TRAITEMENTS DES HEMORRAGIES INTRACEREBRALES

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IUF institut universitaire de France

DISCLOSURES

Stocks

None

Drug trials (< 5 years)*

Astra-Zeneca	2015	Socrates	(investigator)
Daiichi	2016	DS-xxxx	(investigator)
Servier	2017	Brain restore	(investigator)
Astra-Zeneca	2019	Thales	(investigator)
Biogen	2019	Charm	(investigator)

Board (<5 years)*

Medtronic – Pfizer/BMS

Speaker honoraria (<2 years)

Pfizer - Boehringer Ingelheim

Travels (<1 year)

None

* No personal funding - Funding to Research account (Lille Univ. Hospital) or ADRINORD

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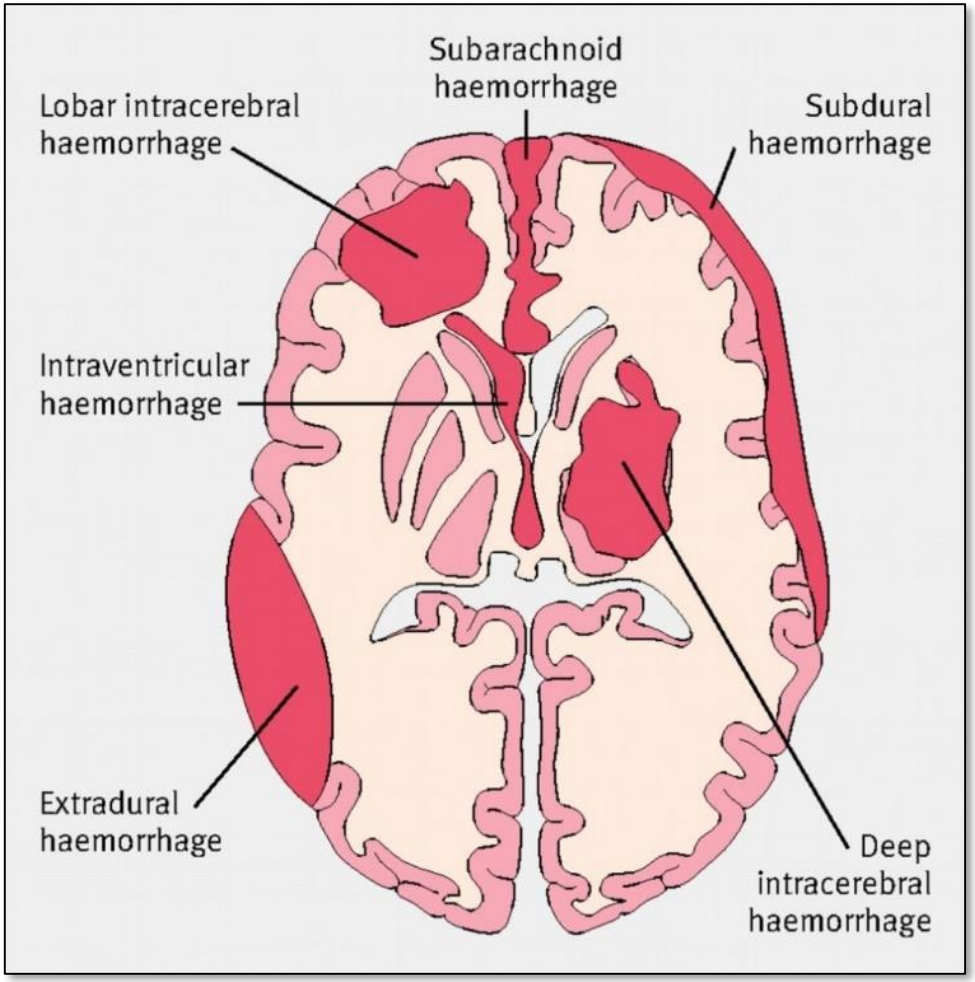
~3.4 million new ICrH worldwide in 2013



Même incidence depuis 30 ans

Mais profil qui a évolué
age plus élevé
moins d'ICH profonde chez les jeunes

plus d'ICH chez les sujets agés,
associées aux antithrombotiques

Béjot Y, et al. Brain 2013

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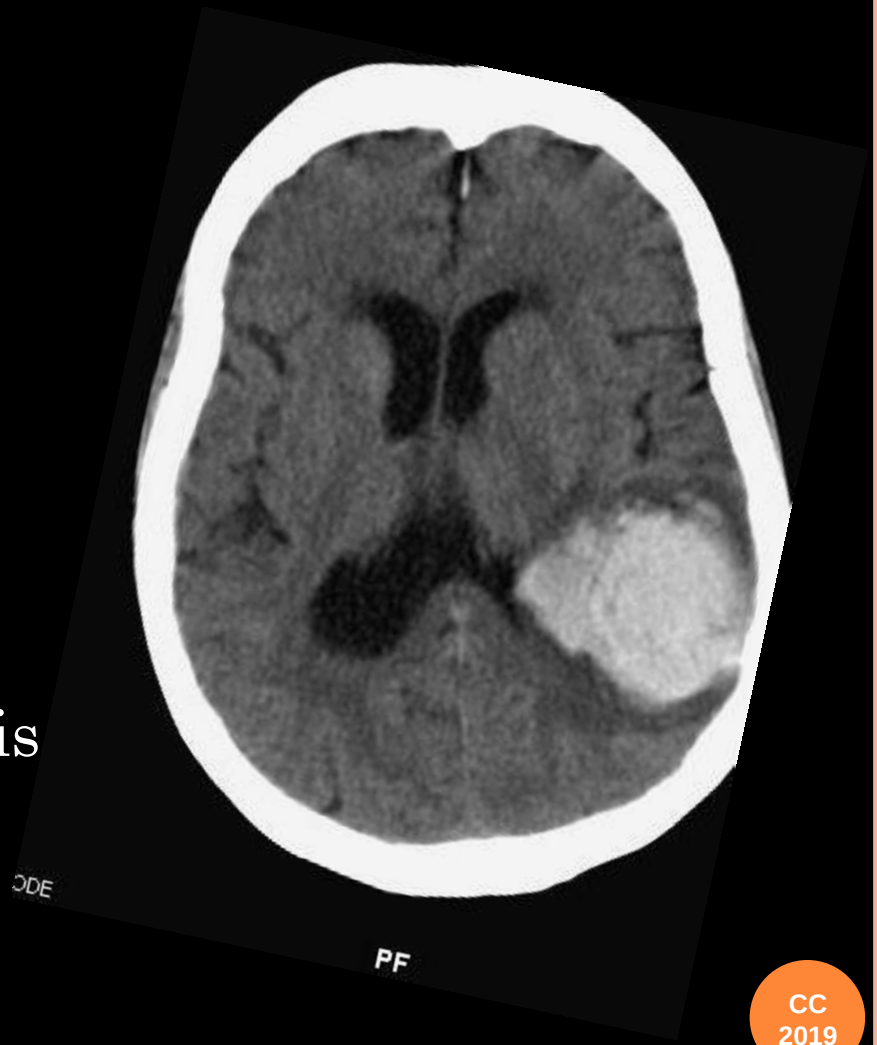
- A 72 year old retired dentist presented with a sudden R hemiparesis.
- No past medical history,

  not known to be hypertensive previously independent.

- GCS=13 (E4 V4 M5)
- Mild dysphasia, R hemiparesis
- Blood pressure: 160/90



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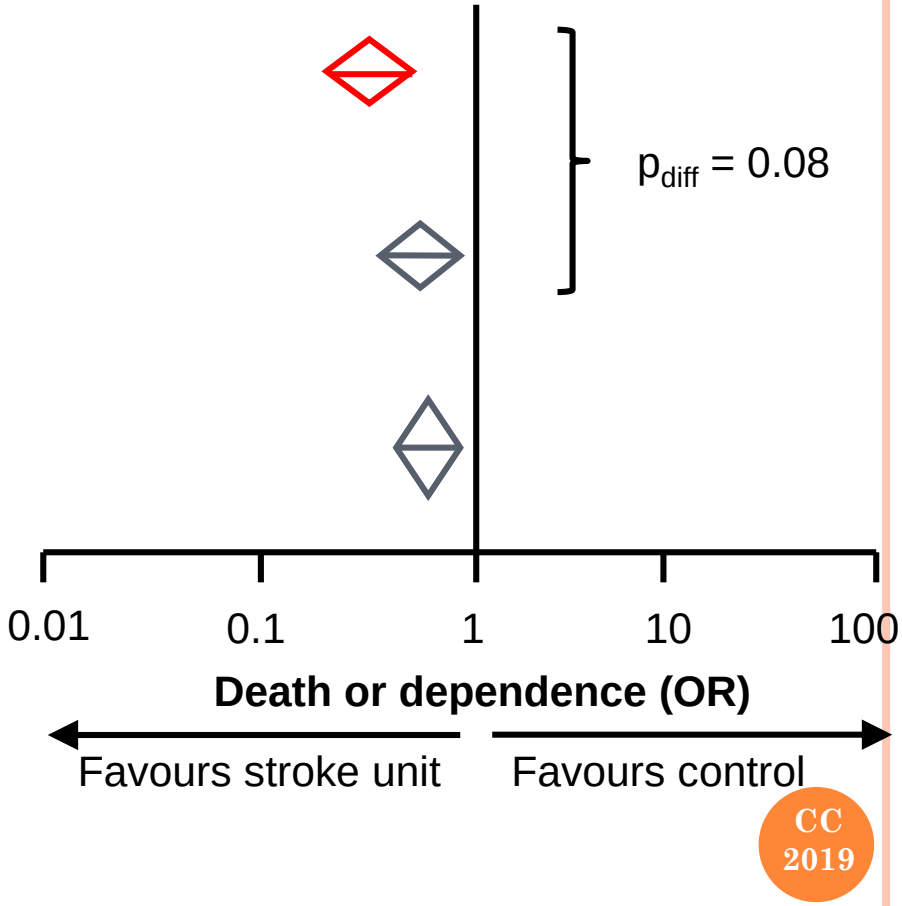
Acute stroke unit care

Stroke type	RCTs	Patients
ICH	8	428
OR 0.37 (95% CI 0.21-0.66), I^2=16%		
Ischaemic stroke	8	2,229
OR 0.67 (95% CI 0.48-0.93), I^2=67%		
All stroke	8	2,657
OR 0.57 (95% CI 0.42-0.79), I^2=61%		



