH**
- GCS 5-14
- ICH **volume 30 – 80mL**
- Intervention can be initiated **within 24 hours** of last known normal
- Historical mRS 0 or 1

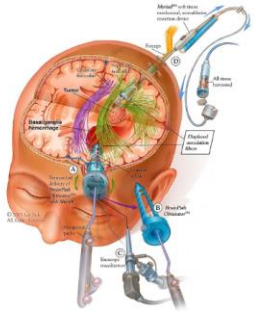
### Exclusion Criteria

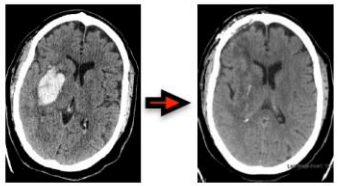
- Secondary cause on vascular imaging (i.e Aneurysm, AVM, etc. on CTA/DSA/MRA)
- NIHSS ≤ 5
- IVH >50% of the lateral ventricles
- Clinical Herniation signs
- Anticoagulants not RAPIDLY reversed
- Uncorrected coagulopathy/known clotting disorder
- No reasonable expectation of recovery, DNR/comfort measures or life expectancy < 6M

ESOC 2023 THE VOICE OF STROKE IN EUROPE

eso-conference.org

## MIPS

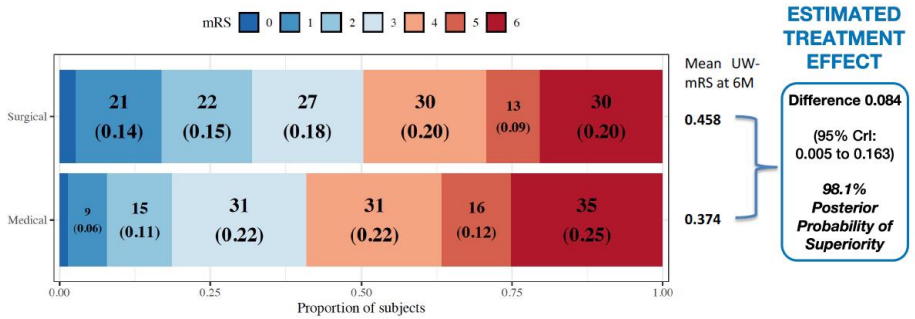




ESOC 2023 THE VOICE OF STROKE IN EUROPE

eso-conference.org

## mRS at 6 months




ESOC 2023 THE VOICE OF STROKE IN EUROPE

eso-conference.org

## Post MIPS Volumes

| Parameter | MIPS (N = 150) |
|---|---|
| EOT ICH volume (mL)* | 14.9 |
| Change in ICH volume (mL) | -43.9 ± 30.1 |
| % ICH reduction, median (IQR)* | 87.7% (64.4, 96.7) |
| Patients with ≥70% ICH reduction | 71.3% |
| Patients with EOT volume ≤ 20 mL | 76.7% |
| Patients with EOT volume ≤ 15 mL | 72.7% |

EOT Vol: OR (95% CI)
0.987 (0.978 – 0.995)
p = 0.005

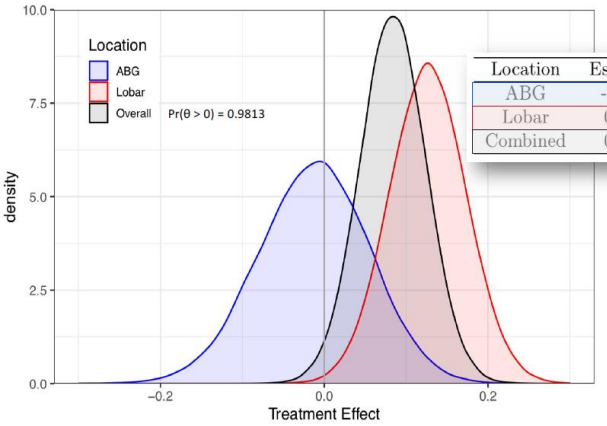
ESOC 2023 THE VOICE OF STROKE IN EUROPE

* Planned Secondary Analysis

eso-conference.org

## Efficacy:

### Posterior Distribution of the Treatment Effect



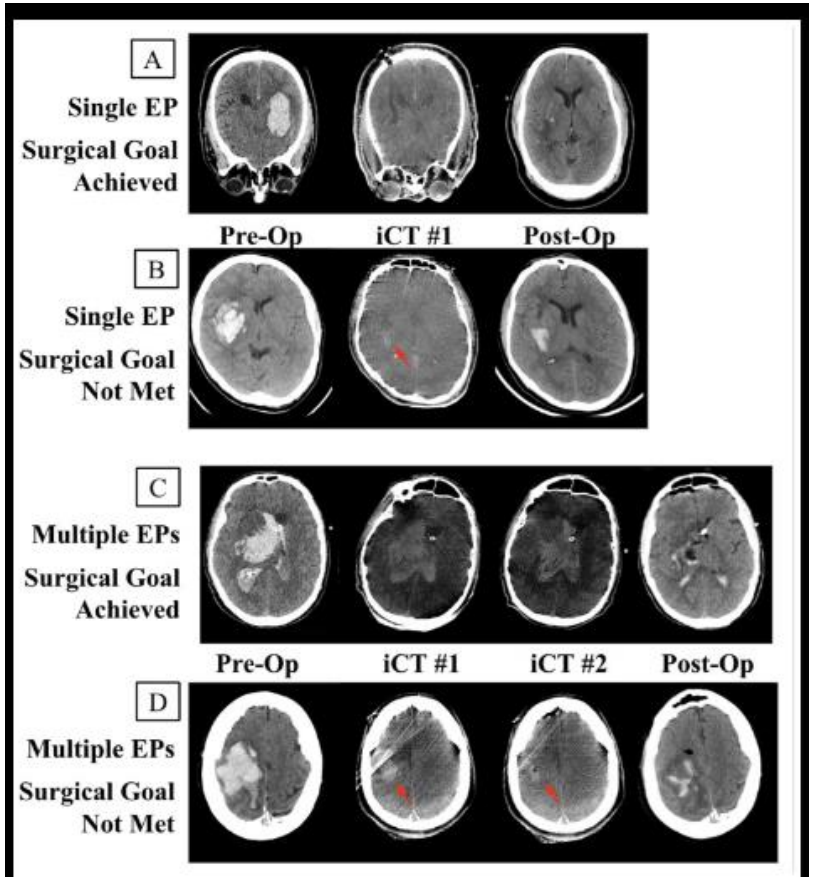

| Location | Estimate | LL | UL | Prob.Sup |
|---|---|---|---|---|
| ABG | -0.013 | -0.147 | 0.116 | 0.4301 |
| Lobar | 0.127 | 0.035 | 0.219 | 0.9968 |
| Combined | 0.084 | 0.005 | 0.163 | 0.9813 |

eso-conference.org

# Neurosurgery – outstanding questions

**Predicting failure**

- Intra-operative imaging




https://doi.org/10.3390/biomedicines1203050

- Criteria for selecting patients
- Benefit of MIS over craniotomy - craniotomy often performed as rescue therapy
- Type of device- ? Surgeon expertise more important

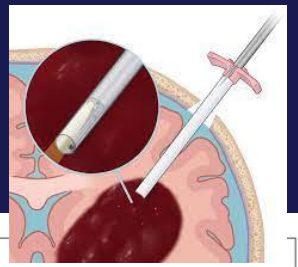
# ENRICH results: Implications?

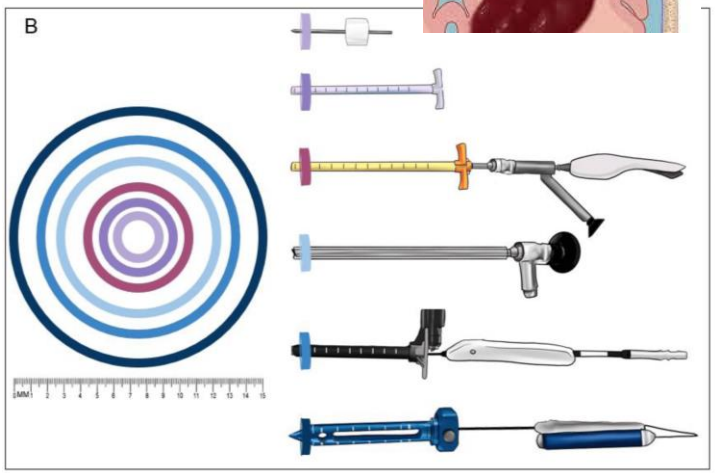
- Bayesian analysis, UW-mRS analysis (*from IS DAWN population*)

- How to explain utility weighted mRS to patients
- Effect seems to be driven by lobar – but not powered –
  is there still equipoise for lobar patients?
  does this exclude a benefit in basal ganglia group?

- MIPS technique and learning curve

# Many outstanding questions re surgery:






- Type of device
- **Location of ICH (deep** vs lobar)
- Timing of surgery

**Early**
Reduced time of blood in brain = less damage

**Later**
Patient more stable = Less risk of bleeding

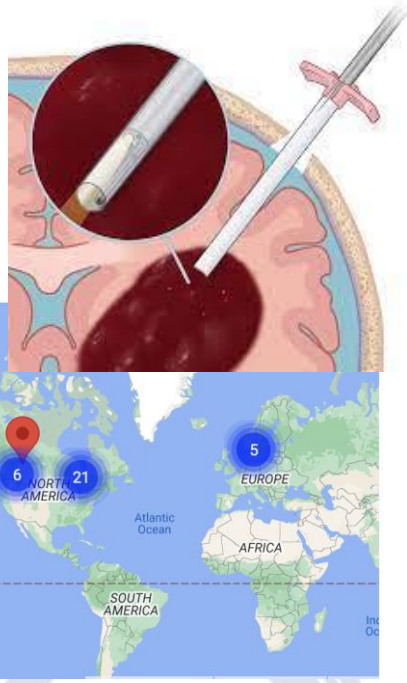
**Trials are ongoing:** US, Australia, Netherlands, Switzerland, Germany

- MIND: Artemis in the Removal of Intracerebral Hemorrhage
- Ultra-Early, Minimally inVAsive intraCerebral Haemorrhage evacUATion Versus Standard trEatment (EVACUATE)
- Dutch ICH Surgery Trial (DIST)
- Early minimally invasive image-guided endoscopic evacuation of intracerebral haemorrhage(EMINENT-ICH)

*Diagnostics* **2021**, *11*(3), 576; https://doi.org/10.3390/diagnostics11030576

# MIND

- MIND: Artemis in the Removal of Intracerebral Hemorrhage
- ClinicalTrials.gov ID NCT03342664
- Sponsor Penumbra Inc.
- Inclusion: ICH 18-80yrs, 20-80mls, NIHSS >= 15,
  CT from onset< 24hrs, surgery < 72 hours
- Exclusion: Spot sign, DOAC, INR > 1.4, t
- Device – Artemis Penumbra




Currently on hold pending publication of ENRICH resu
DSMC has ceased enrollment to the lobar group
? Resume enrolment in the deep basal ganglia group?
Decision expected very soon…

# EVACUATE:

15TH WORLD STROKE CONGRESS 2023 OCTOBER 10-12 TORONTO, CANADA

Ultra-Early, Minimally inVAsive intraCerebral Haemorrhage evacUATion Versus Standard trEatment (EVACUATE)

- ClinicalTrials.gov ID NCT04434807
- Bruce Campell
- Inclusion: ICH, HV >= 20mls, < 8 hours
  Enrolling both lobar and basal ganglia ICH
- Device: Aurora surgiscope and evacuator (Integra Lifesciences)
- Ongoing…



ONE WORLD VOICE FOR STROKE one voice

worldstrokecongress.org

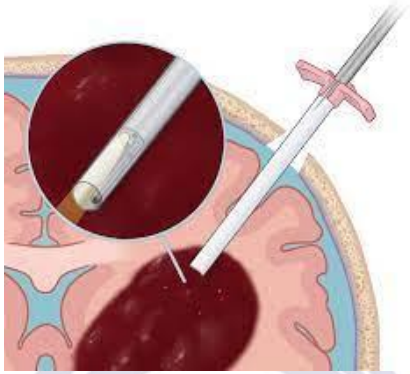
# Dutch ICH Surgery Trial (DIST):

- RCT endoscopic surgery < 8 hours n=400
- clinicaltrials.gov/ct2/show/NCT03608423
- *SELECTION in the ambulance*
- *Deferred consent model*
- *Primary outcome death*

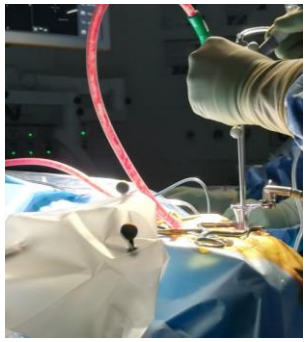
- *UPDATE:*

*36 recruited from 3 sites – 5/10 sites open now*

*Enrolling both lobar and basal ganglia ICH patients –*
*Has been discussed and decision to continue*
*Different device/procedure, different timing*



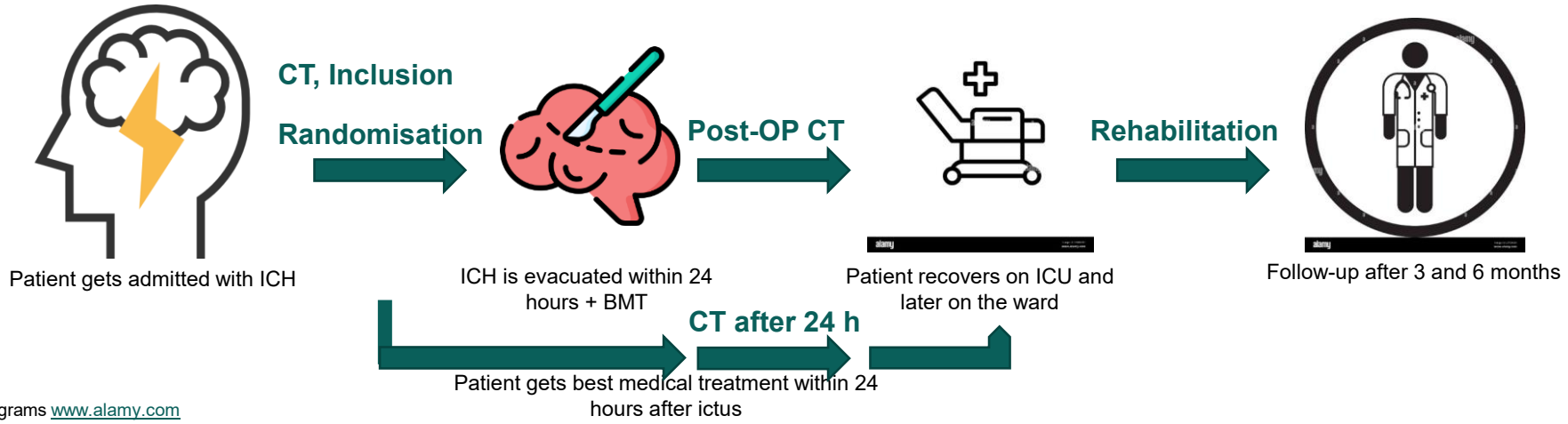
# EMINENT-ICH RCT



- Superiority multicenter **RCT**

Contact: eminent-ich@usb.ch

- Endoscopy + best medical care vs. best medical care
- SSE: **200 patients**
- Primary endpoint: mRS ≤ 3 at 6 months
- Secondary endpoints: PROMs, mortality and morbidity




Pictograms www.alamy.com

Brain Icons made by Freepik and Eucalyp from www.flaticon.com

Universitätsspital Basel

Front Neurol. 2022; 13: 884157.
Published online 2022 May 2. doi: 10.3389/fneur.2022.884157
PMCID: PMC9108381
PMID: 35585845