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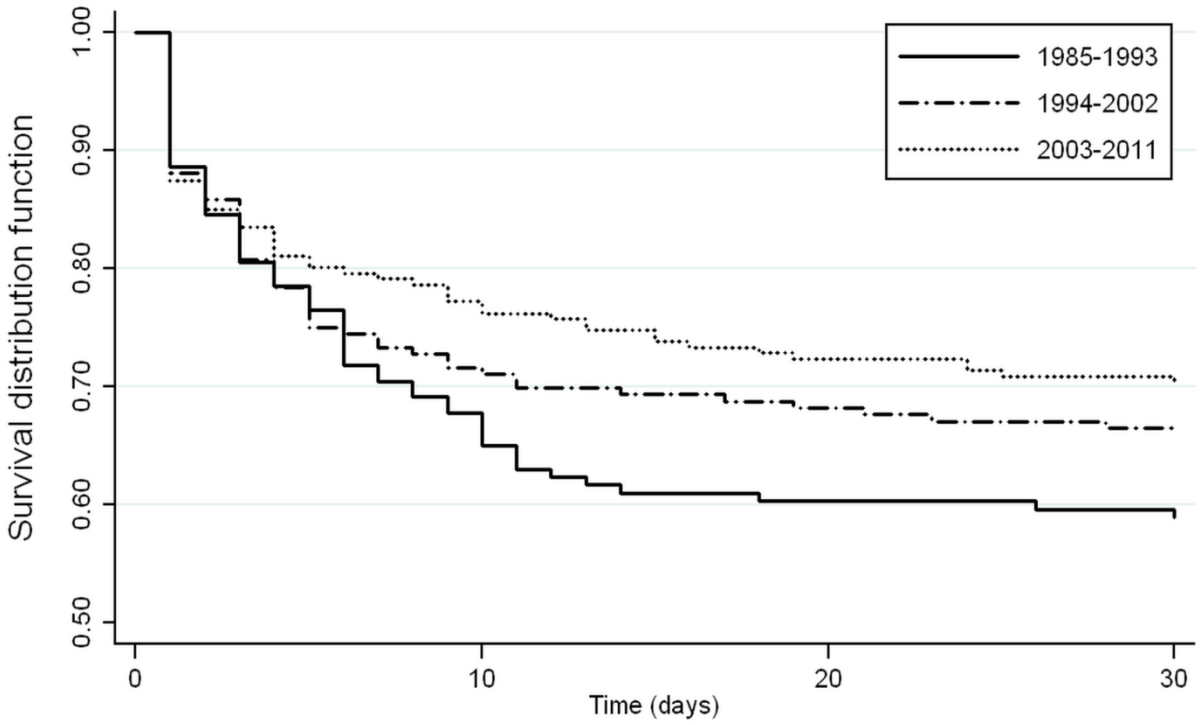
Stroke 2013;44:3044-9



	HR	95% CI	p
1985-1993	*Ref.*		
1994-2002	0.71	0.47-1.07	0.106
2003-2011	0.49	0.32-0.73	<0.001

Analyse multivariée

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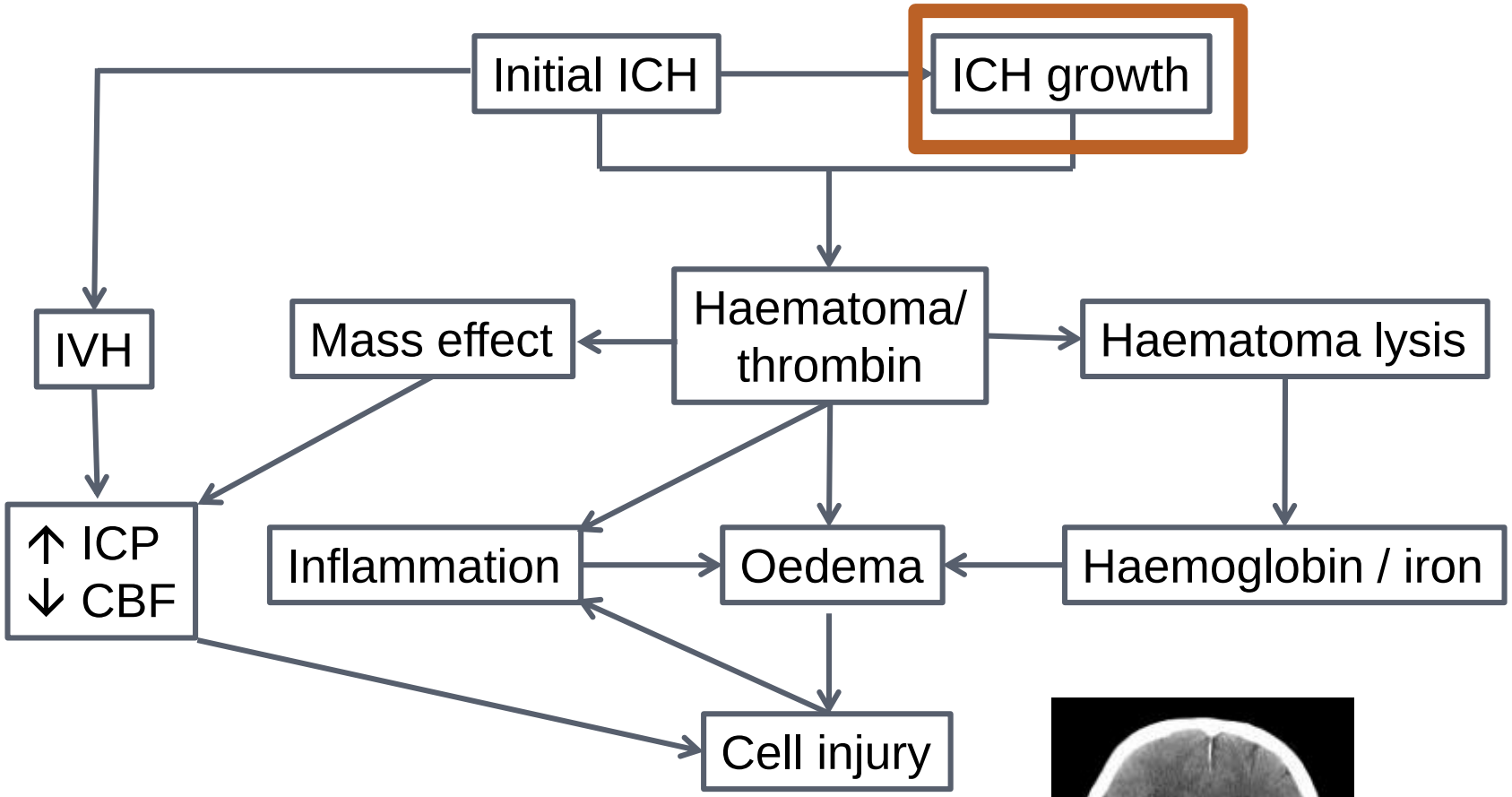
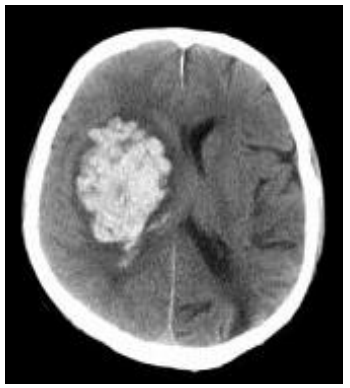
REGISTRE DIJONNAIS des AVC

Béjot Y. Neurology 2018

Pathophysiological targets





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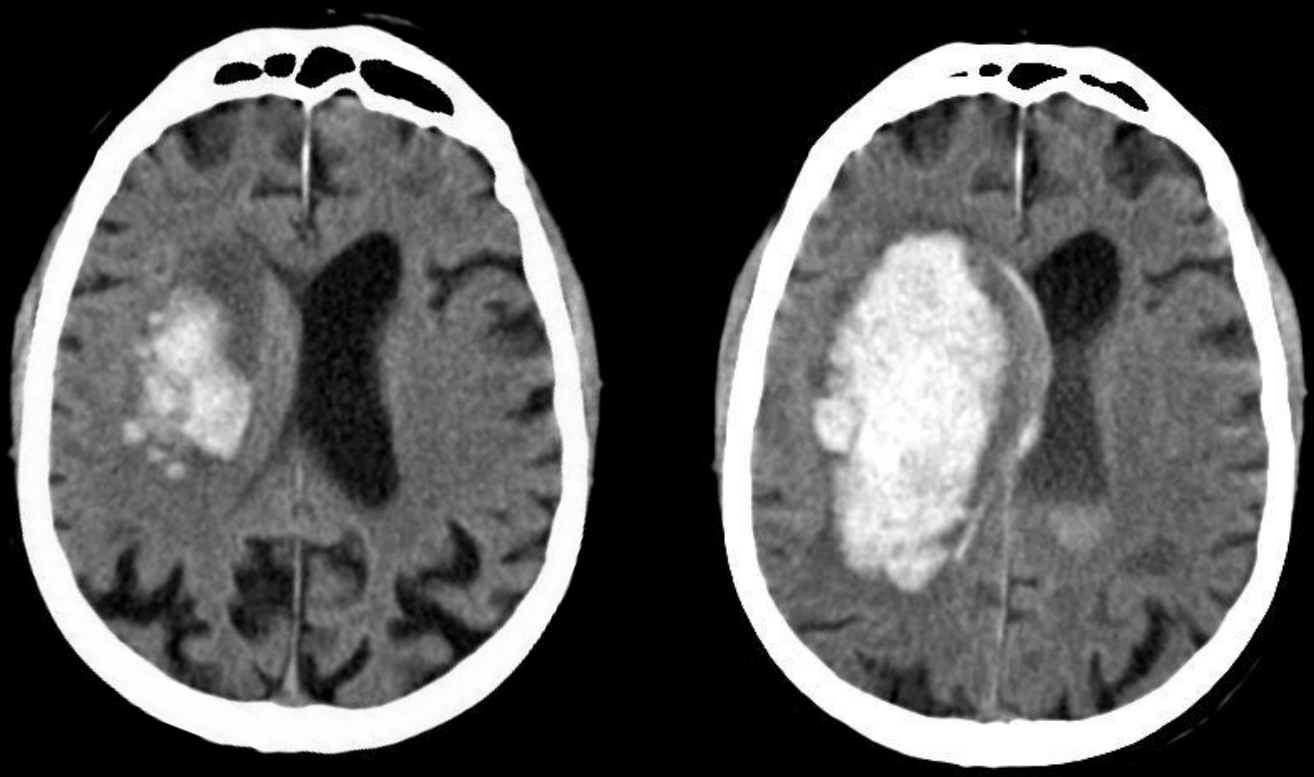
Lancet Neurol 2012;11:720-31

At admission

5 hours later



Time is brain

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HOW TO FIGHT AGAINST HAEMATOMA EXPANSION?

- Correct Haemostasis?
- Manage Blood Pressure?

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ICH & antithrombotic agents: A Frequent problem

- 15% of ICH are associated with OAC / VKAs

  (Lovelock C. Lancet Neurol 2007) (Cordonnier C. J Neurol 2009)

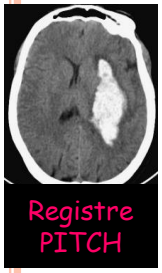
- 26% of ICH patients are treated with antiplatelet agents

  Pasquini M et al. Stroke 2014

  - Higher in-hospital mortality rate

    Dequatre-Ponchelle N et al. Stroke 2013

  - Reasons
    - Do Not Resuscitate Orders
    - Comorbidities
    - ICH Volume



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ICH & Antiplatelet agents Available evidence

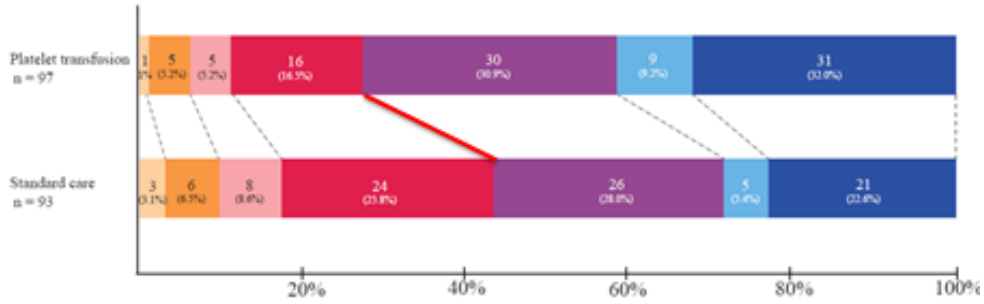
- Randomised, open, masked endpoint parallel group trial (PROBE)
- Multicentre: 36 Netherlands, 13 UK, 11 France

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†*

*Contributed equally

Outcome (ITT)



Adjusted common OR 2.05 (95%CI 1.18 to 3.56), p=0.0114

mRS 4-6, OR 2.04 (95%CI 1.12 to 3.74), p=0.0195

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ICH & Oral Anticoagulants

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In real life, what do we do?

ANNALS *of Neurology*

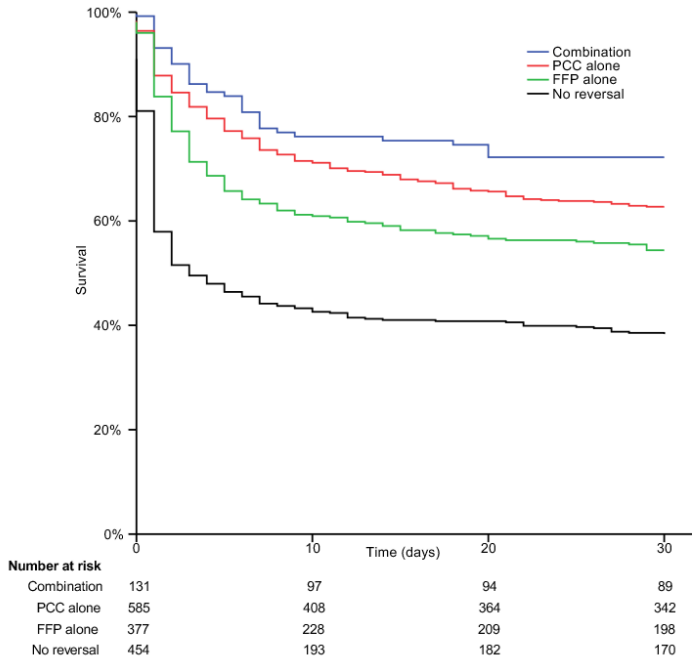

FIGURE 2: Kaplan–Meier survival analysis of 30-day survival after intracerebral hemorrhage stratified by treatment strategy. FFP = fresh frozen plasma; PCC = prothrombin complex concentrate. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

10282 ICH
including 1547 treated with VKA

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Parry-Jones A. et al. Ann Neurol 2015

ONE RECENT RCT

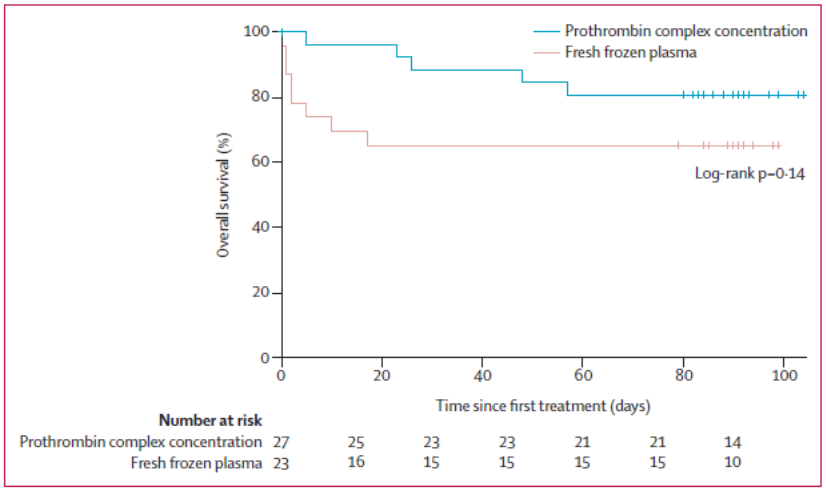

Figure 3: **Kaplan-Meier survival curve**
Crosses represent censored patients.

INCH STUDY: CCP VS PFC

Hémorragies sous AVK
Objectif INR <1.4
CCP + vit K
Contrôle INR à H1

	FFP (n=23)		PCC (n=27)	Odds ratio (95% CI)*	p value†
	FFP only (n=4)‡	FFP plus PCC (after 3 h; n=19)‡§			
Number of patients with at least one SAE	2	8	16	0·65 (0·16–2·49)	0·55
Number of SAEs	5	15	23	N/A	N/A
SAE classified as haematoma expansion	2	7	7	N/A	N/A
SAE classified as haematoma expansion leading to death	2	4	1	N/A	N/A
Thromboembolic events¶					
Myocardial infarction	0	..	0	N/A	N/A
Ischaemic stroke	1	1	2	N/A	N/A
Pulmonary embolism	0	0	4	N/A	N/A
Deep vein thrombosis	0	0	1	N/A	N/A

FFP=fresh frozen plasma. N/A=not applicable. PCC=prothrombin complex concentrate. SAE=serious adverse event. *FFP plus PCC vs PCC only. †Fisher's exact test. ‡Two of 21 patients who did not reach the primary endpoint in the FFP did not receive PCC (protocol violation). §According to the protocol, patients in whom the international normalised ratio after 3 h was not below or equal to 1·2 received PCC. ¶One stroke in the FFP only group and one stroke and one pulmonary embolism in the PCC group occurred within the first 3 days after start of treatment.

Table 3: **Safety outcomes**

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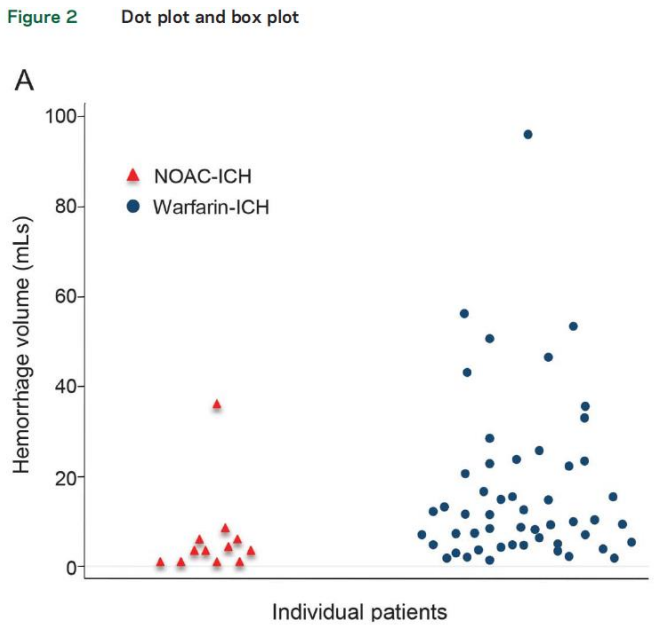
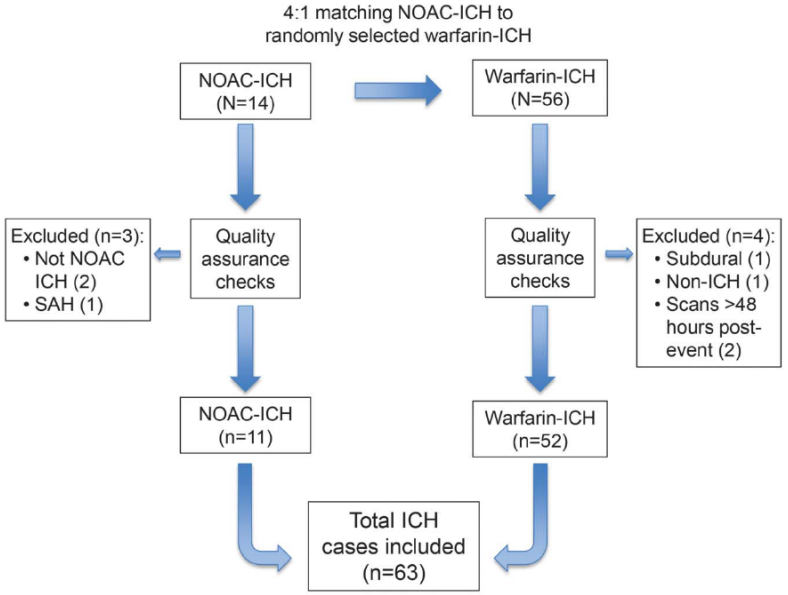
Steiner T. Lancet Neurol 2016

ICH: VKA VERSUS DOAC





- Associated factors with volumes: VKA

Wilson D. Neurology 2016
Tsivgoulis G. Ann Neurol 2018

- Same outcome

Tsivgoulis G. Ann Neurol 2018

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Antidotes?