# Minimally Invasive Surgery for Spontaneous Intracerebral Hematoma. Real-Life Implementation Model and Economic Estimation

| | MISTIE III | DIST | ENRICH |
|---|---|---|---|
| Inclusion criteria | - Spontaneous supratentorial ICH ≥ 30 mL, with a Glasgow Coma Scale (GCS) ≤ 14 or a NIHSS ≥ 6.<br>- Clot stability on CT scan done at least 6 hours after diagnostic CT (growth < 5 mL).<br>- Symptoms < 24 hours prior to diagnostic CT<br>- Ability to randomize between 12 and 72 hours after first CT.<br>- Systolic Blood Pressure < 180 mmHg sustained for 6 hours.<br>- Historical mRS 0 or 1.<br>- Age ≥ 18 | - Age ≥ 18<br>- NIHSS ≥ 2<br>- Supratentorial ICH confirmed by CT, without a CT-angiography confirmed causative vascular lesion<br>- Minimal lesion size 10 mL<br>- Intervention can be started within 8 hours from symptoms onset; or for controls presentation within 8 hours of symptom onset.<br>- Patient's or legal representative's written informed consent | - Age 18-80 years<br>- Pre-randomization head CT demonstrating an acute, spontaneous, primary ICH<br>- Manual ICH volume between 30 - 80 mL<br>- Study intervention can reasonably be initiated within 24 hours after the onset of stroke symptoms. If the actual time of onset is unclear, then the onset will be considered the time that the subject was last known to be well<br>- GCS 5 - 14<br>- Historical mRS 0 or 1 |

- 1 in 10 suitable for catheter based surgery
- 4 in 10 suitable for endoscopic surgery
- Endoscopic more expensive BUT more effective – therefore more cost effective
- More patients suitable for DIST criteria -

# Decompression craniectomy for ICH:

## Decompressive craniectomy plus best medical treatment versus best medical treatment alone for spontaneous severe deep supratentorial intracerebral haemorrhage: a randomised controlled clinical trial

*Jürgen Beck, Christian Fung, Daniel Strbian, Lukas Bütikofer, Werner J Z'Graggen, Matthias F Lang, Seraina Beyeler, Jan Gralla, Florian Ringel, Karl Schaller, Nikolaus Plesnila, Marcel Arnold, Werner Hacke, Peter Jüni, Alexander David Mendelow, Christian Stapf, Rustam Al-Shahi Salman, Jenny Bressan, Stefanie Lerch, Arsany Hakim, Nicolas Martinez-Majander, Anna Piippo-Karjalainen, Peter Vajkoczy, Stefan Wolf, Gerrit A Schubert, Anke Höllig, Michael Veldeman, Roland Roelz, Andreas Gruber, Philip Rauch, Dorothee Mielke, Veit Rohde, Thomas Kerz, Eberhard Uhl, Enea Thanasi, Hagen B Huttner, Bernd Kallmünzer, L Jaap Kappelle, Wolfgang Deinsberger, Christian Roth, Robin Lemmens, Jan Leppert, Jose L Sanmillan, Jonathan M Coutinho, Katharina A M Hackenberg, Gernot Reimann, Mikael Mazighi, Claudio L A Bassetti, Heinrich P Mattle, Andreas Raabe, Urs Fischer, on behalf of the SWITCH study investigators**

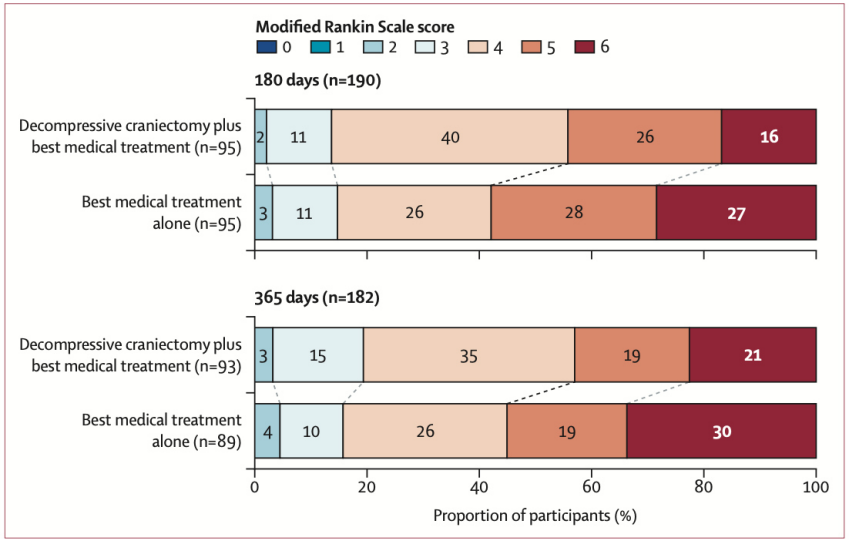
### Summary

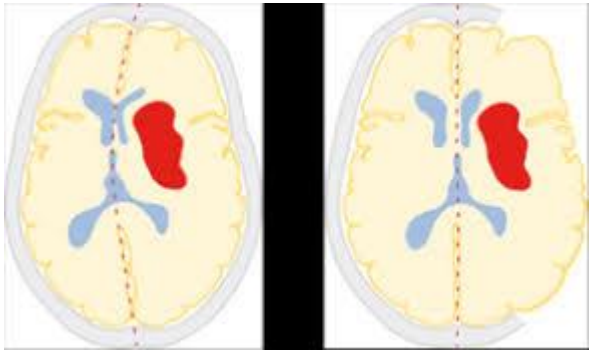
**Background** It is unknown whether decompressive craniectomy improves clinical outcome for people with spontaneous severe deep intracerebral haemorrhage. The SWITCH trial aimed to assess whether decompressive craniectomy plus best medical treatment in these patients improves outcome at 6 months compared to best medical treatment alone.

**Methods** In this multicentre, randomised, open-label, assessor-blinded trial conducted in 42 stroke centres in Austria, Belgium, Finland, France, Germany, the Netherlands, Spain, Sweden, and Switzerland, adults (18–75 years) with a severe intracerebral haemorrhage involving the basal ganglia or thalamus were randomly assigned to receive either decompressive craniectomy plus best medical treatment or best medical treatment alone. The primary outcome was a score of 5–6 on the modified Rankin Scale (mRS) at 180 days, analysed in the intention-to-treat population. This trial is registered with ClincalTrials.gov, NCT02258919, and is completed.

**Findings** SWITCH had to be stopped early due to lack of funding. Between Oct 6, 2014, and April 4, 2023, 201 individuals were randomly assigned and 197 gave delayed informed consent (96 decompressive craniectomy plus best medical treatment, 101 best medical treatment). 63 (32%) were women and 134 (68%) men, the median age was 61 years (IQR 51–68), and the median haematoma volume 57 mL (IQR 44–74). 42 (44%) of 95 participants assigned to decompressive craniectomy plus best medical treatment and 55 (58%) assigned to best medical treatment alone had an mRS of 5–6 at 180 days (adjusted risk ratio [aRR] 0·77, 95% CI 0·59 to 1·01, adjusted risk difference [aRD] –13%, 95% CI –26 to 0, p=0·057). In the per-protocol analysis, 36 (47%) of 77 participants in the decompressive craniectomy plus best medical treatment group and 44 (60%) of 73 in the best medical treatment alone group had an mRS of 5–6 (aRR 0·76, 95% CI 0·58 to 1·00, aRD –15%, 95% CI –28 to 0). Severe adverse events occurred in 42 (41%) of 103 participants receiving decompressive craniectomy plus best medical treatment and 41 (44%) of 94 receiving best medical treatment.

**Interpretation** SWITCH provides weak evidence that decompressive craniectomy plus best medical treatment might be superior to best medical treatment alone in people with severe deep intracerebral haemorrhage. The results do not apply to intracerebral haemorrhage in other locations, and survival is associated with severe disability in both groups.



*Article*

# Incidence and Outcomes of Hemorrhagic Stroke among Adults in Spain (2016–2018) According to Sex: A Retrospective, Cohort, Observational, Propensity Score Matched Study

Jose M. de Miguel-Yanes [1], Ana Lopez-de-Andres [2,*], Rodrigo Jimenez-Garcia [2], Valentin Hernandez-Barrera [3], Javier de Miguel-Diez [4], Manuel Méndez-Bailón [5], Napoleón Pérez-Farinós [6], Nuria Muñoz-Rivas [7], David Carabantes-Alarcon [2] and Marta López-Herranz [8]

- Men more likely to have ICH
- Women more likely to have SAH
- Women had increased mortality
- Decompressive hemicraniectomy improved outcome in both sexes
- Women less likely to have

| Variables | IHM Before PSM | | | IHM After PSM | | |
|---|---|---|---|---|---|---|
| | Women | Men | *p*-Value | Women | Men | *p*-Value |
| Nontraumatic intracerebral hemorrhage, *n* (%) | 4598 (33.5) | 5180 (29.2) | <0.001 | 4598 (33.5) | 4137 (28.9) | <0.001 |

IHM: in-hospital mortality. PSM: propensity score matching. SD: standard deviation. CCI: Charlson comorbidity index. The *p*-values are for comparisons between men and women.

https://doi.org/10.3390%2Fjcm10163753

# Andexanet for Factor Xa Inhibitor–Associated Acute Intracerebral Hemorrhage

S.J. Connolly, M. Sharma, A.T. Cohen, A.M. Demchuk, A. Członkowska, A.G. Lindgren, C.A. Molina, D. Bereczki, D. Toni, D.J. Seiffge, D. Tanne, E.C. Sandset, G. Tsivgoulis, H. Christensen, J. Beyer-Westendorf, J.M. Coutinho, M. Crowther, P. Verhamme, P. Amarenco, R.O. Roine, R. Mikulik, R. Lemmens, R. Veltkamp, S. Middeldorp, T.G. Robinson, T.J. Milling, Jr., V. Tedim-Cruz, W. Lang, A. Himmelmann, P. Ladenvall, M. Knutsson, E. Ekholm, A. Law, A. Taylor, T. Karyakina, L. Xu, K. Tsiplova, S. Poli, B. Kallmünzer, C. Gumbinger, and A. Shoamanesh, for the ANNEXA-I Investigators*

ABSTRACT

**BACKGROUND**

Patients with acute intracerebral hemorrhage who are receiving factor Xa inhibitors have a risk of hematoma expansion. The effect of andexanet alfa, an agent that reverses the effects of factor Xa inhibitors, on hematoma volume expansion has not been well studied.

**METHODS**

We randomly assigned, in a 1:1 ratio, patients who had taken factor Xa inhibitors within 15 hours before having an acute intracerebral hemorrhage to receive andexanet or usual care. The primary end point was hemostatic efficacy, defined by expansion of the hematoma volume by 35% or less at 12 hours after baseline, an increase in the score on the National Institutes of Health Stroke Scale of less than 7 points (scores range from 0 to 42, with higher scores indicating worse neurologic deficit) at 12 hours, and no receipt of rescue therapy between 3 hours and 12 hours. Safety end points were thrombotic events and death.

**RESULTS**

A total of 263 patients were assigned to receive andexanet, and 267 to receive usual care. Efficacy was assessed in an interim analysis that included 452 patients, and safety was analyzed in all 530 enrolled patients. Atrial fibrillation was the most common indication for factor Xa inhibitors. Of the patients receiving usual care, 85.5% received prothrombin complex concentrate. Hemostatic efficacy was achieved in 150 of 224 patients (67.0%) receiving andexanet and in 121 of 228 (53.1%) receiving usual care (adjusted difference, 13.4 percentage points; 95% confidence interval [CI], 4.6 to 22.2; P=0.003). The median reduction from baseline to the 1-to-2-hour nadir in anti–factor Xa activity was 94.5% with andexanet and 26.9% with usual care (P<0.001). Thrombotic events occurred in 27 of 263 patients (10.3%) receiving andexanet and in 15 of 267 (5.6%) receiving usual care (difference, 4.6 percentage points; 95% CI, 0.1 to 9.2; P=0.048); ischemic stroke occurred in 17 patients (6.5%) and 4 patients (1.5%), respectively. There were no appreciable differences between the groups in the score on the modified Rankin scale or in death within 30 days.

**CONCLUSIONS**

Among patients with intracerebral hemorrhage who were receiving factor Xa inhibitors, andexanet resulted in better control of hematoma expansion than usual care but was associated with thrombotic events, including ischemic stroke. (Funded by Alexion AstraZeneca Rare Disease and others; ANNEXA-I ClinicalTrials.gov number, NCT03661528.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Connolly can be contacted at stuart.connolly@phri.ca or at the Population Health Research Institute, Hamilton Health Sciences, McMaster University, 30 Birge St., Room C3-204, Hamilton ON L8L 0A6, Canada.

*A list of the ANNEXA-I investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was updated on June 13, 2024, at NEJM.org.

N Engl J Med 2024;390:1745-55.
DOI: 10.1056/NEJMoa2313040


CME

**Table 2. Efficacy End Points.**

| End Point | Andexanet (N=224) | Usual Care (N=228) | Adjusted Difference per 100 Patients (95% CI)* | P Value* |
|---|---|---|---|---|
| | *no./total no. (%)* | | *percentage points* | |
| Hemostatic efficacy | 150/224 (67.0) | 121/228 (53.1) | 13.4 (4.6 to 22.2) | 0.003 |
| Hematoma volume change ≤35%† | 165/215 (76.7) | 137/212 (64.6) | 12.1 (3.6 to 20.5) | |
| NIHSS score change <7 points | 188/214 (87.9) | 181/218 (83.0) | 4.6 (–2.0 to 11.2) | |
| No receipt of rescue therapy between 3 hr and 12 hr | 218/224 (97.3) | 213/228 (93.4) | 3.8 (0.0 to 7.6) | |
| Hematoma volume increase ≥12.5 ml‡ | 24/216 (11.1) | 36/214 (16.8) | –5.6 (–12.0 to 0.8) | |
| Hemostatic efficacy, excluding patients nonevaluable for administrative reasons | 150/218 (68.8) | 121/225 (53.8) | 14.5 (5.7 to 23.4) | |

**Table 3. Thrombotic Events and Deaths at 30 Days.***

| Event | Andexanet (N=263) | Usual Care (N=267) | Increase per 100 Patients (95% CI)† | P Value† |
|---|---|---|---|---|
| | *no. of patients (%)* | | *percentage points* | |
| ≥1 Thrombotic event | 27 (10.3) | 15 (5.6) | 4.6 (0.1 to 9.2) | 0.048 |
| Transient ischemic attack | 0 | 0 | — | |
| Ischemic stroke | 17 (6.5) | 4 (1.5) | 5.0 (1.5 to 8.8) | |
| Myocardial infarction | 11 (4.2) | 4 (1.5) | 2.7 (–0.2 to 6.1) | |
| Deep-vein thrombosis | 1 (0.4) | 2 (0.7) | –0.4 (–2.4 to 1.5) | |
| Pulmonary embolism | 1 (0.4) | 6 (2.2) | –1.9 (–4.5 to 0.2) | |
| Arterial systemic embolism | 3 (1.1) | 2 (0.7) | 0.4 (–1.7 to 2.7) | |
| Death | 73 (27.8) | 68 (25.5) | 2.5 (–5.0 to 10.0) | 0.51 |

# Bundles of care

INTERACT-3, ABC, ESO Guidelines

# Bundles of care: INTERACT-3

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

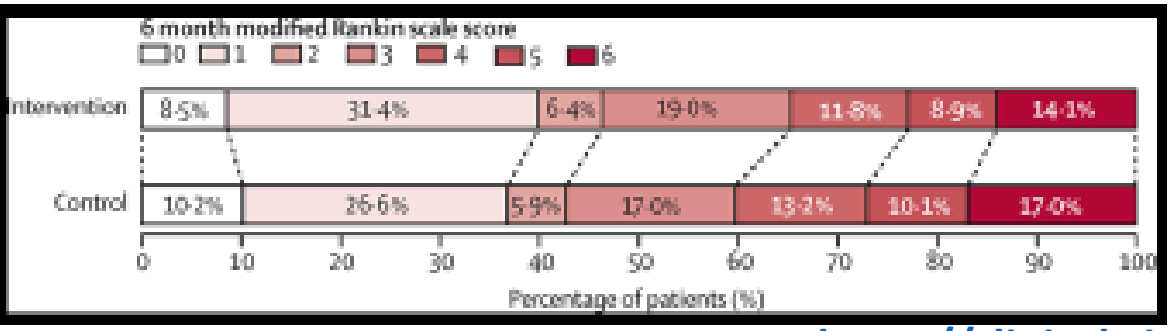
Step wedge RCT

Goal directed care Bundle:

1. Early intensive BP lowering (target < 140mmHg)
2. Intensive glucose control (target 6.1–7.8 mmol/L and 7.8–10.0 mmol/L for DM) for 7 days
3. Treatment of pyrexia (≥37.5 °C)
4. Reversal of anticoagulation



**Results:** The likelihood of a poor outcome was lower in the care bundle group common odds ratio **0·86; 95% CI 0·76–0·97; p=0·015**




https://clinicaltrials.gov/ct2/show/NCT03209258

# General Care

## Glucose and Temperature Management

### Glucose Management

**Monitor serum glucose to reduce both hyper/hypoglycemia. (1)**

**Treat serum glucose <40-60 mg/dL to reduce mortality. (1)**

- In critically ill, **target of <180 mg/dL** associated with lower mortality than target of 81-108 mg/dL.
- Intensive glucose control (target 81-108 mg/dL) more likely to result in severe hypoglycemic events compared to control.