- Yes but … no RCTs

- Idaruzicumab for dabigatran

- Andexanet alfa for Xa inhibitors

- Per977 for everything (not yet approved)

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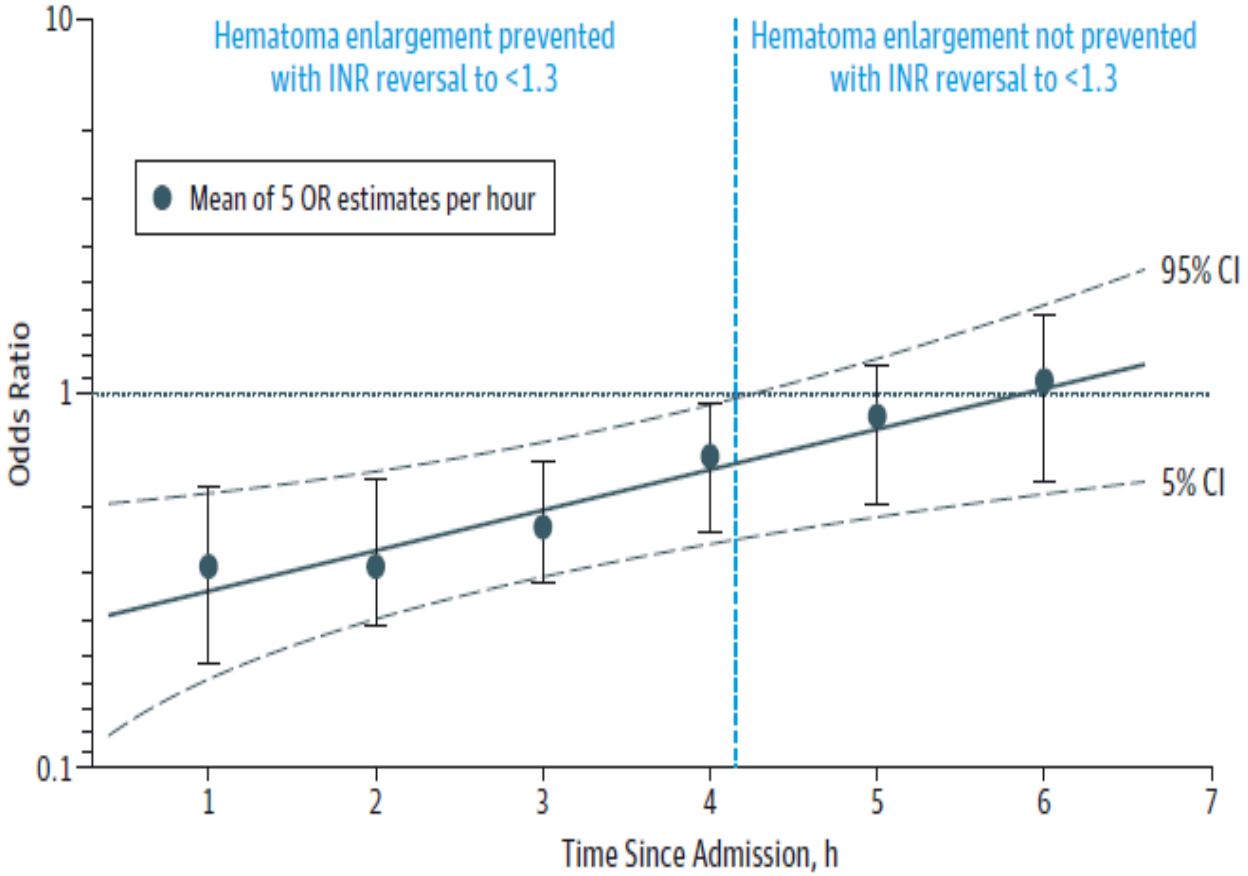
Time is brain in ICH too.....



Patients with hematoma enlargement, shown as No./No. achieving INR (%)

INR <1.3	5/26 (19.2)	9/51 (17.6)	14/73 (19.2)	15/67 (22.4)	7/22 (31.8)	9/25 (36.0)
INR ≥1.3	6/17 (35.3)	11/30 (36.7)	25/64 (39.1)	27/64 (42.2)	11/28 (39.3)	13/29 (44.8)

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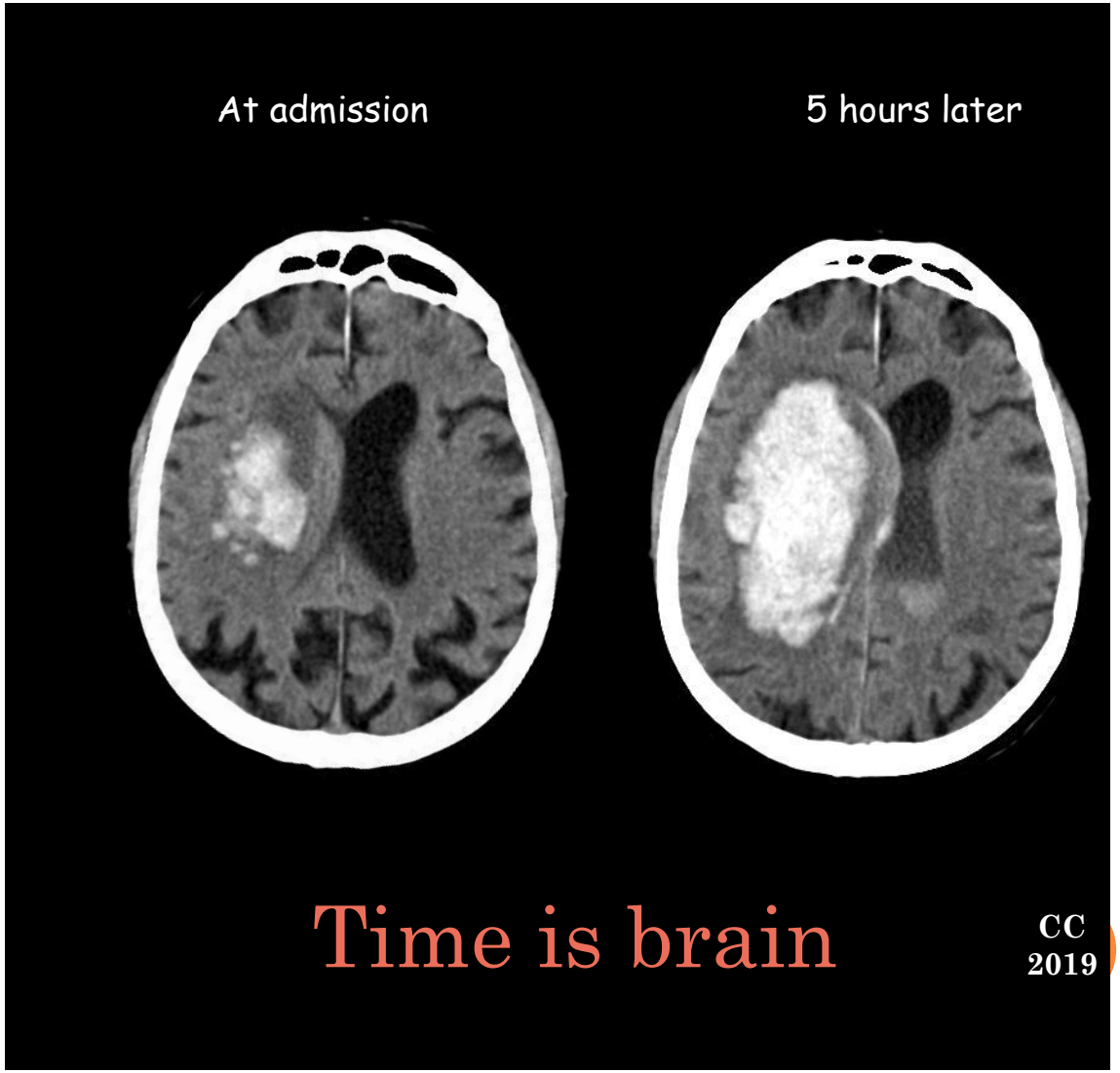
Kuramatsu et al. (2015) *JAMA* 313: 824-36.

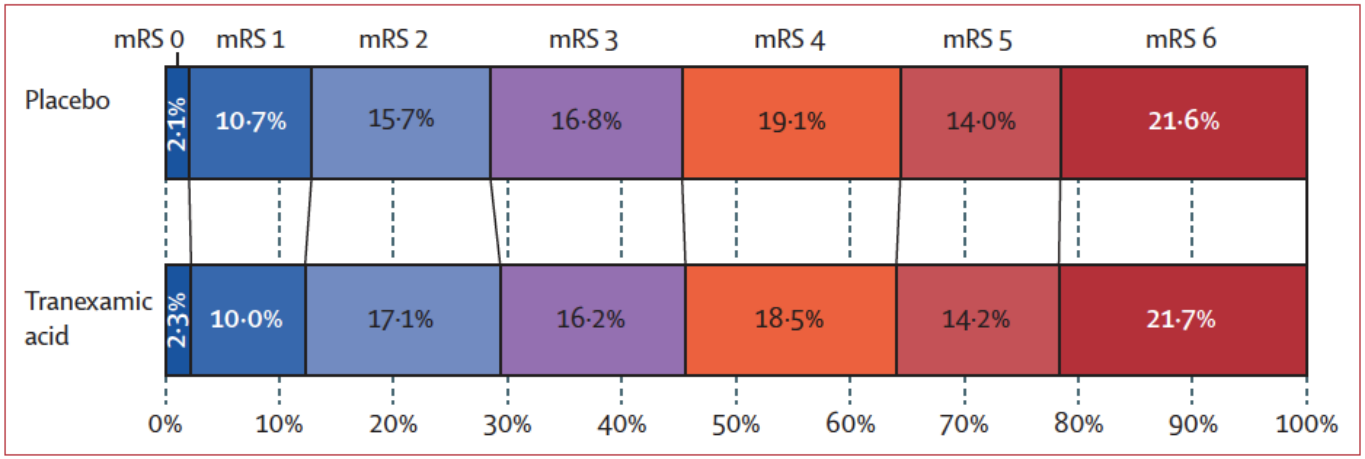
Why did every ICH trials fail?

- Most of trials have targeted the ICH Growth
  - rFVIIa
  - Tranexamic acid



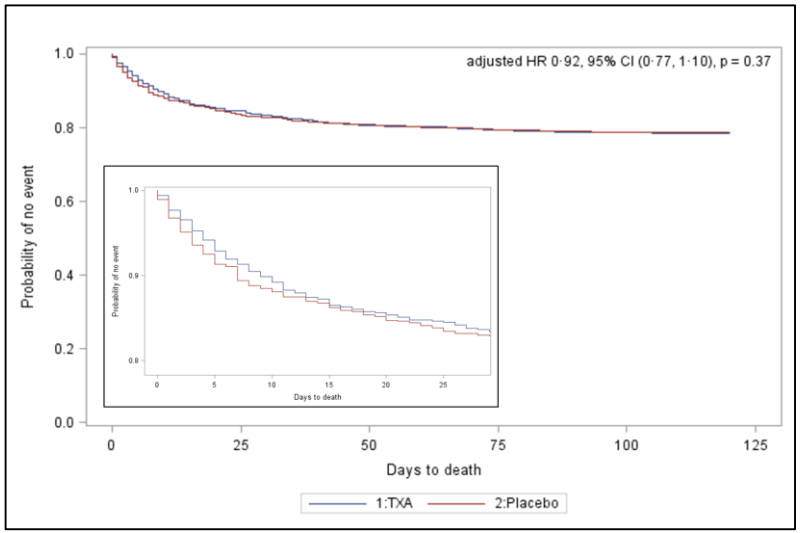
PRIMARY OUTCOME: SHIFT ANALYSIS MRS DAY

- No significant difference in primary outcome OR 0.88 (0.76 – 1.03) p=0.11



- No significant difference in cumulative mortality

- Adjusted HR 0.92 (0.77-1.01 p=0.37)



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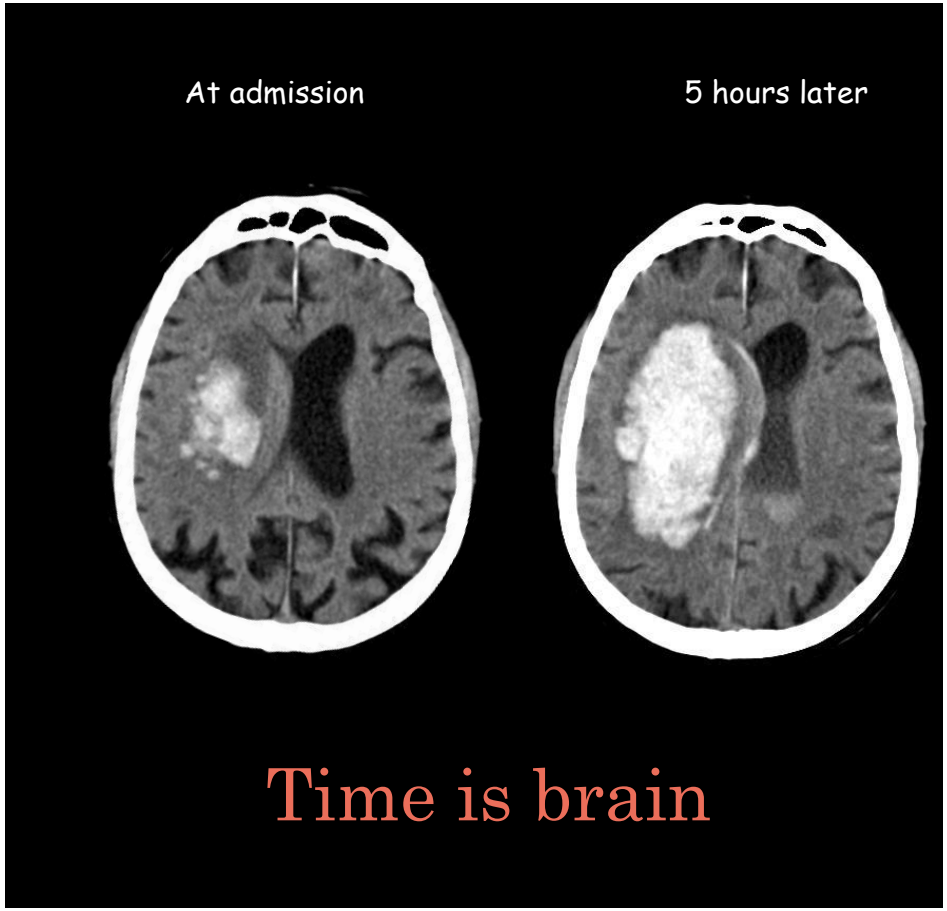
Sprigg N. Lancet 2018

Why did every ICH trials fail?

- Wrong strategy?



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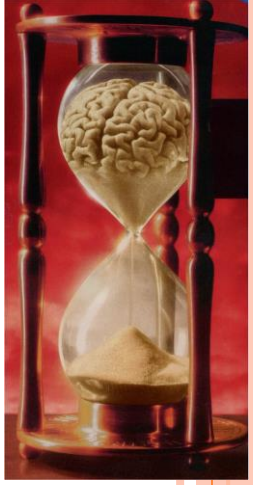
The crucial Time Window



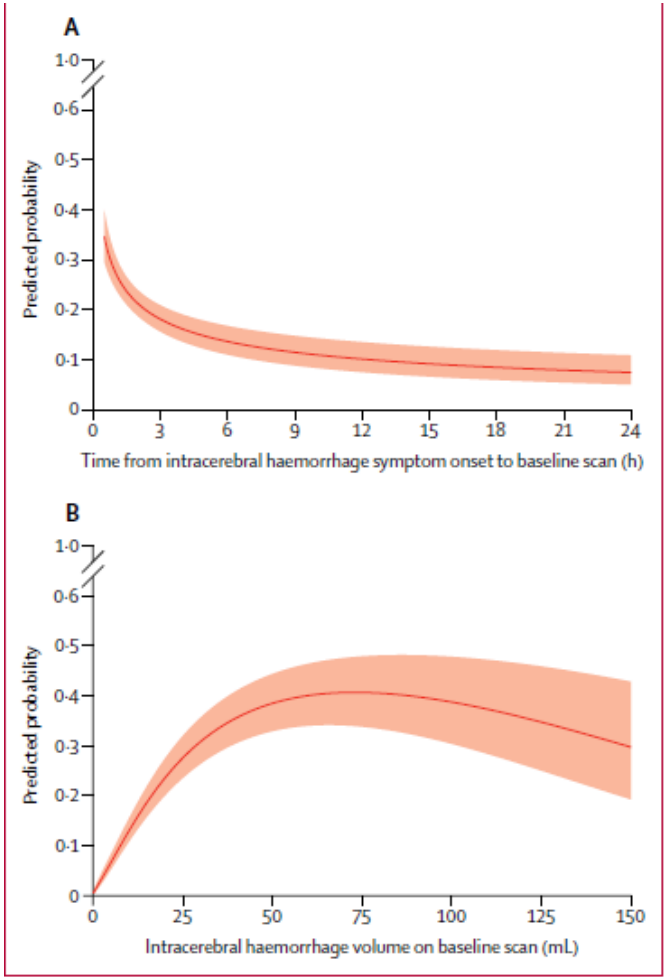


***Figure 2*: Predicted probability of intracerebral haemorrhage growth >6 mL**
Data calculated on 5076 patients who were not taking anticoagulant therapy at symptom onset. (A) Predicted probability by time from intracerebral haemorrhage symptom onset to baseline imaging, and (B) according to intracerebral haemorrhage volume on baseline imaging. The solid line indicates predicted probability and the shaded region indicates the 95% CIs.

	Comparison	Four predictors		Four predictors with the addition of CT angiography spot sign	
		Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Time from symptom onset to baseline imaging, h*	5·1 vs 1·5	0·50 (0·36–0·70)	<0·0001	0·61 (0·44–0·84)	0·0030
Intracranial haemorrhage volume on baseline imaging, mL*	33 vs 6	7·18 (4·46–11·56)	<0·0001	5·35 (3·25–8·81)	<0·0001
Antiplatelet therapy at symptom onset	Yes vs no	1·68 (1·06–2·66)	0·026	1·45 (0·89–2·35)	0·13
Anticoagulant therapy at symptom onset	Yes vs no	3·48 (1·96–6·16)	<0·0001	2·80 (1·53–5·10)	0·0008
CT angiography spot sign	Present vs absent	..	..	4·46 (2·95–6·75)	<0·0001

Data were calculated on 837 patients from six cohorts (appendix). *Odds ratios for time from symptom onset to baseline imaging and intracranial haemorrhage volume on baseline imaging are for upper quartile vs lower quartile.

***Table 3*: Multivariable models of predictors of intracerebral haemorrhage growth >6 mL in patients with assessment of CT angiography spot sign, data on antiplatelet therapy, and data on anticoagulant therapy use at symptom onset**

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Al-Shahi Salman R. Lancet Neurol 2018

HOW TO FIGHT AGAINST HAEMATOMA EXPANSION?

- Correct Haemostasis?
- Manage Blood Pressure?

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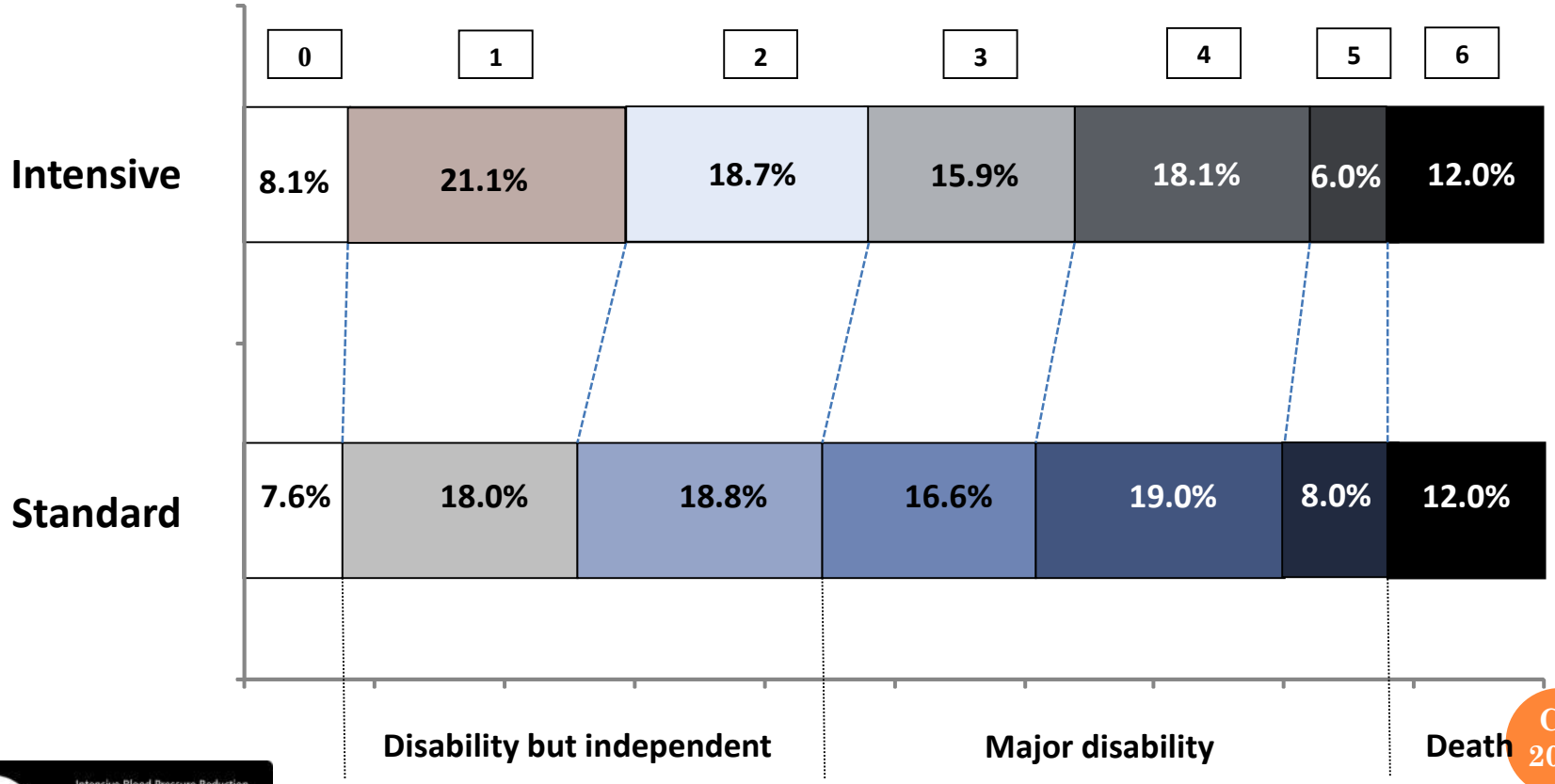
Key Secondary Outcome

Ordinal shift in mRS scores (0-6)

Odds ratio 0.87 (95%CI 0.77 to 1.00); P=0.04



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Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial
interact

Anderson CS. NEJM 2013

GUIDELINES

POST- INTERACT2/ PRE-ATACH-II

- European Stroke Organisation 2014
  - In acute ICH within 6h of onset, intensive BP reduction (**SBP target <140 in <1h**) is safe and may be superior to an SBP target <180. No specific agent can be recommended.