**In patients with spontaneous ICH, treating moderate to severe hyperglycemia (>180–200 mg/dL, >10.0–11.1 mmol/L) is reasonable to improve outcomes. (2a)**

### Temperature Management

**In patients with spontaneous ICH, pharmacologically treating an elevated temperature may be reasonable to improve functional outcomes. (2b)**

**The usefulness of therapeutic hypothermia (<35°C/95°F) to decrease peri-ICH edema is unclear. (2b)**

As a general standard, acetaminophen and cooling blankets are recommended for almost all patients with sustained fever in excess of 38.3°C (101.0°F), despite the lack of prospective randomized controlled trials supporting this approach.

.

American Heart Association.

Greenberg, S. M. 2022 AHA/ASA . Guideline for the Management of Patients with Spontaneous Intracerebral Hemorrhage. *Circulation.*

# Process of care : ABC Bundle in UK

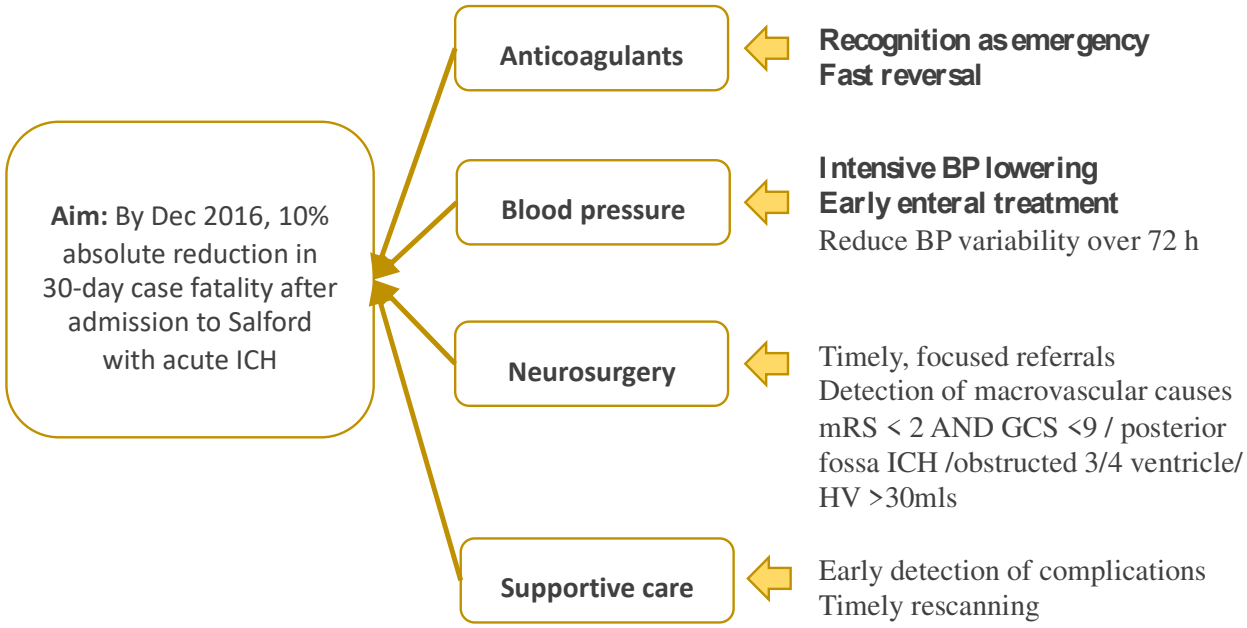
MANCHESTER 1824
The University of Manchester

Salford Royal NHS
NHS Foundation Trust

## Implementation of an acute care bundle for intracerebral haemorrhage and 30-day case fatality at a UK comprehensive stroke centre

MANCHESTER 1824
The University of Manchester

### Driver diagram




Slide courtesy of Adrian Parry Jones, Manchester

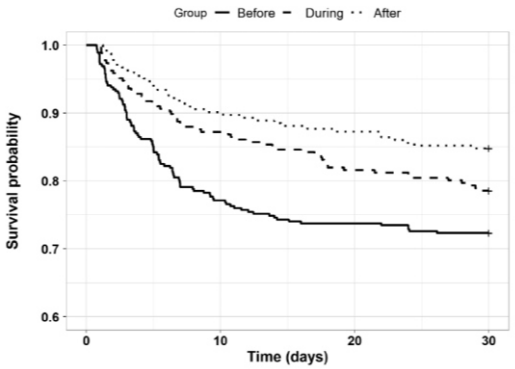
1. Parry Jones et.al , Ann Neurol Vol 86 2019

# Results: ABC Bundle reduced mortality by 30%

MANCHESTER 1824
The University of Manchester

Salford Royal NHS
NHS Foundation Trust

**Implementation of an acute care bundle for intracerebral haemorrhage and 30-day case fatality at a UK comprehensive stroke centre**




- >30% reduction in mortality[1]
- Rapid D2N time for anti-coagulant reversal
- Increase in use of anti-hypertensives with lower BP
- Increased referral to surgery
- Decrease in do not resuscitate decisions
- Perception that treatment was not futile

1. Parry Jones et.al , Ann Neurol Vol 86 2019

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<br>Coagulation tests |
| < 30 min | Reverse anticoagulant<br>Start intensive BP lowering |
| < 60 min | SBP < 140, Consult Neurosurgery<br>Achieve T < 37.5°C |
| 7 days | Maintain SBP < 140; T < 37.5°C<br>Maintain normoglycaemia |

## Conclusion

**Multiple simultaneous interventions** improve functional outcome

**Rapid bundled care** should be introduced

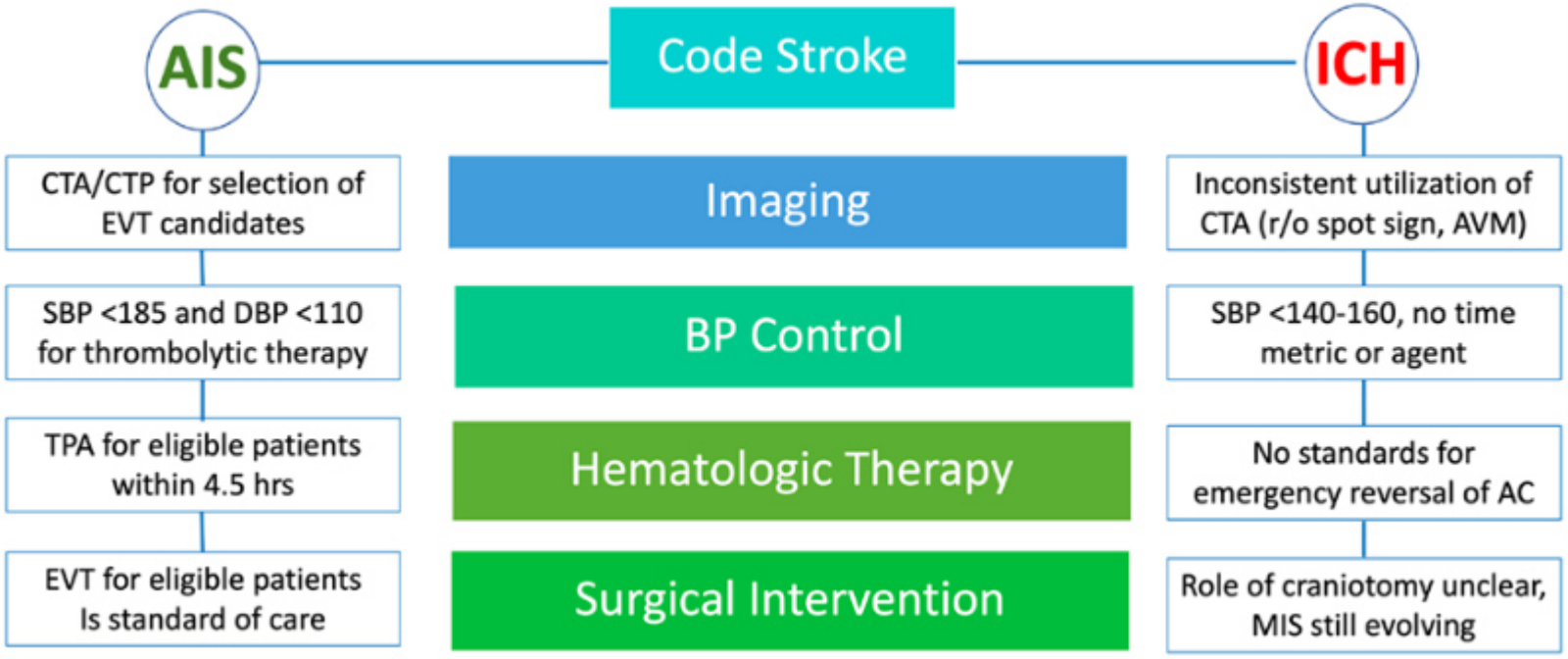
**Quality improvement** will help achieve **ambitious process targets**

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

# Systems of care for ICH

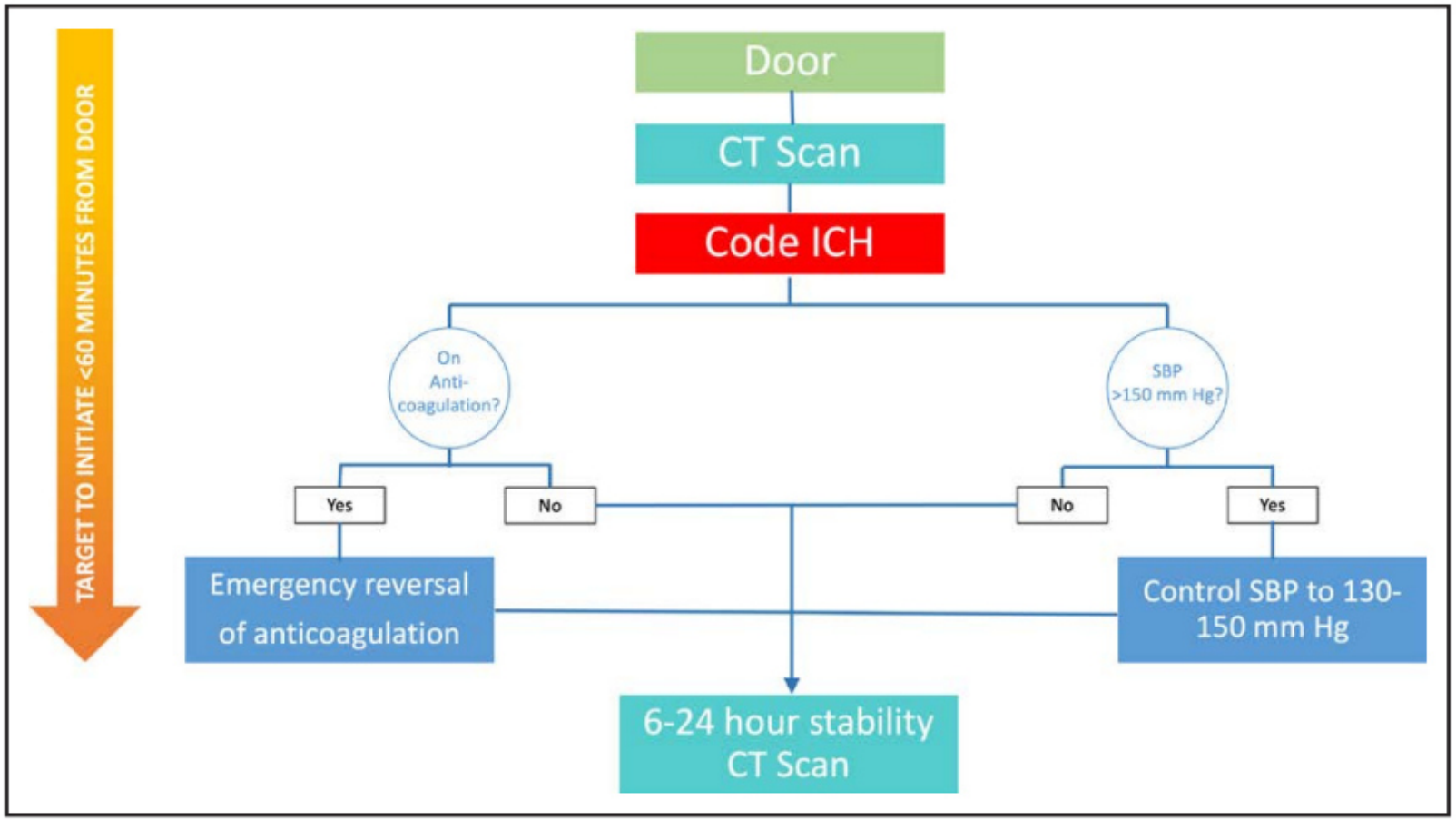
CODE ICH

# CODE ICH – organized rapid systems of care for ICH US example




https://www.ahajournals.org/doi/10.1161/STROKEAHA.123.043033

# CODE ICH – Anticoagulation reversal, BP lowering



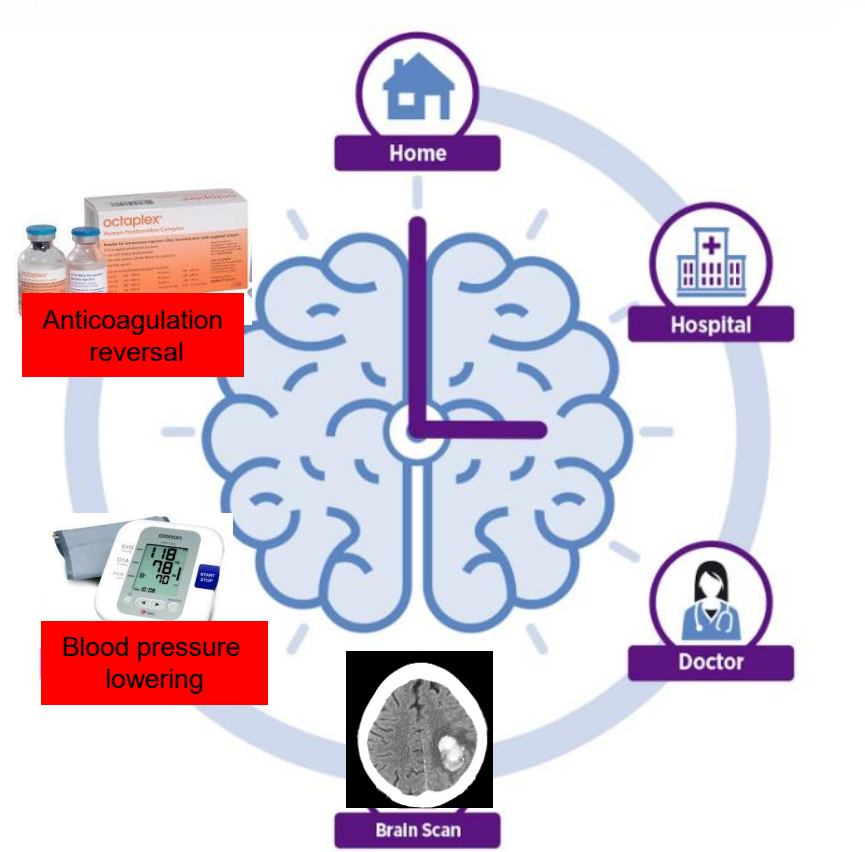

https://www.ahajournals.org/doi/10.1161/STROKEAHA.123.043033

# Time is brain for ICH too – measure processes of care

https://currents.neurocriticalcare.org/Leading-Insights/Article/time-is-brain-for-ich-too

| CODE ICH<br>Proposed Hemorrhagic Stroke Time Metrics | |
|---|---|
| Door to Doc | ≤ 10 minutes |
| Door to Stroke Team | ≤ 15 minutes |
| Door to CT scan start | ≤ 25 minutes |
| Door to CT scan read | ≤ 45 minutes |
| **Door to Lab results** | **≤ 45 minutes** |
| **Door to BP control** | **≤ 60 minutes** |
| **Door to reversal agent** | **≤ 60 minutes** |
| **Door to burr/evacuation** | **≤ 90/180 minutes** |

https://currents.neurocriticalcare.org/Leading-Insights/Article/time-is-brain-for-ich-too




https://www.noca.ie/news-events/time-is-brain-key-message-from-stroke-report-launch/