- American Heart Association 2015
  - For ICH patients presenting with SBP between 150 and 220mmHg and without contraindication to acute BP treatment, acute lowering of **SBP to 140mmHg** is safe and can be effective for improving functional outcome.

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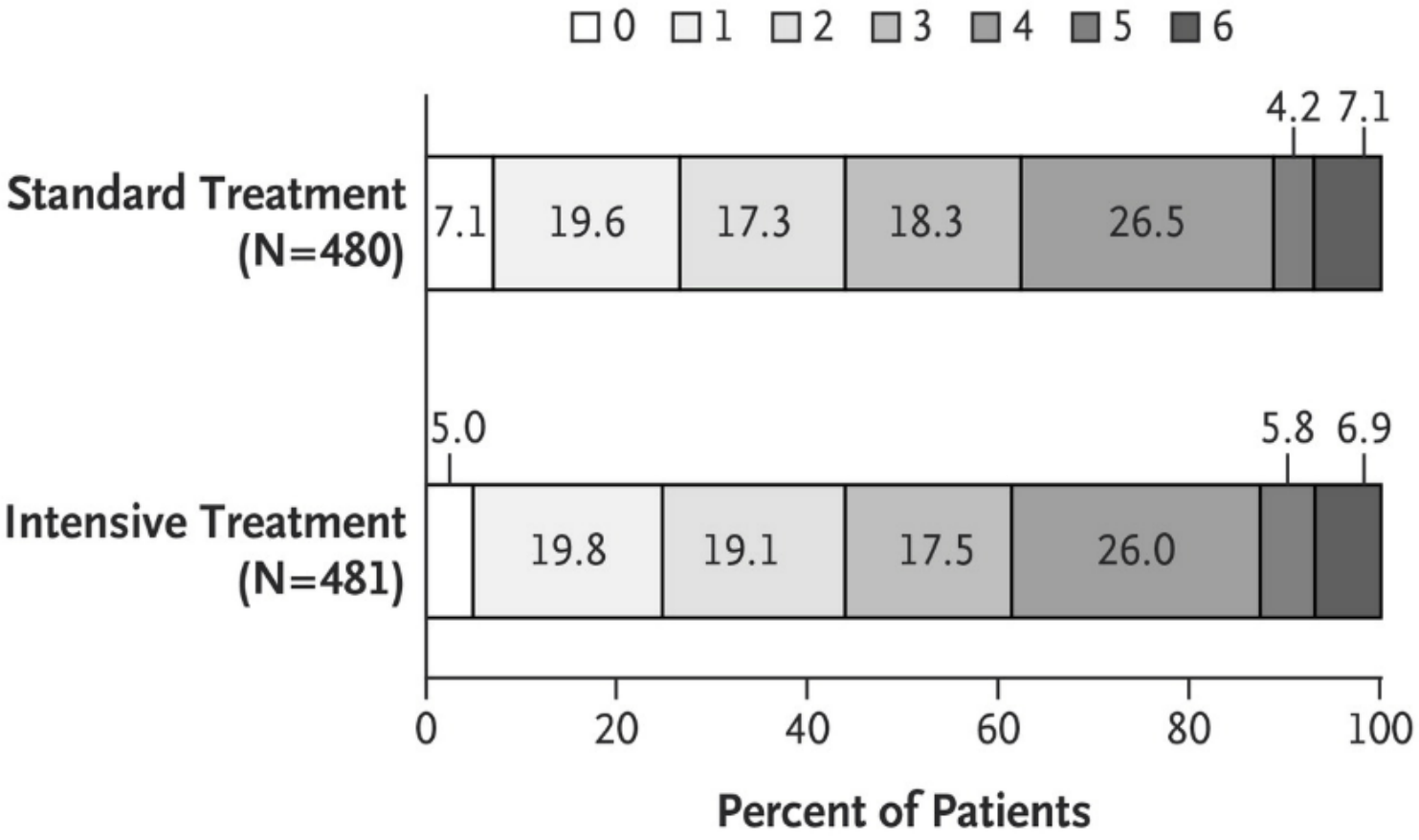
ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Key Secondary Outcome

Distribution of mRS scores (0-6)

Odds ratio 1.07; P=0.56



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Qureshi AI. NEJM 2014

What Now? – SBP <140 mmHg

- Within 6 hours of Spontaneous ICH onset, irrespective of baseline SBP (between 150 and 220 mmHg)
  - GET THERE → Systolic BP 130-140
    - As early as possible
  - STAY THERE
    - With reduced SBP variability
    - For at least 24 hours (and up to 7 days)

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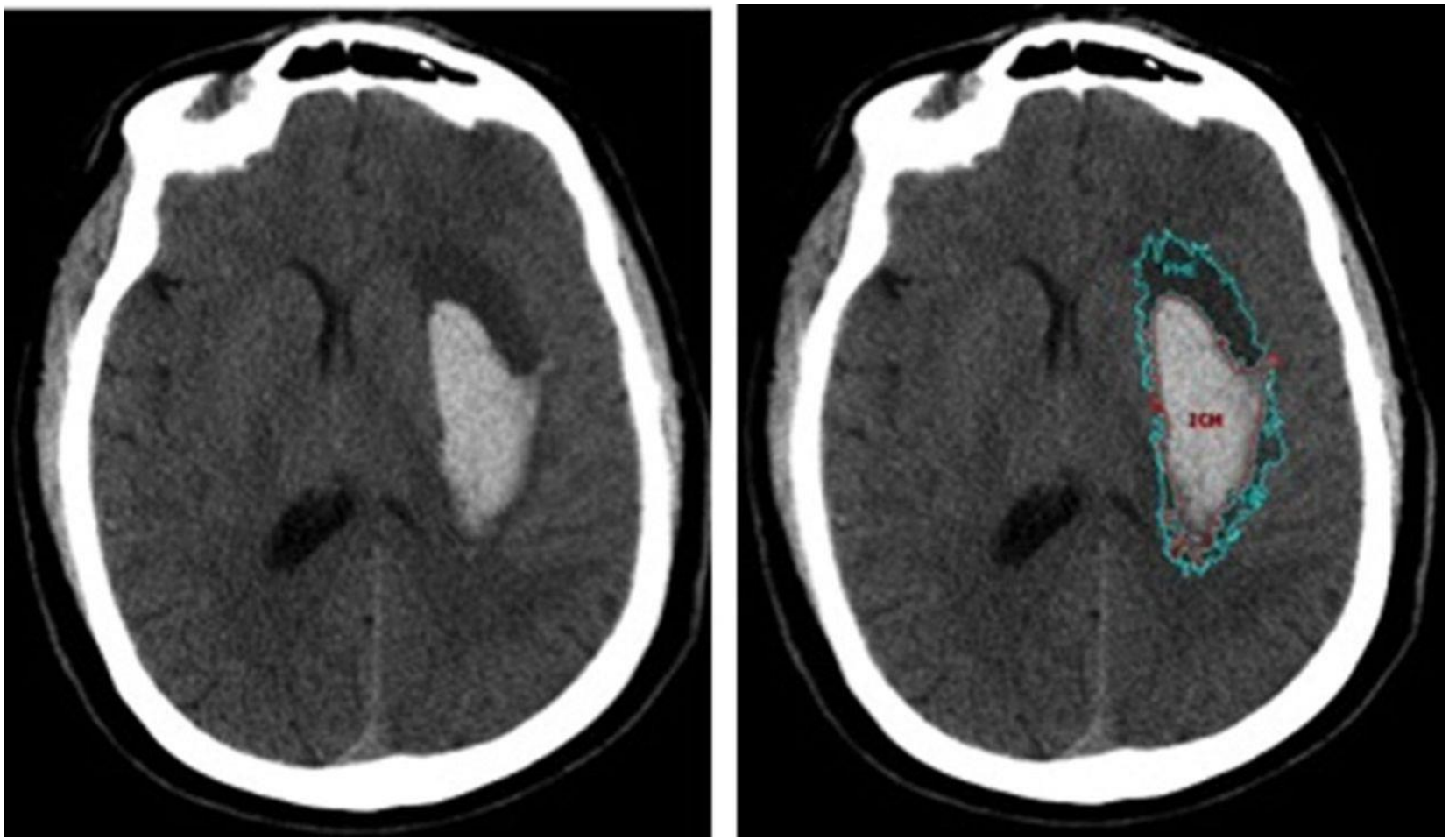
There will be blood…but not only: brain edema



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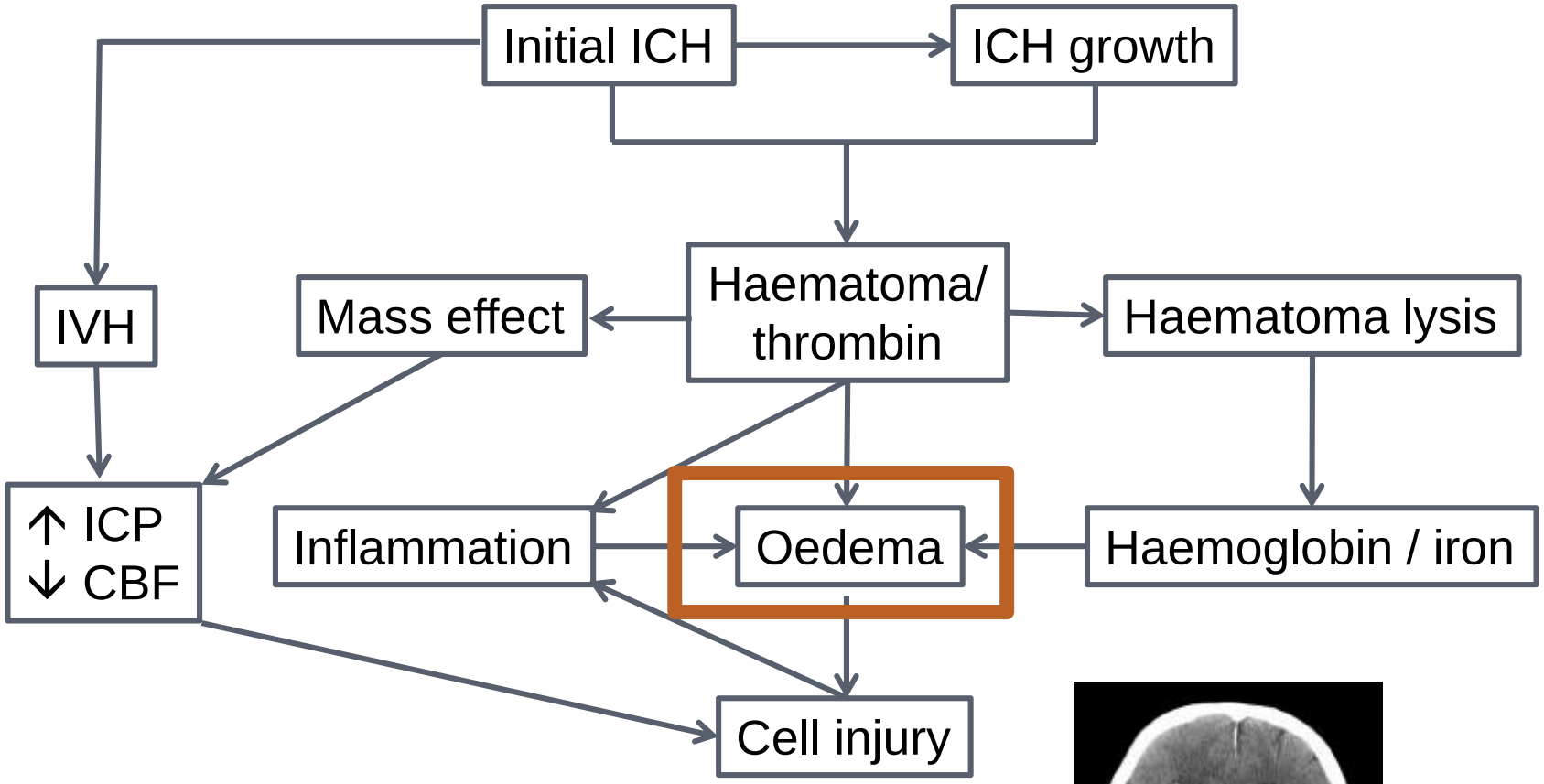
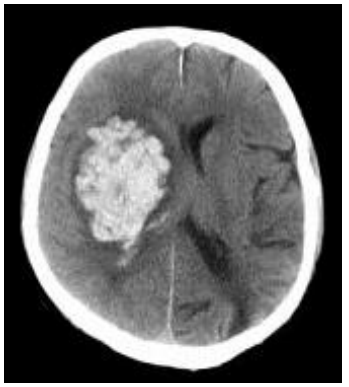
Urday S. Stroke 2015