# Using technology to improve pathways of care:

9. Facilitating interpretation of head CT by stroke physicians without requiring formal radiology report


Viz.ai

Viz ICH

**Activate ICH team**

## Emergency Department

- Blood pressure lowering, anticoagulation reversal, avoid fever, treat hyperglycaemia
- Swallow assessment

## Neurosurgeons

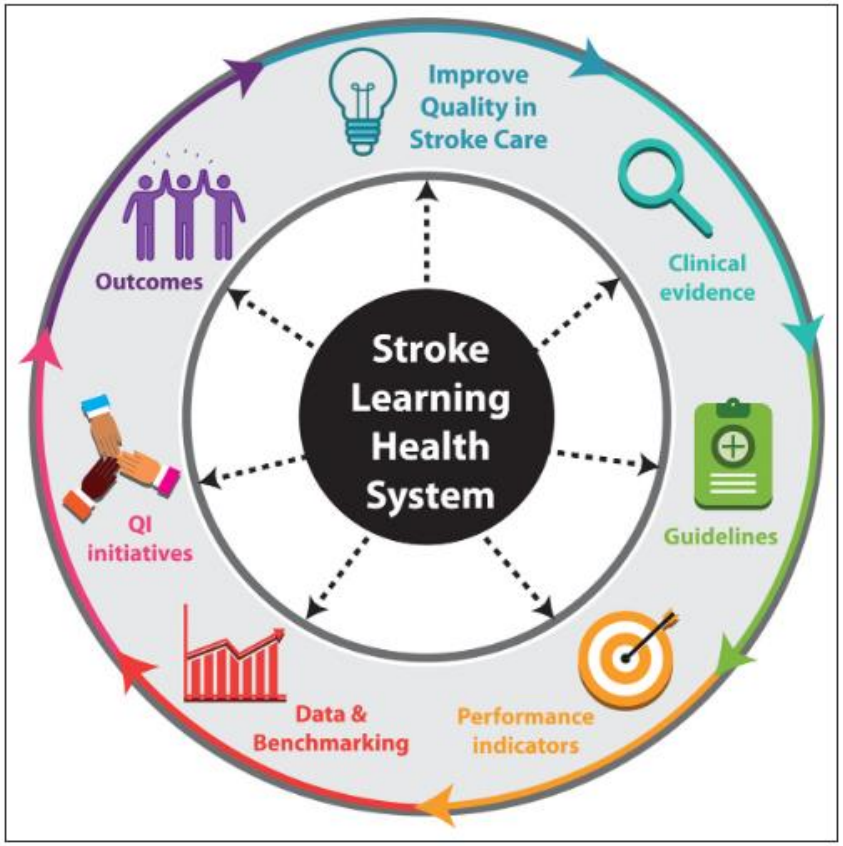
- ? Candidate for neurosurgery

## Neurologists

- Continue blood pressure lowering, anticoagulation reversal, avoid fever, treat hyperglycaemia
- Swallow assessment, VTE prevention

# Quality improvements in ICH care – core components

- Multi-disciplinary teams
- Audit and feedback
- Education
- Learning from other
- Process mapping
- De-implementation
- **Quality improvement projects focusing on ICH are a priority**




https://doi.org/10.1161/STROKEAHA.123.042310

# Outstanding questions: Transfer of care

Editorial

August 21, 2023

# Bypassing Closest Stroke Center for Intracerebral Hemorrhage—Not So Fast!

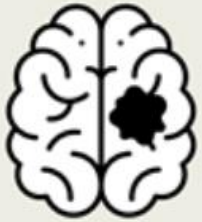
Paul M. Wechsler, MD[1]; Babak B. Navi, MD, MS[1]

JAMA Neurology

## RCT: Bypassing the Closest Stroke Center in Patients With Intracerebral Hemorrhage

### POPULATION

**204 Men, 98 Women**



Adults suspected of having a large vessel occlusion stroke with final diagnosis of intracranial hemorrhage (ICH).

**Mean age, 71.7 y**

### INTERVENTION

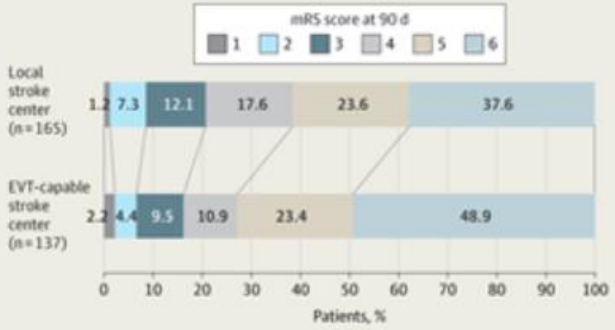
**1401** Patients randomized

**165 Drip and ship**
Regular transfer to the nearest local stroke center

**137 Mothership**
Bypassing protocol by direct transportation to an endovascular treatment (EVT)-capable stroke center

### FINDINGS

Direct transfer to an EVT stroke center resulted in reduced chances of functional independence and higher mortality at 90 d for patients with a final diagnosis of ICH




**Adjusted common odds ratio**
0.63 (95% CI, 0.41-0.96)

### SETTINGS / LOCATIONS

**28 Stroke centers in Catalonia, Spain**

### PRIMARY OUTCOME

The primary outcome was the shift analysis of disability at 90 d, as assessed by the modified Rankin Scale (mRS), with scores ranging from 0 (no symptoms) to 6 (death)

Ramos-Pachón A, Rodríguez-Luna D, Martí-Fàbregas J, et al; RACECAT Trial Investigators. Effect of bypassing the closest stroke center in patients with intracerebral hemorrhage: a secondary analysis of the RACECAT randomized clinical trial. Published online August 21, 2023. *JAMA Neurol.* doi:10.1001/jamaneurol.2023.2754

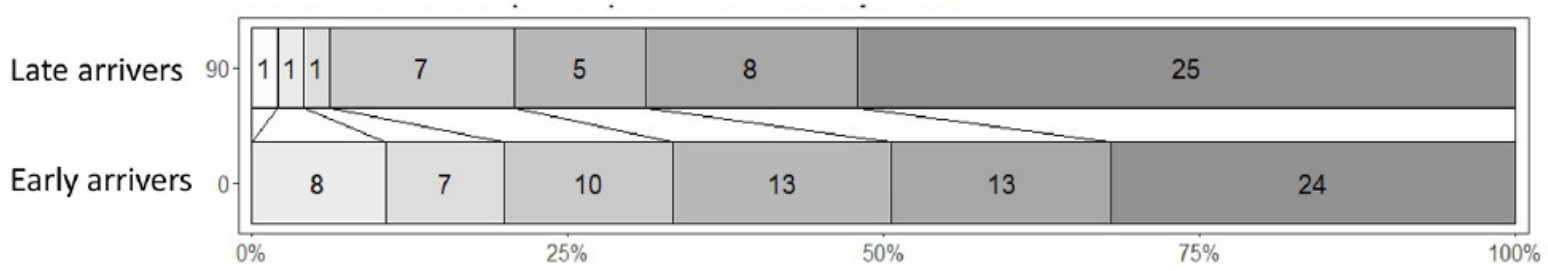
# ICH- Pre-hospital care – 2024 data

Patients with acute intracerebral hemorrhage and severe symptoms are highly sensitive to prehospital delay. A subgroup analysis from the RESIST and TRIAGE-STROKE trials

Rates of severe dependency and death increased by 9% per hour while the same rates for patients with AIS only increased by 2.5%.

**A**

**ICH with a positive prehospital stroke severity score**



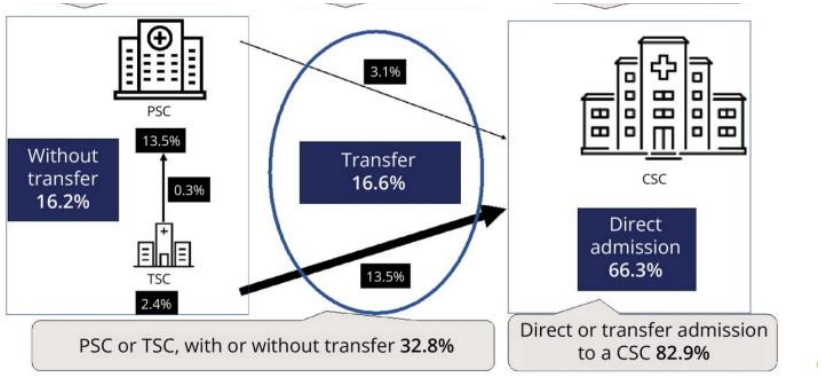

https://doi.org/10.3389/fstro.2024.1437746

RESEARCH ARTICLE

# Influence of Hospital Type on Outcomes of Patients With Acute Spontaneous Intracerebral Hemorrhage

## A Population-Based Study

- The hospital of initial admission (CSC vs TSC/PSC) was not associated with outcome (adjusted common OR 1.13, 95% CI 0.93–1.38). A
- PSM analysis indicated that transfer to a CSC was not associated with more favorable outcomes (OR 0.77, 95% CI 0.55–1.10; p
- CSC = comprehensive stroke center; scale; NIHSS = NIH Stroke Scale; PSC = primary stroke center; PSM = propensity score matching; TSC = telestroke center. = 0.16).




**A Triage Model for Interhospital Transfers of Low Risk Intracerebral Hemorrhage Patients**

*Kaleem, Safa et al.*

*Journal of Stroke Cerebrov Dis, Vo 30, Issue 4, 105616*

1. Initial Glasgow Coma Scale >13,
2. ICH <15ml, absence of IVH,
3. Supratentorial location

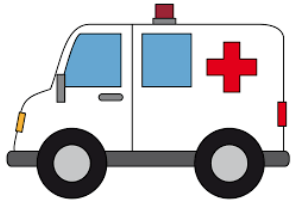
**Unlikely to benefit from transfer**

(area under curve 0.72, specificity 91.4%, sensitivity of52.6%)


# Prospective Validation of Glial Fibrillary Acidic Protein, D-Dimer, and Clinical Scales for Acute Large-Vessel Occlusion Ischemic Stroke Detection

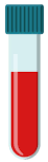
Yasir Durrani, MBBS, Jakob V. E. Gerstl, MBBS, Danielle Murphy, Ashley Harris MS, Imane Saali, MD, Toby Gropen, MD, Shashank Shekhar, MD , ... SHOW ALL ..., and Joshua D. Bernstock, MD, PhD, MPH AUTHOR INFO & AFFILIATIONS

Stroke: Vascular and Interventional Neurology • Volume 4, Number 4 • https://doi.org/10.1161/SVIN.123.001304

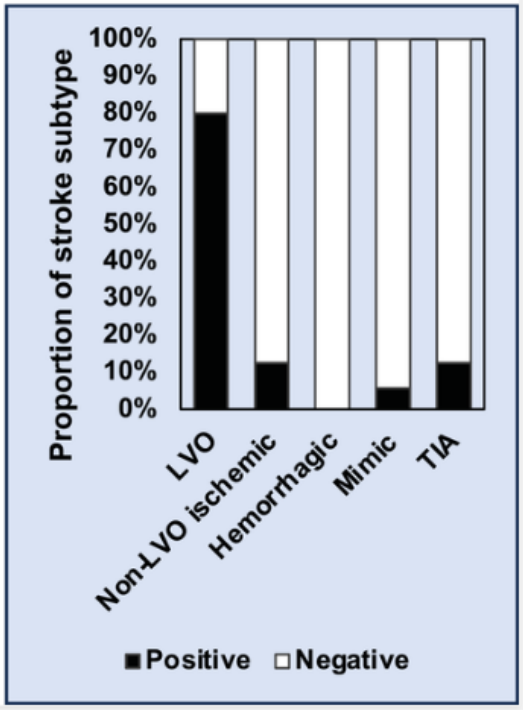


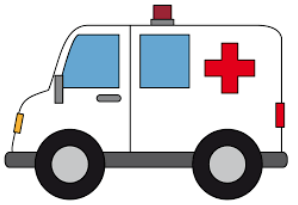
1. **D dimer**
2. **GFAP**
3. **FAST-ED NIHSS and time**

**Biomarkers – to exclude ICH in the ambulance – CAN START treatments ??**



- **GFAP (213pg/mL) and D-dimer (600ng/mL) performed best with FAST-ED**
- **Sensitivity at <6/18h for LVO detection = 81/71%**
- **Specificity at <6/18h for LVO detection = 93/94%**
- **All ICH cases ruled out**
- **Utility for LVO/ICH triage**



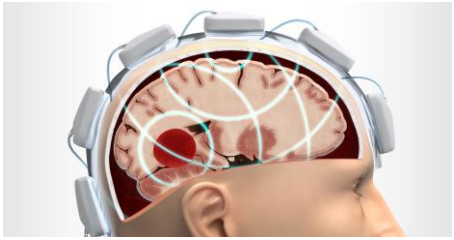
# Prehospital identification of intracerebral haemorrhage: a scoping review of early clinical features and portable devices

Mohammed Almubayyidh [1, 2], Ibrahim Alghamdi [1, 3], Adrian Robert Parry-Jones [1, 4], David Jenkins [5]

**4 technologies:**

1. Microwave imaging
2. Volumetric impedance phase shift spectroscopy (VIPS)
3. Transcranial ultrasound
4. Electroencephalopathy

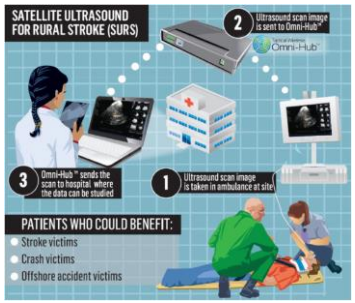
**1**



**2**

**4**

**3**



# Secondary prevention after ICH:

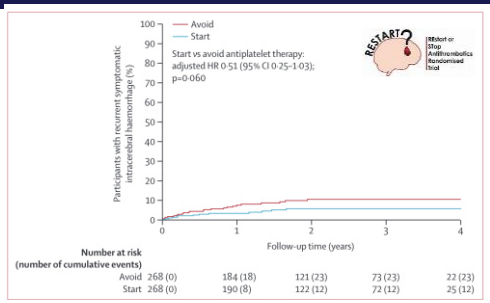
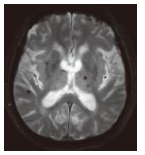



*Figure 2:* **Kaplan-Meier plot of the first occurrence of recurrent symptomatic intracerebral haemorrhage**
Numbers at risk refer to survivors under follow-up at the start of each year according to treatment allocation. Cumulative events indicate the participants in follow-up with a first event. HR=hazard ratio.