Pathophysiological targets





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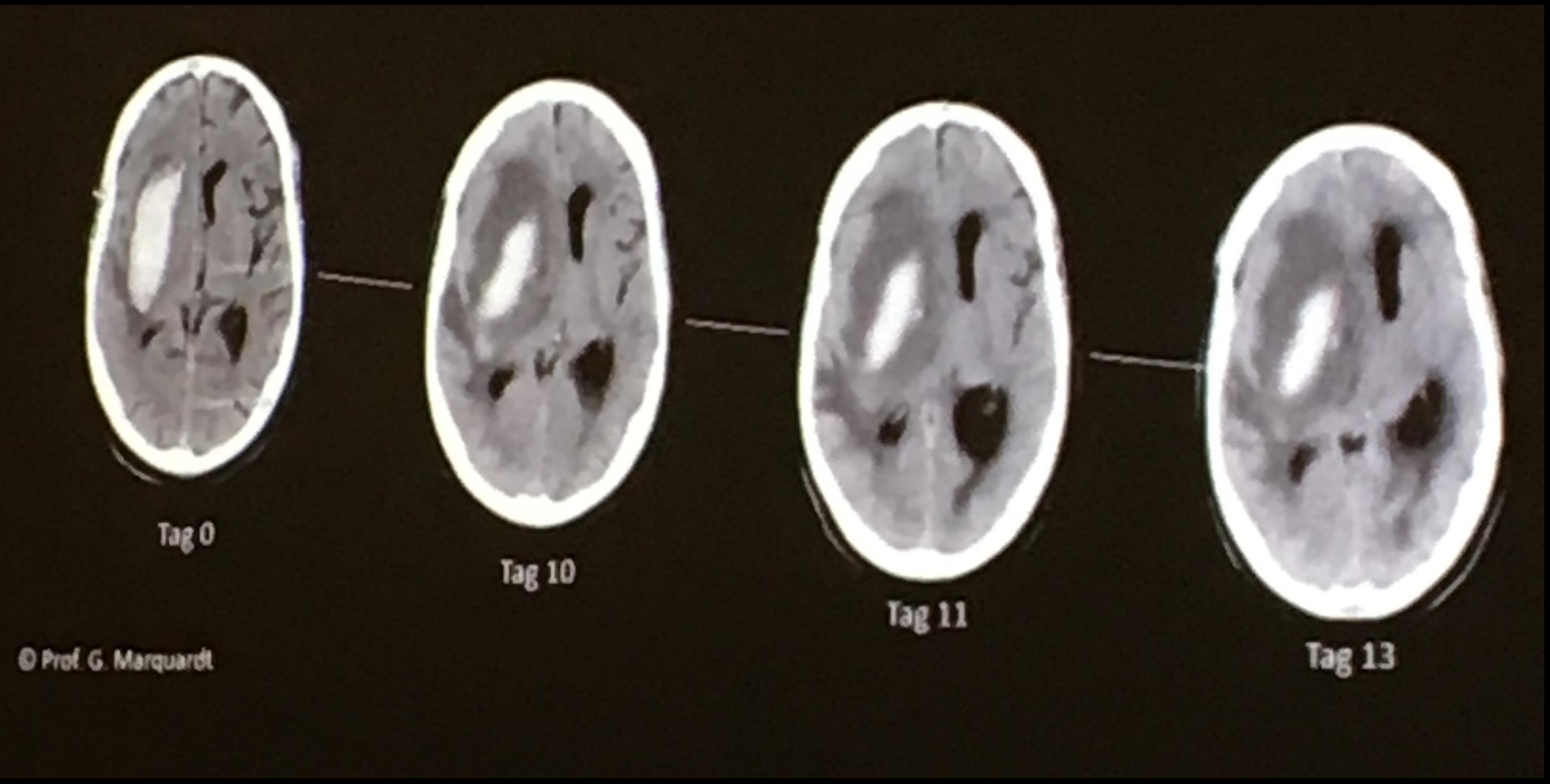
Lancet Neurol 2012;11:720-31



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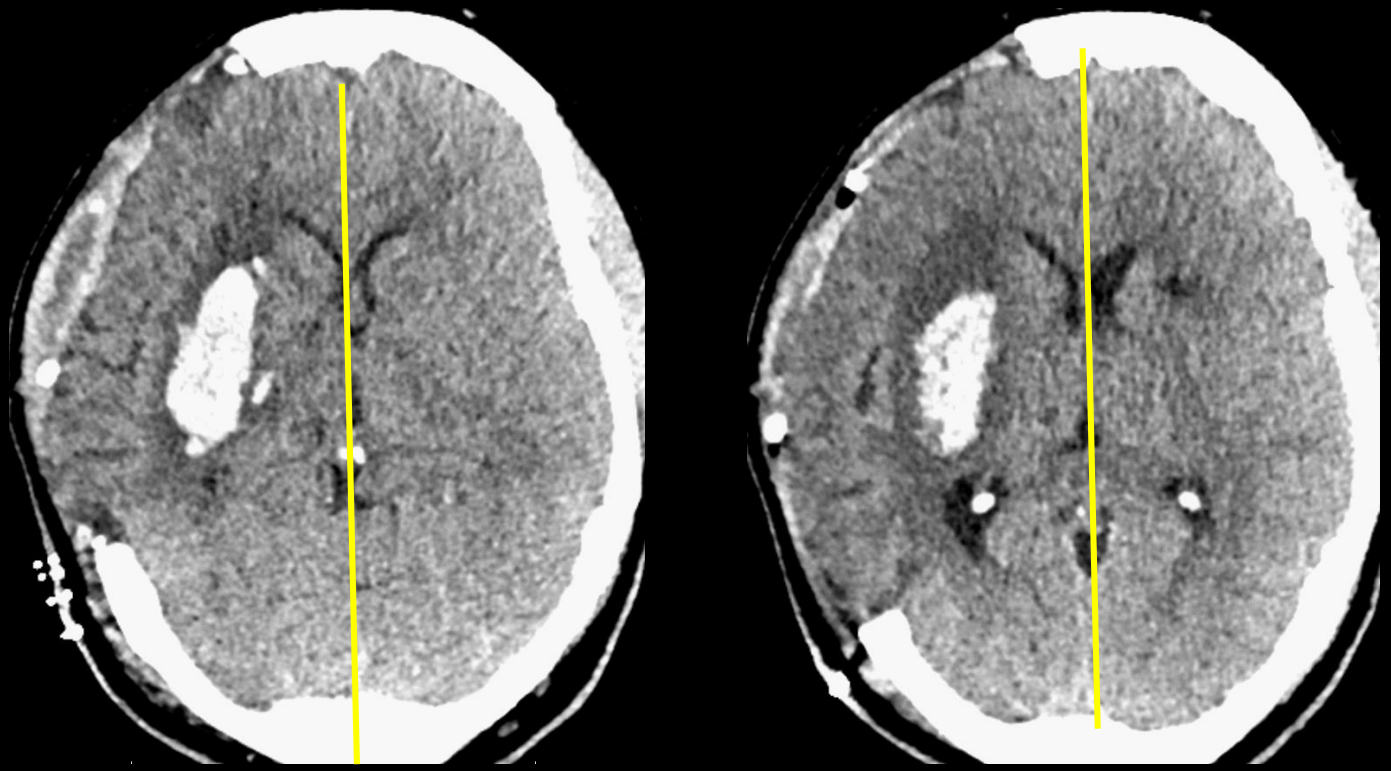
Dégradation @ J5 avec tb de la vigilance



J5

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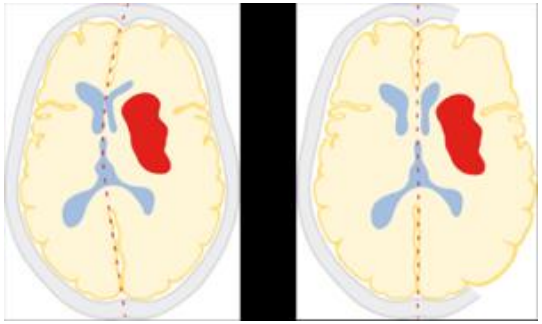
On going trial

- The SWITCH Trial
- Decompressive craniectomy vs best medical ttt



- Pis: Profs Beck & Fisher, Bern

Number of randomized patients: 100 **Number of recruiting sites:** 33

Key inclusion criteria:

- Age: ≥18 to ≤75 years
- Acute stroke syndrome due to a spontaneous ICH
- Haemorrhage into basal ganglia, or thalamus that may extend into cerebral lobes, ventricles or subarachnoid space
- Glasgow coma scale (GCS) <14 and >7 at randomization
- NIHSS ≥10 and ≤30
- Surgical treatment within 72 hours after ictus
- Volume of hematoma ≥30ml and ≤100ml

Key exclusion criteria:

- Aneurysm, arteriovenous malformation, tumor, trauma, thrombolysis
- Cerebellar or brainstem hemorrhage
- Exclusive lobar hemorrhage
- Moribund patients (GCS 3–7)

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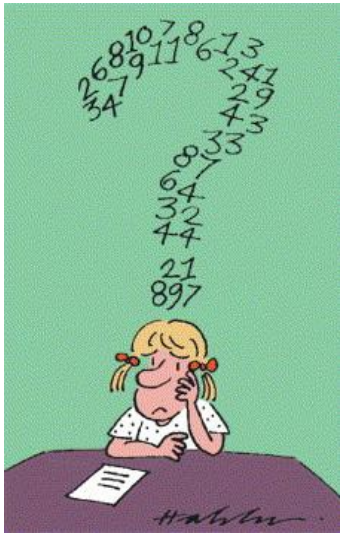
GUIDELINES



Minimally Invasive Surgery plus rtPA?
MISTIE
found reductions in hematoma & edema volume from intervention, but no overall difference in clinical outcomes & more asymptomatic hemo.