**Anti-platelets: Re-START**[1] trial

- No increased ICH in those on anti-platelets
- Most patients > 70yrs few > 80yrs. No interaction with age.
- Few patients with CMB included



- **Anti-coagulants: AF**
  **OAC (DOAC) vs none vs left atrial occlusion device** Randomised data needed – suggest randomise to on-going RCTS: ENRICH-AF, PRESTIGE AF

ENRICH-AF

PRESTIGE-AF
PREVENTION OF STROKE IN INTRACEREBRAL HAEMORRHAGE SURVIVORS WITH ATRIAL FIBRILLATION

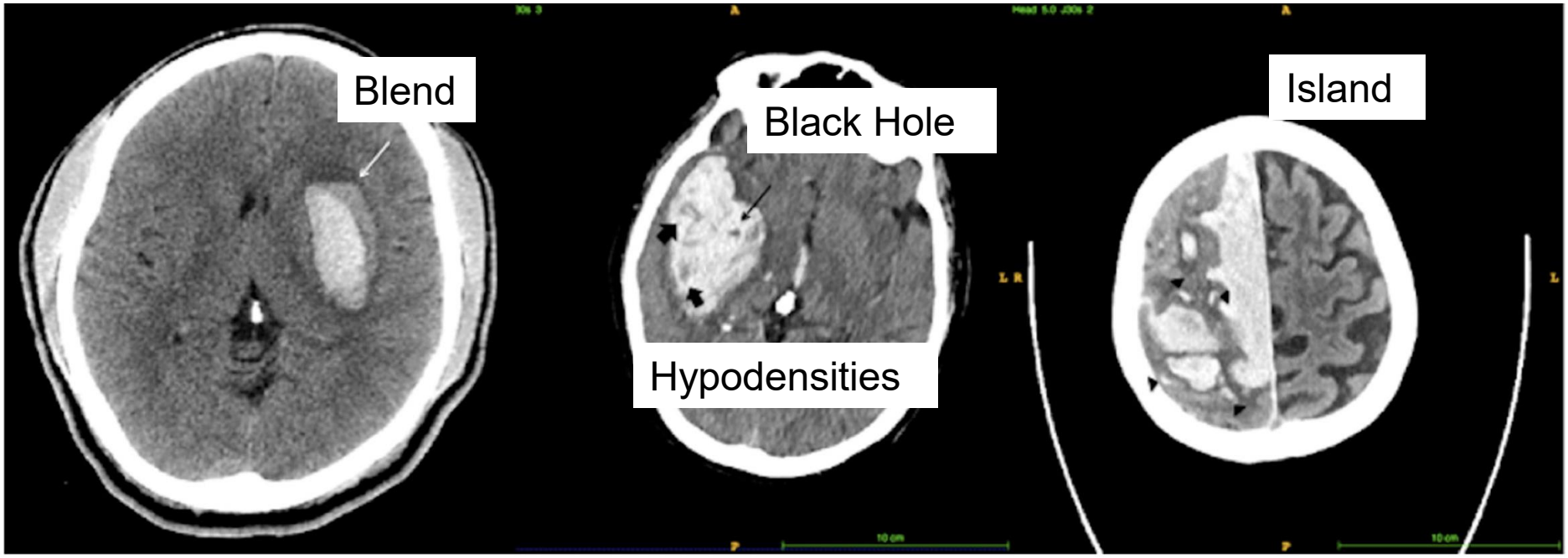
[1] Al-Shahi Salaman Lancet 2019 [2] Al-Shahi Salaman Lancet Neurology 2019 [3] Kuramatsu Eur Heart Journal 2018

# Treatment targets for ICH

Haemostatic therapies

# Some patients are higher risk – prioritize these patients

Predictors of expansion on plain CT head – associated with worse outcome

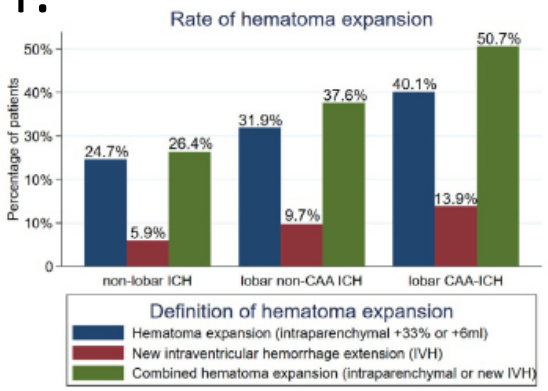


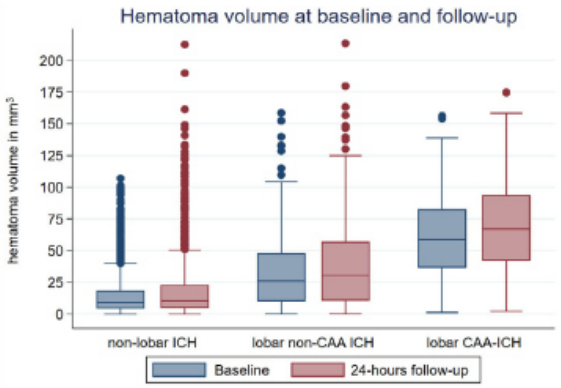

Target blood pressure lowering in these patients
Consider other treatments to stop bleeding – e.g tranexamic acid as part of clinical trials

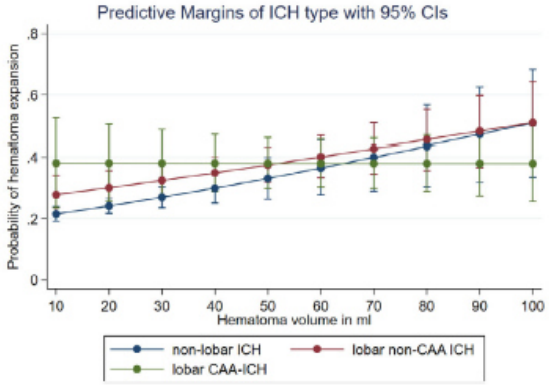
# Haematoma location:

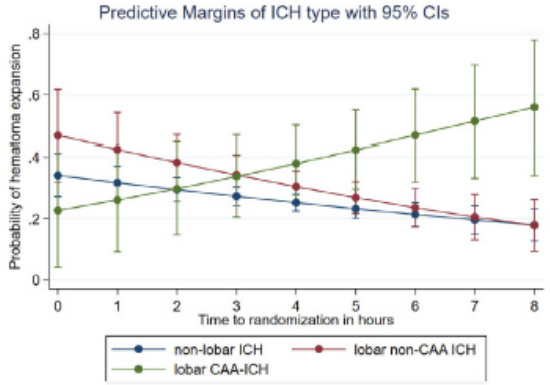
- Increasing risk HE
  Non lobar
  Lobar non CAA
  Lobar CAA
- Not associated with risk of HE or function after adjustment for covaraties
- Risk HE increase with time but constant across volumes in in lobar CAA ICH

Seiffge et al: CAA in the TICH-2 Trial



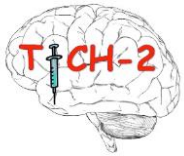



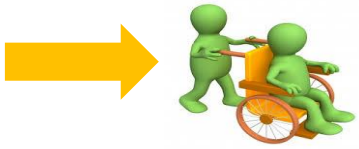

ANN NEUROL 2022;92:921–930

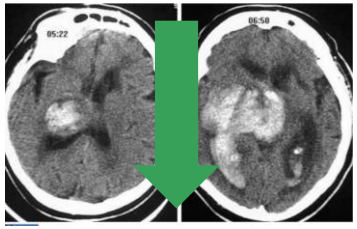
# Tranexamic acid for ICH: TICH-2




- 2,325 participants ICH enrolled < 8 hours
  No maximum haematoma volume specified

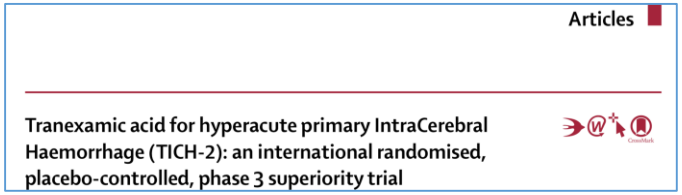
- Primary outcome: No significant benefit on function
  modified Rankin Scale day 90 shift analysis
  No significant benefit aOR 0.88 (95% CI 0.76-1.03)





- Secondary outcomes – Significant reductions:
  Early death (day 2,7)
  Haematoma expansion
  Serious adverse events
  Day 365 - No benefit on function
  Day 365 - Reduced death

TICH-2 https://doi.org/10.1016/S0140-6736(18)31033-X


Articles

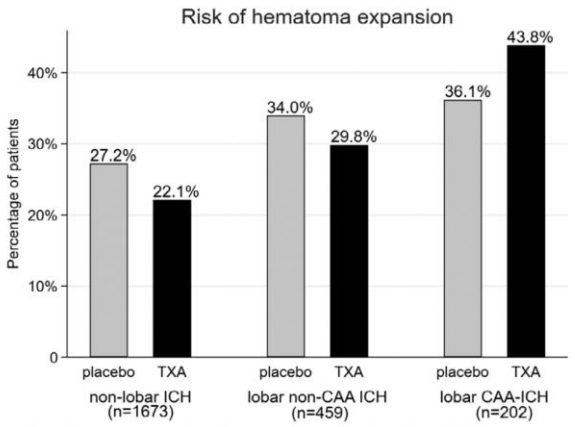
Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial

# TXA reduces haematoma expansion:

- Tranexamic significantly reduced haematoma growth and neurological deterioration[1]

| | TXA | Placebo | MD/OR 95%CI | p |
|---|---|---|---|---|
| **Neurological deterioration*** | | | | |
| All ≤7 days | 338 (29.1). | 366 (31.4) | **0.75 (0.60, 0.94)** | **0.013** |
| Early (<48 hours) | 275 (23.7). | 291 (25.0) | **0.75 (0.59, 0.96)** | **0.022** |
| **Radiological outcome** | | | | |
| Haematoma expansion | 265 (25.5). | 305 (29.3) | **0.77 (0.63, 0.94)** | **0.011** |

- TXA reduced HE in both lobar and non lobar ICH
  No interaction between treatment with TXA and type of ICH[2]




1. Z Kang et. al. : https://link.springer.com/article/10.1007/s12975-020-00845-6 Trans Str Res 2021, 2 ANN NEUROL 2022;92:921–930
:

# TICH-3 Synopsis

- ICH emergency condition - facilitate rapid enrolment

**Design:** Double blind randomised clinical trial, pragmatic streamlined design
**Participants:** Inclusion: < 4.5 hours of stroke onset
**Exclusion:** Massive ICH (Glasgow Coma Scale < 6 or Haematoma Volume > 60ml) seizures
**Consent:** Rapid emergency process – oral consent followed by written consent
**Intervention:** Tranexamic 1g IV bolus then 1g infusion 8hrs or saline by identical regime
**Randomisation:** Simple - use the lowest available treatment pack number
**Primary Outcome:** Early death (day 7)
**Secondary outcome:** Function-Shift analysis modified Rankin Scale day at 6 months
**Sample size:** 5500 (3900 UK and 1900 Internationally)
**Cost/funder:** UK NIHR plus others internationally
**Duration:** 7.25 years - Aim start UK recruitment early 2022

# Treatment of Intracerebral Hemorrhage in Patients on Non-vitamin K Oral Anticoagulants with Tranexamic Acid

## Methods

TICH-NOAC
Tranexamic acid in NOAC-associated ICH

- double-blind, randomized, placebo-controlled trial at 6 Swiss Stroke Centers
- registered at ClinicalTrials.gov (NCT02866838); funded by the Swiss National Science Foundation

- **Inclusion criteria:**
  - acute ICH within 12 hours of symptom onset
  - prior treatment with NOAC (apixaban, dabigatran, edoxaban or rivaroxaban; last intake within 48hours or proven NOAC activity by NOAC-specific coagulation assays)
  - age >18 years
- **Exclusion criteria (main):**
  - severe preexisting disability (mRS score >4)
  - secondary ICH (e.g., vascular malformation, tumor, trauma)
  - GCS score <5
  - planned neurosurgical hematoma evacuation within 24 hours (before follow-up imaging)
  - pulmonary embolism / deep vein thrombosis within the preceding 2 weeks

ESOC 2022 University of Basel Universitätsspital Basel

Stroke 2023 Sep;54(9):2223-2234. doi: 10.1161/STROKEAHA.123.042866.

# TICH-NOAC

## Results – primary outcome

| | Placebo (N=31) | Tranexamic acid (N=32) | Odds ratio (95% CI) | p value |
|---|---|---|---|---|
| **Hematoma expansion*** | 14 (45%) | 15 (47%) | 0.98 (0.36 to 2.71)† | 0.97 |

* missing follow-up imaging for 2 patients (both died before follow-up imaging; one tranexamic acid and one placebo; included in the primary outcome analysis assuming hematoma expansion)

† logistic regression adjusted for baseline hematoma volume



## Results – secondary outcomes

| | Placebo (N=31) | Tranexamic acid (N=32) | Effect size (95% CI) | p value |
|---|---|---|---|---|
| **Symptomatic hematoma expansion*** | 9 (29%) | 8 (25%) | 0.74 (0.23 to 2.32)† | 0.60 |
| **Absolute hematoma volume change***, ml | 1.8 (0.1-8.7) | 3.3 (0.6-8.8) | -0.33 (-3.80 to 3.14)‡ | 0.85 |
| **Ordinal mRS score at 90 days** | | | | |
| 0 | 0 (0%) | 0 (0%) | | |
| 1 | 3 (10%) | 2 (6%) | | |
| 2 | 3 (10%) | 3 (9%) | | |
| 3 | 3 (10%) | 3 (9%) | 1.11 (0.44 to 2.80)§ | 0.83 |
| 4 | 7 (23%) | 6 (19%) | | |
| 5 | 2 (6%) | 3 (9%) | | |
| 6 | 13 (42%) | 15 (47%) | | |

* missing follow-up imaging for 2 patients (both died before follow-up imaging; one assigned to tranexamic acid and one to placebo; included in the analysis of symptomatic HE (assuming HE), but not in the analysis of absolute hematoma volume change)

† odds ratio (logistic regression adjusted for baseline hematoma volume)

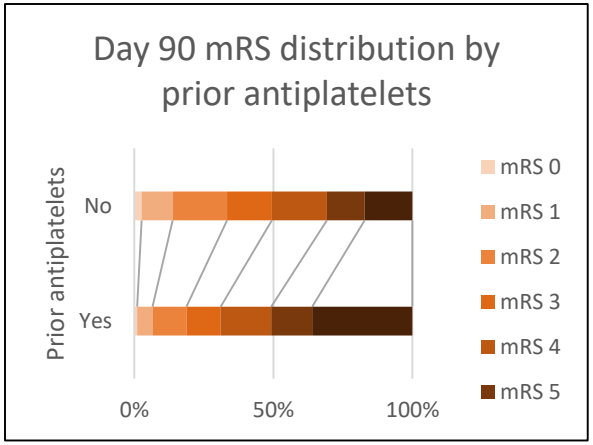
‡ median difference (median regression with bootstrapped standard error estimation and 1000 repetitions, adjusted for baseline hematoma volume)

§ common odds ratio (ordinal logistic regression adjusted for baseline hematoma volume)

# ICH on prior antiplatelets: Data TICH-2

- Patients older, more co-morbidities, larger baseline haematoma
- Increased risk of haematoma expansion, neurological deterioration and death day 7 and 90

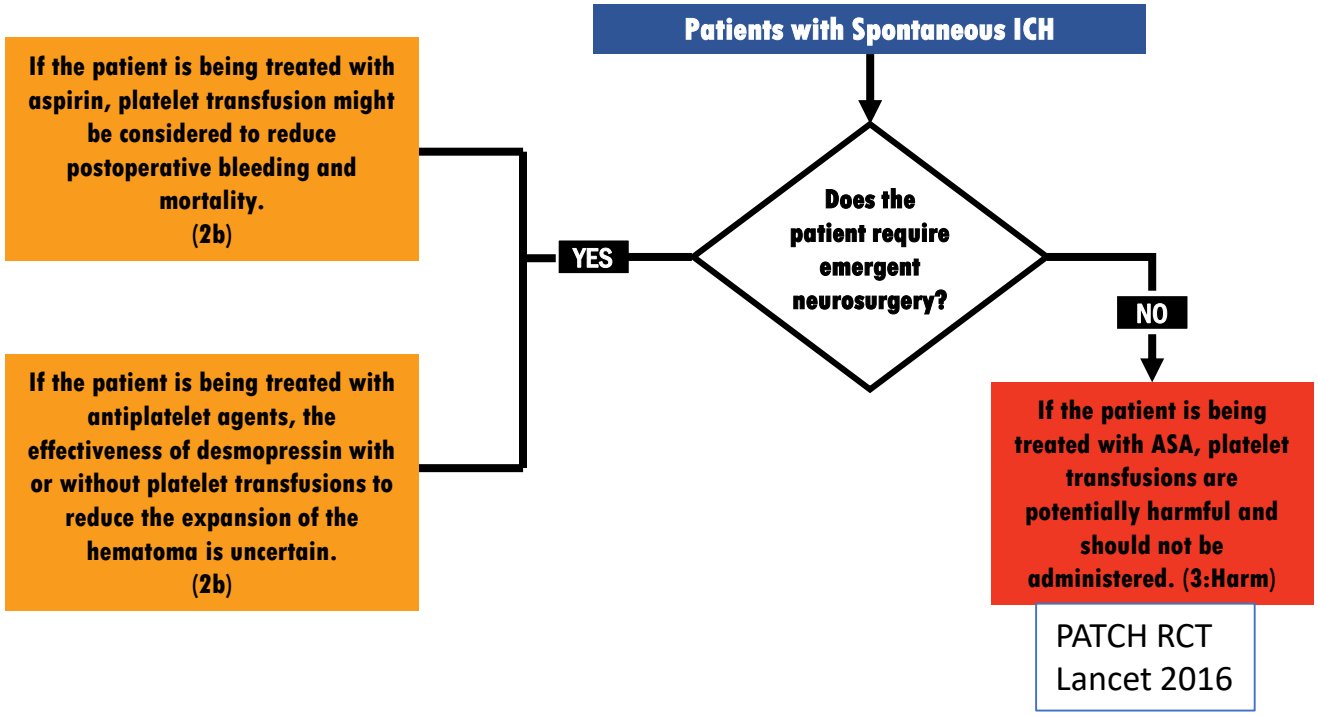
| Outcomes | Antiplatelet | No Antiplatelet | OR/MD (95% CI)* | *P* Value |
|---|---|---|---|---|
| Radiological, 24-h CT | | | | |
| Hematoma volume, mean (SD), mL | 33.8 (39.3) | 24.8 (27.4) | 9.0 (5.4, 12.6) | <0.001 |
| Hematoma growth, mean (SD), mL | 7.3 (21.4) | 3.3 (13.5) | 3.2 (1.7, 4.8) | <0.001 |
| Hematoma expansion† | 165 (30.7%) | 403 (25.1%) | 1.28 (1.01, 1.63) | 0.046 |
| New interventricular hemorrhage | 53 (9.8%) | 126 (7.8%) | 1.58 (1.12, 2.24) | 0.010 |
| Subarachnoid extension‡ | 47 (8.7%) | 75 (4.7%) | 1.99 (1.36, 2.91) | <0.001 |
| Day 7 | | | | |
| Neurological deterioration§ | 245 (40.1%) | 402 (23.5%) | 1.52 (1.21, 1.91) | <0.001 |
| Death | 106 (17.3%) | 118 (6.9%) | 1.94 (1.40, 2.69) | <0.001 |
| DNAR | 215 (35.2%) | 294 (17.2%) | 1.64 (1.25, 2.15) | <0.001 |
| Day 90 | | | | |
| Death | 212 (34.8%) | 287 (16.9%) | 1.63 (1.25, 2.11) | <0.001 |
| mRS >3 | 417 (68.4%) | 841 (49.6%) | 1.52 (1.17, 1.98) | 0.002 |




J Am Heart Assoc 2021 Feb;10(5):e019130.

# Hemostasis & Coagulopathy

## Antiplatelet-Related Hemorrhage in Spontaneous ICH




AHA ICH Guidelines 2022 https://doi.org/10.1161/str.0000000000000407

# ICH on anti-platelet treatment:

## Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial

*M Irem Baharoglu*, Charlotte Cordonnier*, Rustam Al-Shahi Salman*, Koen de Gans, Maria M Koopman, Anneke Brand, Charles B Majoie, Ludo F Beenen, Henk A Marquering, Marinus Vermeulen, Paul J Nederkoorn, Rob J de Haan, Yvo B Roos, for the PATCH Investigators†*

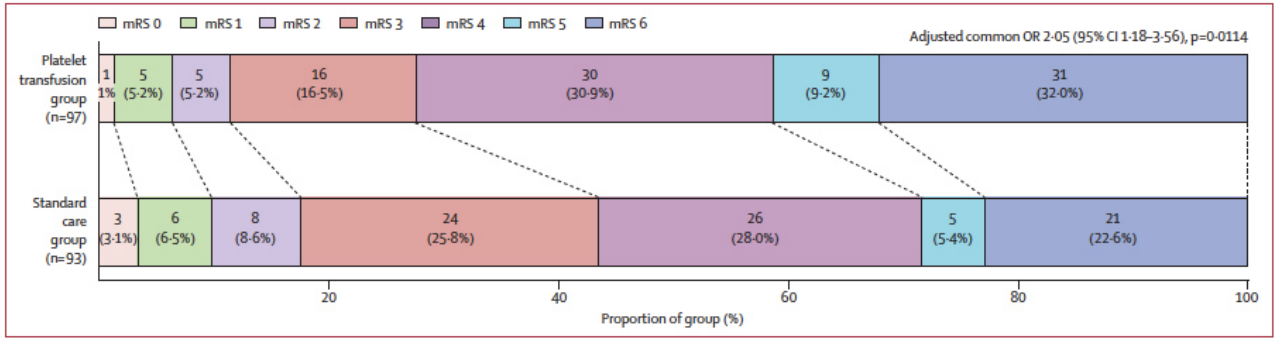
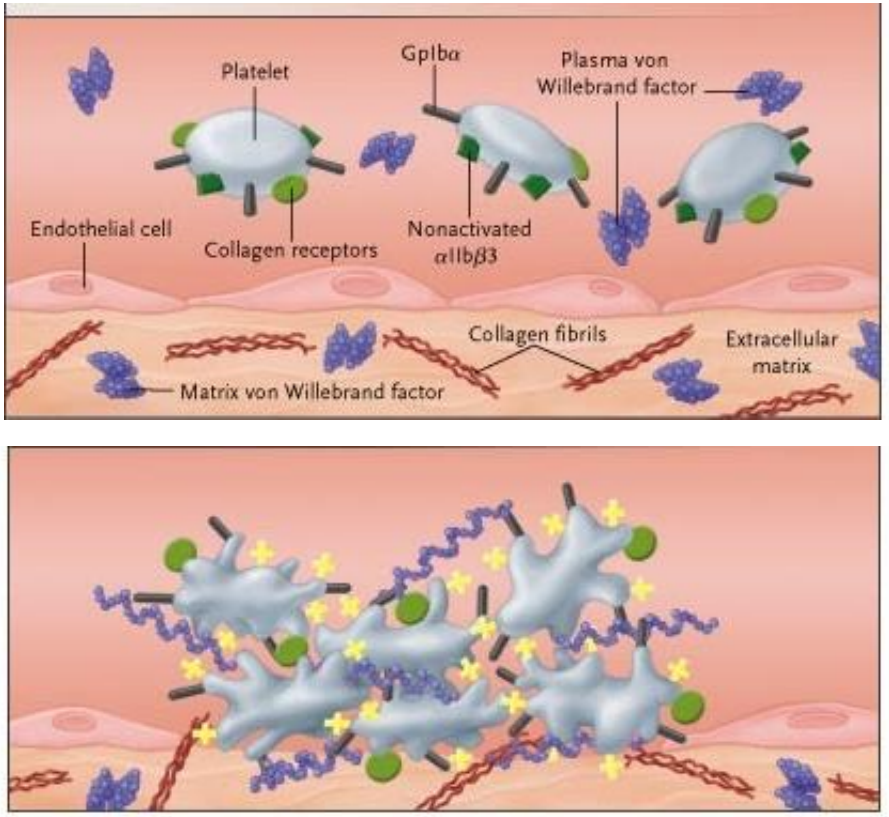



***Figure 2*: Distribution of mRS score at 3 months**

# Desmopressin

- Used for inherited bleeding conditions
- Induces endothelium to release stores of vWF
- vWF casues platelets to adhere to damaged endothelium
- 2 small non controlled studies[1,2] – safe and feasible
- Recommended for traumatic brain injury[3]
- Neurocritical care guidelines in US




*Desmopressin stimulates release of Von Willebrand Factor increasing platelet adhesion*

1: Kapapa et al. Neurology Research International 2014; 2: Naidech et al Stroke 45:2451-3 2014 3: Mappus et.al. 2017 Trauma

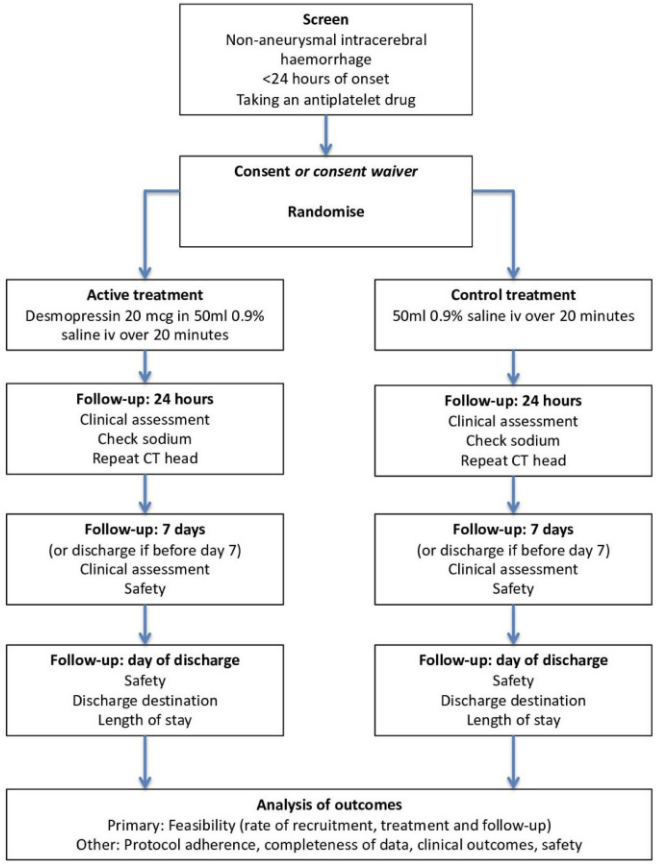
# DASH pilot study: ISRCTN 67038373

- Desmopressin for reversal of antiplatelet drugs in stroke due to haemorrhage

  - **Participants:** ICH < 24 hours on anti-platelet therapy
  - **Objectives:** to assess the feasibility of RCT Desmopressin or placebo to inform a definitive trial
  - **Primary outcome:** number of eligible participants receiving treatment

    Definitive study primary outcome: Death or dependency at Day 90 (mRS, shift analysis)
  - Completed 54 participants enrolled – Results Dec 2022

https://DASHprotocol2020bmjopen

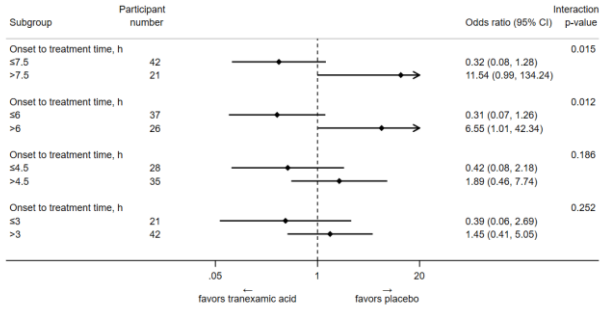


# TICH-NOAC

Tranexamic acid in NOAC-associated ICH

26 out of 63 patients were treated within 4.5h and hematoma volume ≤ 60ml.
Treatment within 4.5h: 28/63 patients
hematoma volume ≤ 60ml: 58/63

Interaction with onset-to-treatment time:
Trend for better outcome (i.e., less hematoma expansion) with tranexamic acid in the early treatment window, but the interaction is no longer significant (see plot).




When analysing time as a continuous measure, its interaction with treatment is significance (p-interaction = 0.025).

- ***Data Courtesy of Philippe Lyrer on behalf of the TICH-NOAC Investigators***

# Blood pressure

- Interaction with BP < 170n
  TICH-2 and TICH NOAC

BMJ Neurology Open

**Effects of blood pressure and tranexamic acid in spontaneous intracerebral haemorrhage: a secondary analysis of a large randomised controlled trial**

- Tranexamic acid may improve clinical and radiological outcomes in participants with baseline SBP≤170 mm Hg, despite being older and larger HV
- Reduction in BP associated with less HE and early death
- Future research should aim to establish which subgroups of patients may benefit from tranexamic acid and whether BP lowering is additive or synergistic in the presence of tranexamic acid in acute intracerebral haemorrhage.

http://dx.doi.org/10.1136/bmjno-2023-000423

# Treatment targets

Inflammation

# Role of neuro-inflammation

## Bad prognostic markers

- GCS
- WCC
- Creatine

All more powerful than HV

? Related to neuroinflammation

| Variables | OR | 95% CI | *P* | |
|---|---|---|---|---|
| **Age** (year) | 1.05 | 1.03–1.06 | 0.000 | *** |
| **Severe Score** | | | | |
| GCS | 0.91 | 0.86–0.95 | 0.000 | *** |
| **Laboratory test** | | | | |
| Creatinine (mg/dL) | 1.30 | 1.10–1.55 | 0.000 | *** |
| WBC (K/μL) | 1.10 | 1.05–1.16 | 0.000 | *** |
| **Vital signs** | | | | |
| Temperature (°C) | 1.73 | 1.25–2.41 | 0.000 | *** |
| Glucose (mg/dL) | 1.01 | 1.00–1.01 | 0.000 | *** |
| Urine Output (mL) | 1.00 | 1.00–1.00 | 0.020 | * |
| **Bleeding Volume** ($cm^2$) | 1.02 | 1.01–1.04 | 0.000 | *** |

*P < 0.05, ***P < 0.001.

https://www.frontiersin.org/articles/10.3389/fnins.2022.942100/full#B67

# Ageing brain and ICH:





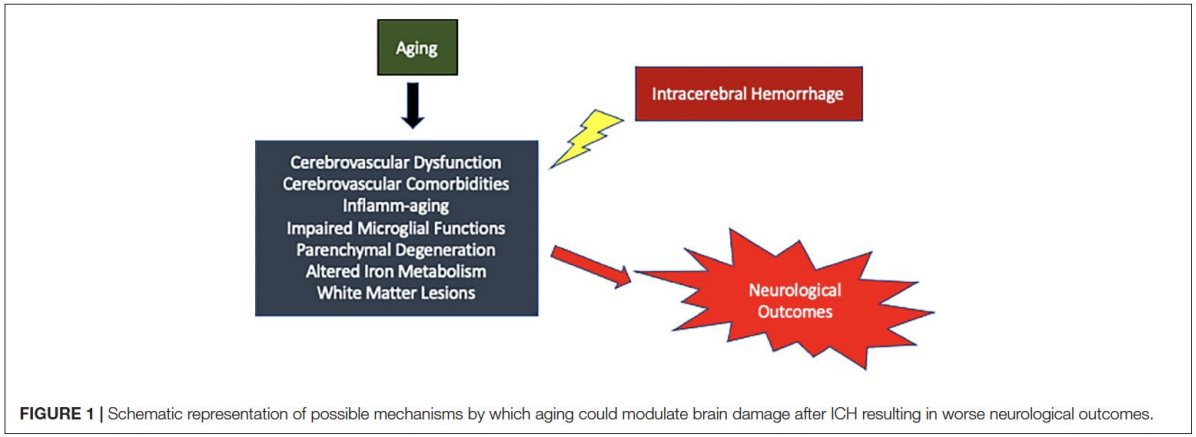



**FIGURE 1 |** Schematic representation of possible mechanisms by which aging could modulate brain damage after ICH resulting in worse neurological outcomes.

https://doi.org/10.3389%2Ffnagi.2022.859067

MANCHESTER 1824
The University of Manchester

FUNDED BY
NIHR | National Institute for Health Research

# BLOC-ICH: Phase II trial of IL-1Ra in ICH

**80 ICH patients:**
< 8 h post-onset
Supratentorial

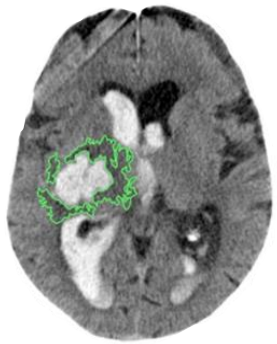
**72 h SC IL-1Ra**
100 mg BD

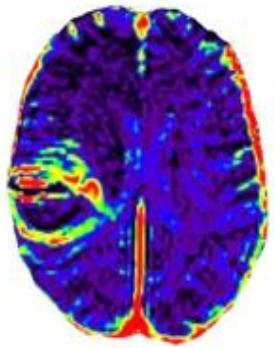
**Matched placebo**

**72 h**
CT Brain
(oedema)

**Day 2-4**
MRI brain
(BBBB)

**3 month**
Clinical outcomes



# iDEF – Deferoxamine for improving recovery after ICH?

Stroke

CLINICAL TRIAL

## Effect of Deferoxamine on Trajectory of Recovery After Intracerebral Hemorrhage: A Post Hoc Analysis of the i-DEF Trial

Lydia Foster, MS; Laura Robinson, MS; Sharon D. Yeatts, PhD; Robin A. Conwit, MD; Amjad Shehadah, MD; Vasileios Lioutas, MD; Magdy Selim, MD, PhD; on behalf of the i-DEF Investigators*

**BACKGROUND:** There are limited data on the trajectory of recovery and long-term functional outcomes after intracerebral hemorrhage (ICH). Most ICH trials have conventionally assessed outcomes at 3 months following the footsteps of ischemic stroke. The i-DEF trial (Intracerebral Hemorrhage Deferoxamine Trial) assessed modified Rankin Scale (mRS) longitudinally at prespecified time points from day 7 through the end of the 6-month follow-up period. We evaluated the trajectory of mRS among trial participants and examined the effect of deferoxamine on this trajectory.

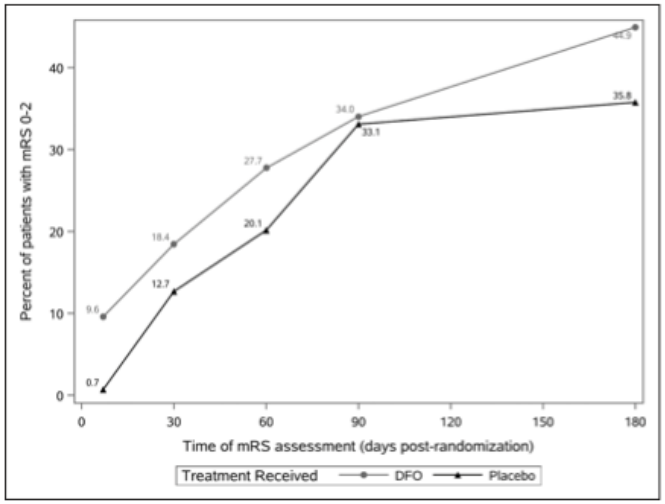
**METHODS:** We performed a post hoc analysis of the i-DEF trial, a multicenter, randomized, placebo-controlled, double-blind, futility-design, phase 2 clinical trial, based on the actual treatment received. Favorable outcome was defined as mRS score of 0–2. A generalized linear mixed model was used to evaluate the outcome trajectory over time, as well as whether the trajectory was altered by deferoxamine, after adjustments for randomization variables, presence of intraventricular hemorrhage, and ICH location.

**RESULTS:** A total of 291 subjects were included in analysis (145 placebo and 146 deferoxamine). The proportion of patients with mRS score of 0–2 continually increased from day 7 to 180 in both groups (interaction $P<0.0001$ for time in main effects model), but treatment with deferoxamine favorably altered the trajectory (interaction $P=0.0010$). Between day 90 and 180, the deferoxamine group improved ($P=0.0001$), whereas there was not significant improvement in the placebo arm ($P=0.3005$).

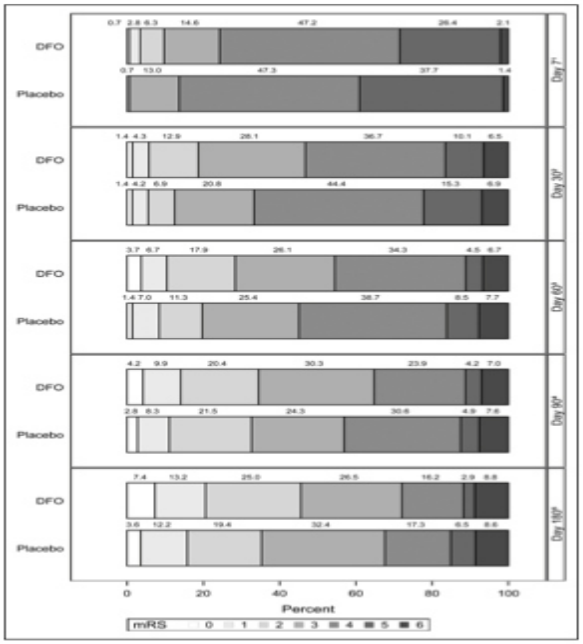
**CONCLUSIONS:** A large proportion of patients continue to improve up to 6 months after ICH. Future ICH trials should assess outcomes past 90 days for a minimum of 6 months. In i-DEF, treatment with deferoxamine seemed to accelerate and alter the trajectory of recovery as assessed by mRS.

**REGISTRATION:** URL: https://www.clinicaltrials.gov; Unique identifier: NCT02175225.

**GRAPHIC ABSTRACT:** A graphic abstract is available for this article.




Proportion of patients with mRS 0-2 continually increase in both groups (interaction p <0.0001 for time)




The proportion of patients with mRS 4-6 continually decreased over time from day 7 through day 180!

Slide courtesy of Magdy Selim

# Treatment targets - neuromodulation

Transcranial magnetic stimulation (TMS)
Transcranial direct current stimulation (tDCS)

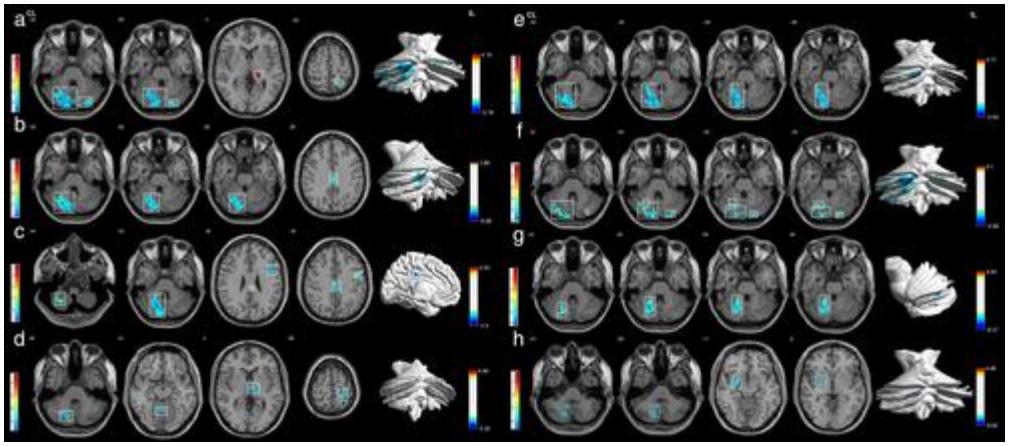
Research Article | Open Access

# Abnormal Local Brain Activity and Cognitive Impairments in Young Non-Disabled Patients With Intracerebral Hemorrhage: A Resting-State Functional MRI Study

Dan Yang MD, Xue Zhang MD, Xiangqi Luo MS, Fengxia Zhang PhD, Shengjun Sun PhD, Liu Shaocheng MD, Xingquan Zhao PhD, Jian Zhou PhD

Static and dynamic alterations in multiple brain regions

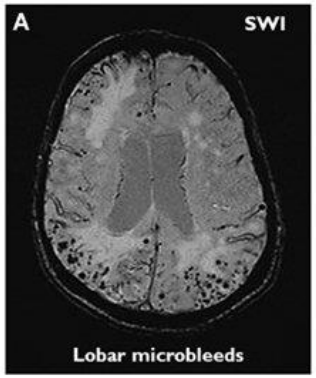
Changes in ipsilateral thalamus and cingulum and contralateral cerebellar posterior lobe important

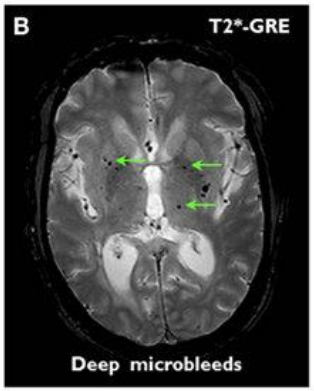


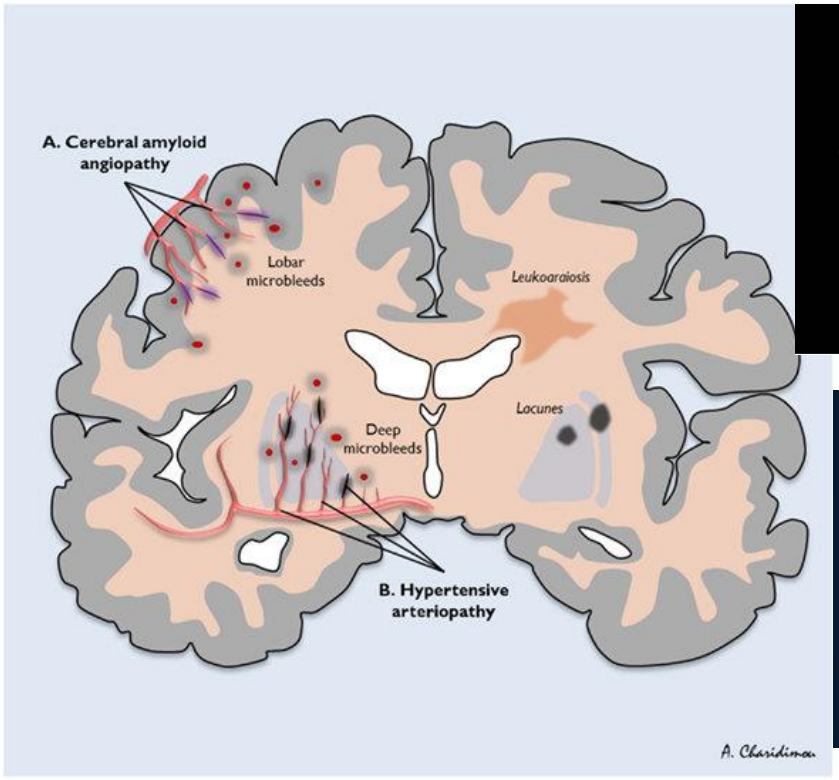

https://doi.org/10.1002/jmri.29166

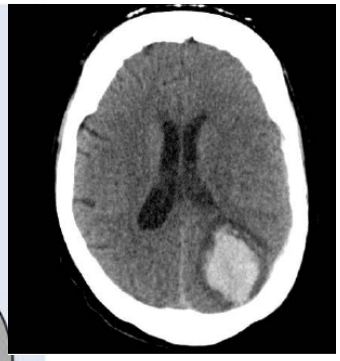
# Predicting outcome after ICH

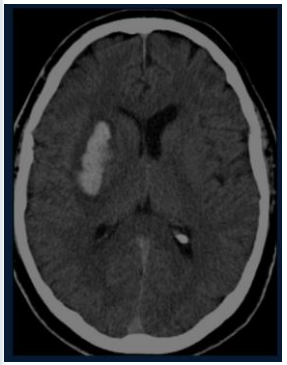
# Causes of spontaneous ICH:



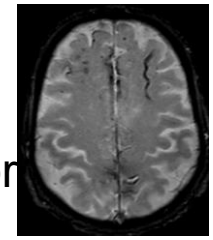





http://dx.doi.org/10.3389/fneur.2012.00133

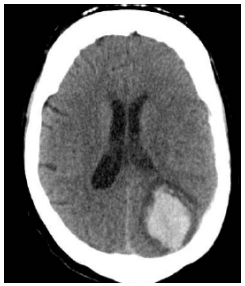
Frontiers in neurology
Werring 2012

# Updated Boston Criteria: v2.0 MRI markers



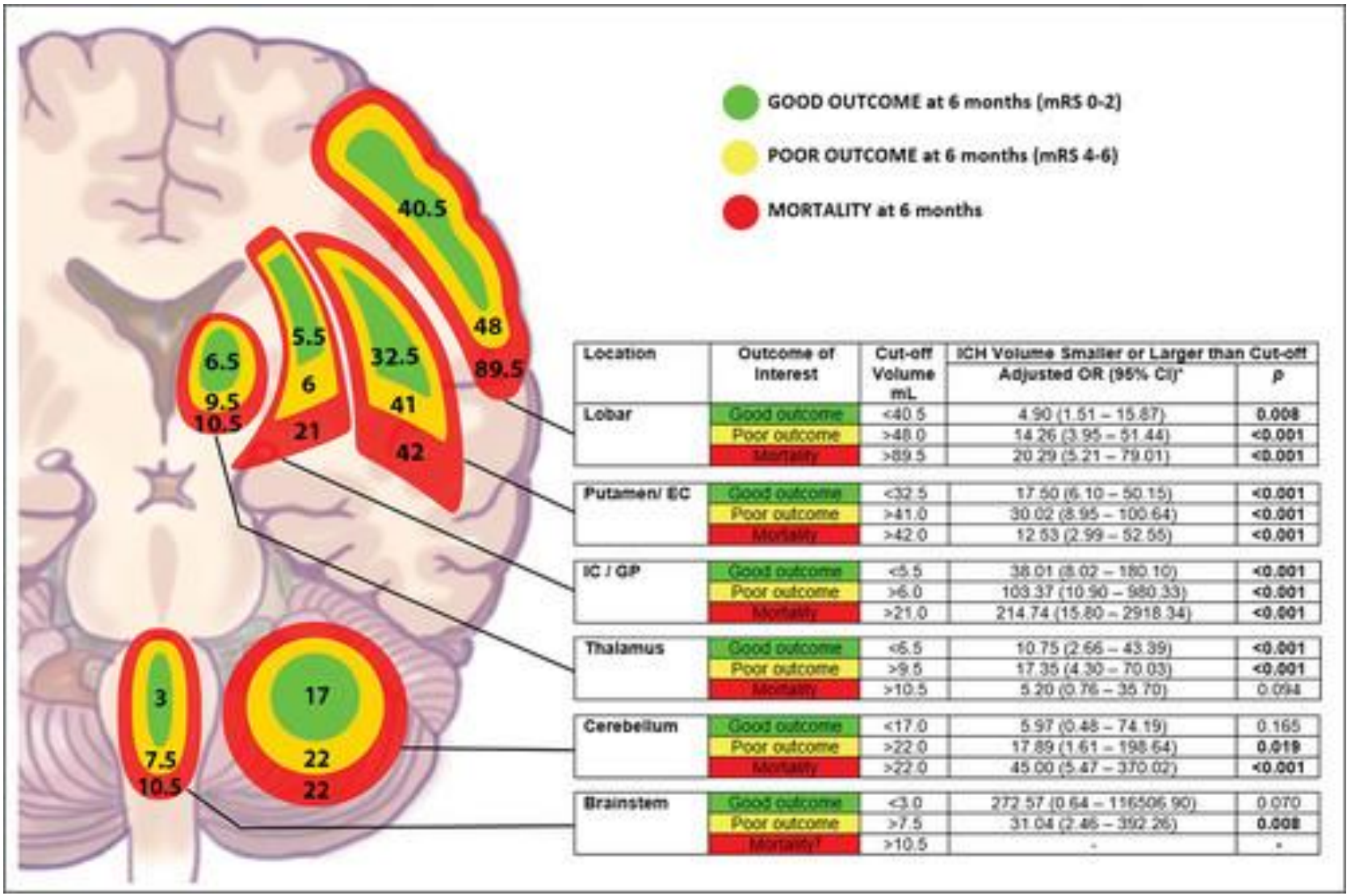
Probable CAA requiring the presence of:

- at least two strictly lobar haemorrhagic lesions (ie, intracerebral haemorrhages, cerebral microbleeds, or foci of cortical superficial siderosis) or
- at least one strictly lobar haemorrhagic lesion and at least one white matter characteristic (ie, severe visible perivascular spaces in centrum semiovale or white matter hyperintensities in a multispot pattern)

https://doi.org/10.1016/S1474-4422(22)00208-3

# Size and location very important -




| Location | Outcome of Interest | Cut-off Volume mL | ICH Volume Smaller or Larger than Cut-off | |
|---|---|---|---|---|
| | | | Adjusted OR (95% CI)* | p |
| Lobar | Good outcome | <40.5 | 4.90 (1.51 – 15.87) | 0.008 |
| | Poor outcome | >48.0 | 14.26 (3.95 – 51.44) | <0.001 |
| | Mortality | >89.5 | 20.29 (5.21 – 79.01) | <0.001 |
| Putamen/ EC | Good outcome | <32.5 | 17.50 (6.10 – 50.15) | <0.001 |
| | Poor outcome | >41.0 | 30.02 (8.95 – 100.64) | <0.001 |
| | Mortality | >42.0 | 12.53 (2.99 – 52.55) | <0.001 |
| IC / GP | Good outcome | <5.5 | 38.01 (8.02 – 180.10) | <0.001 |
| | Poor outcome | >6.0 | 103.37 (10.90 – 980.33) | <0.001 |
| | Mortality | >21.0 | 214.74 (15.80 – 2918.34) | <0.001 |
| Thalamus | Good outcome | <6.5 | 10.75 (2.66 – 43.39) | <0.001 |
| | Poor outcome | >9.5 | 17.35 (4.30 – 70.03) | <0.001 |
| | Mortality | >10.5 | 5.20 (0.76 – 35.70) | 0.094 |
| Cerebellum | Good outcome | <17.0 | 5.97 (0.48 – 74.19) | 0.165 |
| | Poor outcome | >22.0 | 17.89 (1.61 – 198.64) | 0.019 |
| | Mortality | >22.0 | 45.00 (5.47 – 370.02) | <0.001 |
| Brainstem | Good outcome | <3.0 | 272.57 (0.64 – 116506.90) | 0.070 |
| | Poor outcome | >7.5 | 31.04 (2.46 – 392.26) | 0.008 |
| | Mortality† | >10.5 | - | - |

https://doi.org/10.1161/STROKEAHA.122.041246

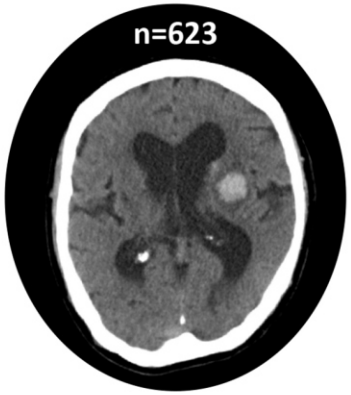
# Early Deterioration, Hematoma Expansion, and Outcomes in Deep versus Lobar Intracerebral Hemorrhage in the FAST Trial

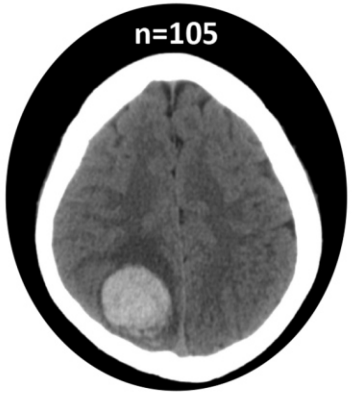
841 patients enrolled in FAST

↓

728 with supratentorial ICH

## DEEP vs. LOBAR




- Numerically LOWER rate of early neurological deterioration

- Numerically HIGHER rate of early neurological deterioration

---

- Smaller baseline hematoma volumes
- ↓ risk for hematoma expansion

- Larger baseline hematoma volumes
- ↑ risk for hematoma expansion

---

- BETTER overall functional outcome
- WORSE functional outcome when adjusting for variables known to correlate with outcome

- WORSE overall functional outcome
- BETTER functional outcome when adjusting for variables known to correlate with outcome

# Predicting long term recovery: 40% of survivors will improve

JAMA Neurology | Original Investigation

## One-Year Outcome Trajectories and Factors Associated with Functional Recovery Among Survivors of Intracerebral and Intraventricular Hemorrhage With Initial Severe Disability

Vishank A. Shah, MD; Richard E. Thompson, PhD; Gayane Yenokyan, PhD; Julian N. Acosta, MD; Radhika Avadhani, MS; Rachel Dlugash, MSPH; Nichol McBee, MPH; Yunke Li, MD; Bjorn M. Hansen, MD, PhD; Natalie Ullman, MD; Guido Falcone, MD, ScD, MPH; Issam A. Awad, MD; Daniel F. Hanley, MD; Wendy C. Ziai, MD, MPH

**IMPORTANCE** Patients who survive severe intracerebral hemorrhage (ICH) and intraventricular hemorrhage (IVH) typically have poor functional outcome in the short term and understanding of future recovery is limited.

**OBJECTIVE** To describe 1-year recovery trajectories among ICH and IVH survivors with initial severe disability and assess the association of hospital events with long-term recovery.

**DESIGN, SETTING, AND PARTICIPANTS** This post hoc analysis pooled all individual patient data from the Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage phase 3 trial (CLEAR-III) and the Minimally Invasive Surgery Plus Alteplase for Intracerebral Hemorrhage Evacuation (MISTIE-III) phase 3 trial in multiple centers across the US, Canada, Europe, and Asia. Patients were enrolled from August 1, 2010, to September 30, 2018, with a follow-up duration of 1 year. Of 999 enrolled patients, 724 survived with a day 30 modified Rankin Scale score (mRS) of 4 to 5 after excluding 13 participants with missing day 30 mRS. An additional 9 patients were excluded because of missing 1-year mRS. The final pooled cohort included 715 patients (71.6%) with day 30 mRS 4 to 5. Data were analyzed from July 2019 to January 2022.

**EXPOSURES** CLEAR-III participants randomized to intraventricular alteplase vs placebo. MISTIE-III participants randomized to stereotactic thrombolysis of hematoma vs standard medical care.

**MAIN OUTCOMES AND MEASURES** Primary outcome was 1-year mRS. Patients were dichotomized into good outcome at 1 year (mRS 0 to 3) vs poor outcome at 1 year (mRS 4 to 6). Multivariable logistic regression models assessed associations between prospectively adjudicated hospital events and 1-year good outcome after adjusting for demographic characteristics, ICH and IVH severity, and trial cohort.

**RESULTS** Of 715 survivors, 417 (58%) were male, and the overall mean (SD) age was 60.3 (11.7) years. Overall, 174 participants (24.3%) were Black, 491 (68.6%) were White, and 49 (6.9%) were of other races (including Asian, Native American, and Pacific Islander, consolidated owing to small numbers); 98 (13.7%) were of Hispanic ethnicity. By 1 year, 129 participants (18%) had died and 308 (43%) had achieved mRS 0 to 3. In adjusted models for the combined cohort, diabetes (adjusted odds ratio [aOR], 0.50; 95% CI, 0.26-0.96), National Institutes of Health Stroke Scale (aOR, 0.93; 95% CI, 0.90-0.96), severe leukoaraiosis (aOR, 0.30; 95% CI, 0.16-0.54), pineal gland shift (aOR, 0.87; 95% CI, 0.76-0.99]), acute ischemic stroke (aOR, 0.44; 95% CI, 0.21-0.94), gastrostomy (aOR, 0.30; 95% CI, 0.17-0.50), and persistent hydrocephalus by day 30 (aOR, 0.37; 95% CI, 0.14-0.98) were associated with lack of recovery. Resolution of ICH (aOR, 1.82; 95% CI, 1.08-3.04) and IVH (aOR, 2.19; 95% CI, 1.02-4.68) by day 30 were associated with recovery to good outcome. In the CLEAR-III model, cerebral perfusion pressure less than 60 mm Hg (aOR, 0.30; 95% CI, 0.13-0.71), sepsis (aOR, 0.05; 95% CI, 0.00-0.80), and prolonged mechanical ventilation (aOR, 0.96; 95% CI, 0.92-1.00 per day), and in MISTIE-III, need for intracranial pressure monitoring (aOR, 0.35; 95% CI, 0.12-0.98), were additional factors associated with poor outcome. Thirty-day event-based models strongly predicted 1-year outcome (area under the receiver operating characteristic curve [AUC], 0.87; 95% CI, 0.83-0.90), with significantly improved discrimination over models using baseline severity factors alone (AUC, 0.76; 95% CI, 0.71-0.80; $P < .001$).

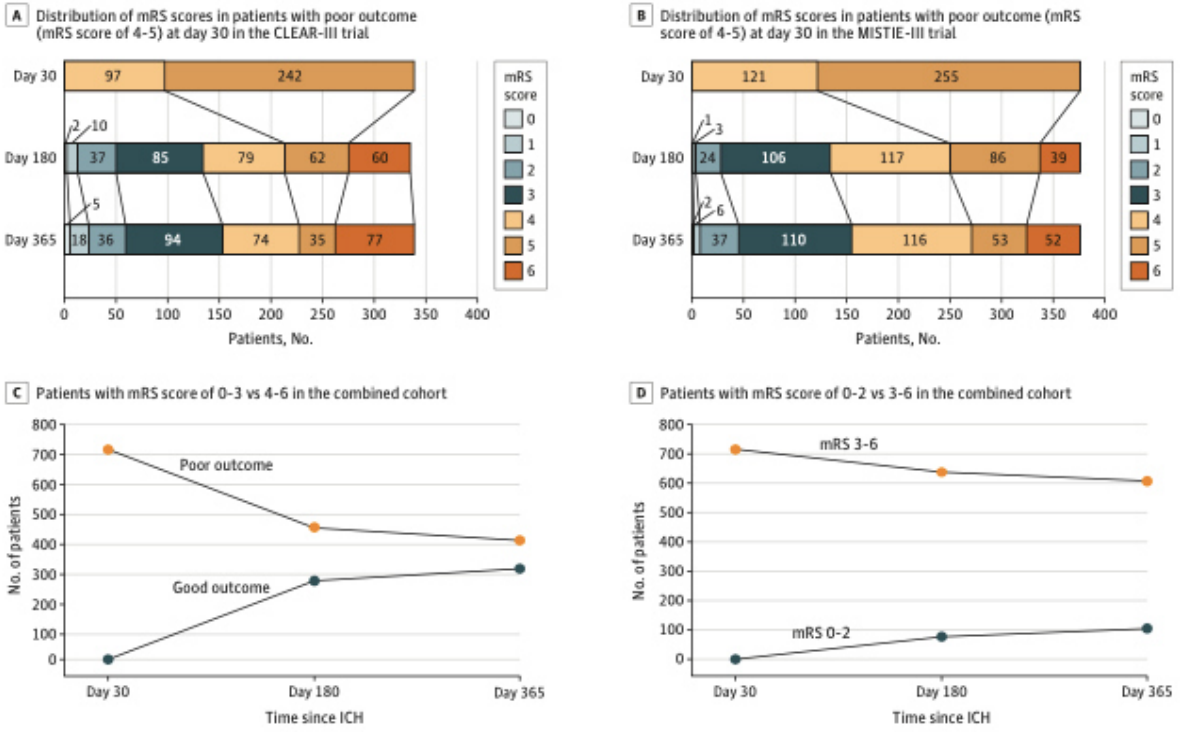
**CONCLUSIONS AND RELEVANCE** Among survivors of severe ICH and IVH with initial poor functional outcome, more than 40% recovered to good outcome by 1 year. Hospital events were strongly associated with long-term functional recovery and may be potential targets for intervention. Avoiding early pessimistic prognostication and delaying prognostication until after treatment may improve ability to predict future recovery.

Editorial

Supplemental content

**Author Affiliations:** Author affiliations are listed at the end of the article.

**Corresponding Author:** Wendy Ziai, MD, MPH, Division of Neurocritical Care, Department of Neurology, Johns Hopkins Univ




A and B, Grotta bars demonstrate ordinal distribution of mRS at days 30, 180, and 365 in patients in CLEAR-III and MISTIE-III with poor outcomes (mRS 4-5) at day 30. C, Number of patients with mRS 0-3 vs 4-6 at days 180 and 365 in the combined cohort of patients in CLEAR-III and MISTIE-III with poor outcomes (mRS 4-5) at day 30. D, Number of patients with mRS 0-2 vs 3-6 at days 180 and 365 in the combined cohort of patients in CLEAR-III and MISTIE-III with poor outcomes at day 30. CLEAR-III indicates Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase 3 Trial; MISTIE-III, Minimally Invasive Surgery Plus

Slide courtesy of Magdy Selim

# Summary for state of the art ICH care:

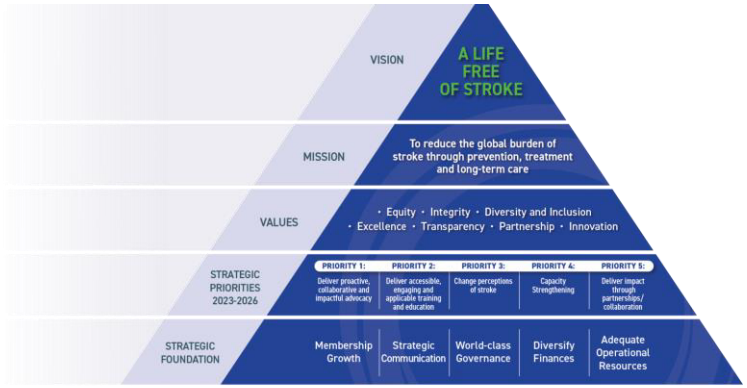
- Education is key – know what the guidelines/processes are

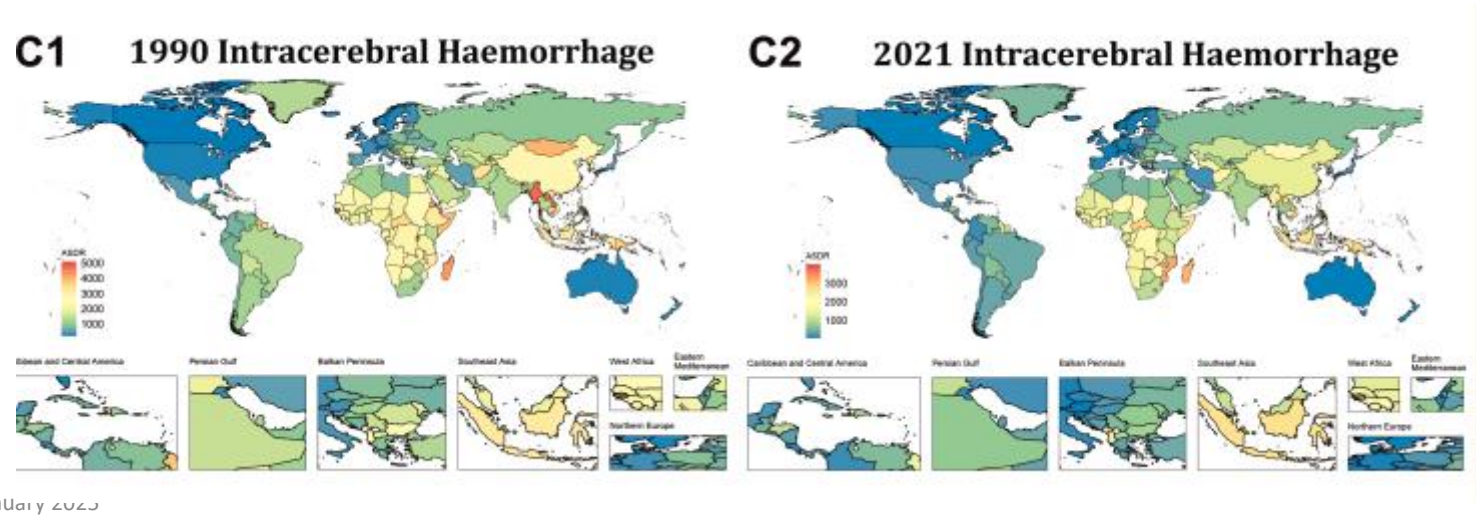
- ICH bundles of care – medical (non-surgical approaches)
  **Anticoagulation** reversal
  **BP lowering**
  Treat **hyperglycaemia**
  Avoid **Fever**
- **Surgical approaches** need better evidence

- **Team based approach**
  Emergency department, neurology, neurosurgery, intensive care, good nursing care (swallow assessment, DVT prevention), therapy (physio, occupational, speech)

- Enrol in clinical trials:
  ? Stop the bleeding – haemostatic agents
  e.g. Tranexamic acid, Desmopressin
  ? Odema therapies -
- Secondary prevention:
  Anti-thrombotics, Blood pressure lowering, statins

# We need ICH care globally and to target inequalities MUCH MUCH better.....

# Need a well trained team for ICH care

Emergency Department

Neurosurgery

Neurology Rehabilitation

Neurology/ Stroke Drs

Intensive Care

# Behind the clinical team need researchers...

S·A·F·E
Stroke Alliance For Europe
THE STROKE PATIENT VOICE IN EUROPE

Always working with patients and their families....

ESO EUROPEAN STROKE ORGANISATION

World Stroke Organization

RESEARCH METHODS

Stroke/Health Organisations

Clinical staff

Pre-clinical scientists

Regulatory authorities

SCIENTIFIC RESEARCH

Thank you – any questions?

nikola.sprigg@nottingham.ac.uk