Mould WA. Stroke 2013
Hanley D. Lancet Neurol 2016

Glycerol & Mannitol: No efficacy

For large variety of nonsurgical & surgical measures commonly applied in clinical practice for lowering raised ICP in ICH patients:
head elevation, osmotic therapy with several agents, hyperventilation, analgesia, sedation, general anesthesia with barbiturates, neuromuscular blockade, hypothermia … → no RCT

Recommendation
There is insufficient evidence from RCTs to make strong recommendations on measures to lower intracranial pressure for adults with acute ICH.
Quality of evidence: Low
Strength of recommendation: Weak

Steiner T. Int J Stroke 2014

ESO EUROPEAN STROKE ORGANISATION

Recommendation:
We do not recommend the use of dexamethasone in patients with acute ICH outside RCTs.
Quality of evidence: Moderate
Strength of recommendation: Weak

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Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial

A David Mendelow, Barbara A Gregson, Helen M Fernandes, Gordon D Murray, Graham M Teasdale, D Terence Hope, Abbas Karimi, M Donald M Shaw, and David H Barer for the STICH investigators*

Lancet 2005; 365: 387–97

See Comment page 361

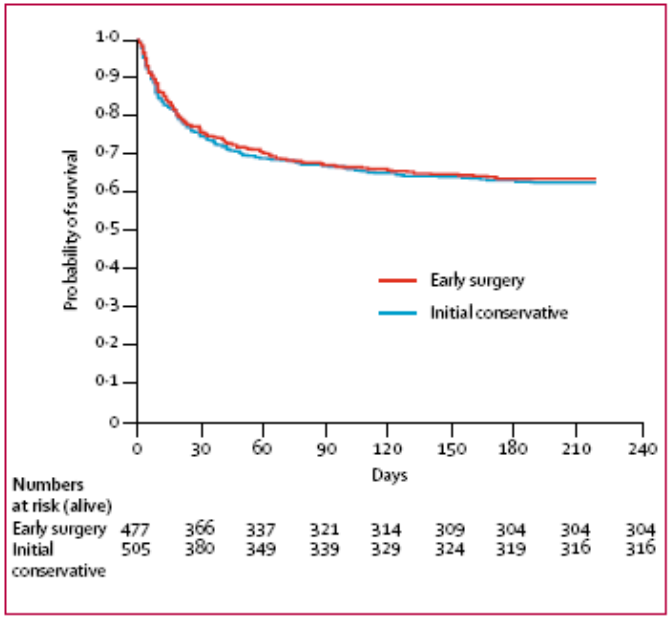

Figure 2: Kaplan-Meier survival curves

	Early surgery (n=468)	Initial conservative treatment (n=497)	Absolute benefit (95% CI)
Primary outcome			
Favourable	122 (26%)	118 (24%)	2·3 (–3·2 to 7·7)
Unfavourable	346 (74%)	378 (76%)	..
Not recorded		1	..
Secondary outcomes			
Mortality			
Alive*	304 (64%)	316 (63%)	1·2 (–4·9 to 7·2)
Dead	173 (36%)	189 (37%)	..
Prognosis-based modified Rankin index			
Favourable	152 (33%)	137 (28%)	4·7 (–1·2 to 10·5)
Unfavourable	312 (67%)	351 (72%)	..
Not recorded	4	9	..
Prognosis-based Barthel index			
Favourable	124 (27%)	110 (23%)	4·1 (–1·4 to 9·5)
Unfavourable	341 (73%)	377 (77%)	..
Not recorded	3	10	..

Data are number (%). *Includes 17 patients who were alive at 6 months but status was unknown.

Table 4: Outcomes at 6 months

Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial

Lancet 2013

A David Mendelow, Barbara A Gregson, Elise N Rowan, Gordon D Murray, Anil Gholkar, Patrick M Mitchell, for the STICH II Investigators

Findings 307 of 601 patients were randomly assigned to early surgery and 294 to initial conservative treatment; 298 and 291 were followed up at 6 months, respectively; and 297 and 286 were included in the analysis, respectively. 174 (59%) of 297 patients in the early surgery group had an unfavourable outcome versus 178 (62%) of 286 patients in the initial conservative treatment group (absolute difference 3·7% [95% CI −4·3 to 11·6], odds ratio 0·86 [0·62 to 1·20]; p=0·367).

Interpretation The STICH II results confirm that early surgery does not increase the rate of death or disability at 6 months and might have a small but clinically relevant survival advantage for patients with spontaneous superficial intracerebral haemorrhage without intraventricular haemorrhage.

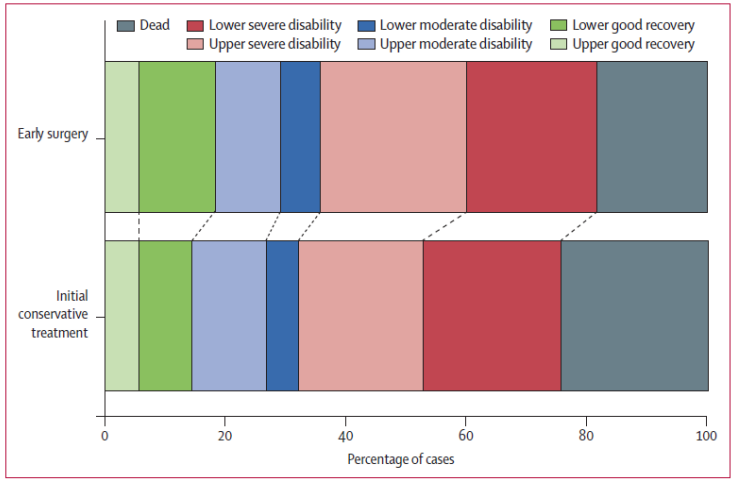

Figure 3: **Extended Glasgow Outcome Scale at 6 months**
Proportional odds model p=0·075.

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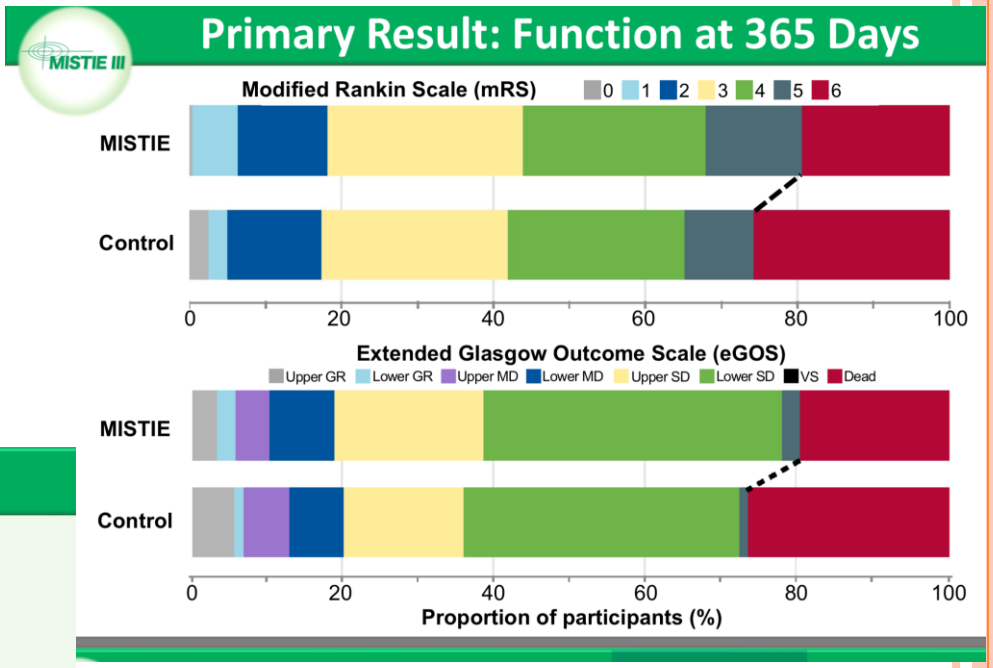
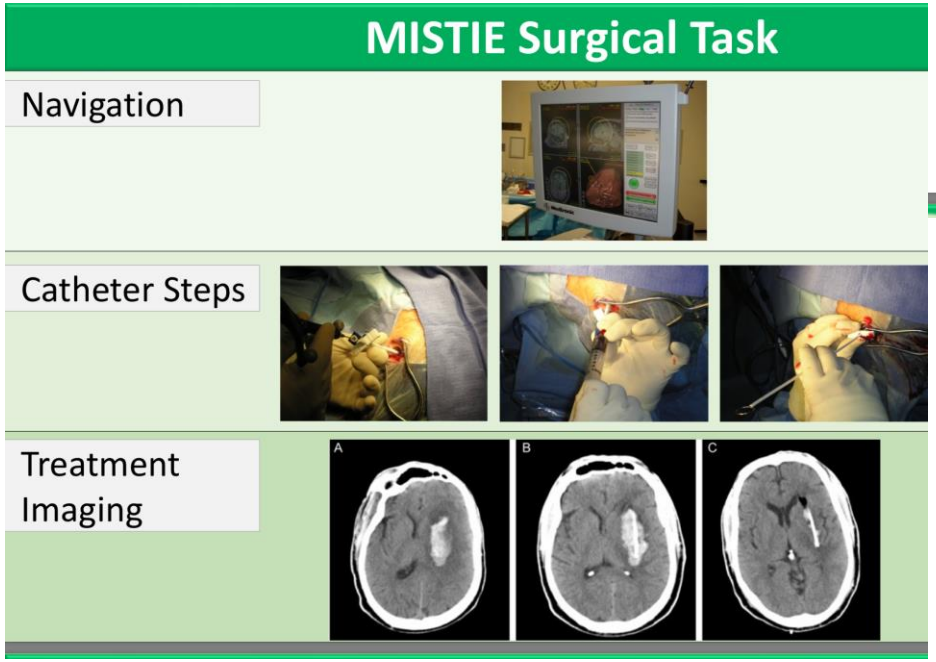
Minimally invasive surgery

- Image guided aspiration via rigid cannula, then placement of soft drainage catheter in the epicenter of the hematoma
- Administration of alteplase (1mg in 1 mL every 8 hours) via the soft catheter, and passive hematoma clearance to < 15 mL or 9 doses of alteplase are given





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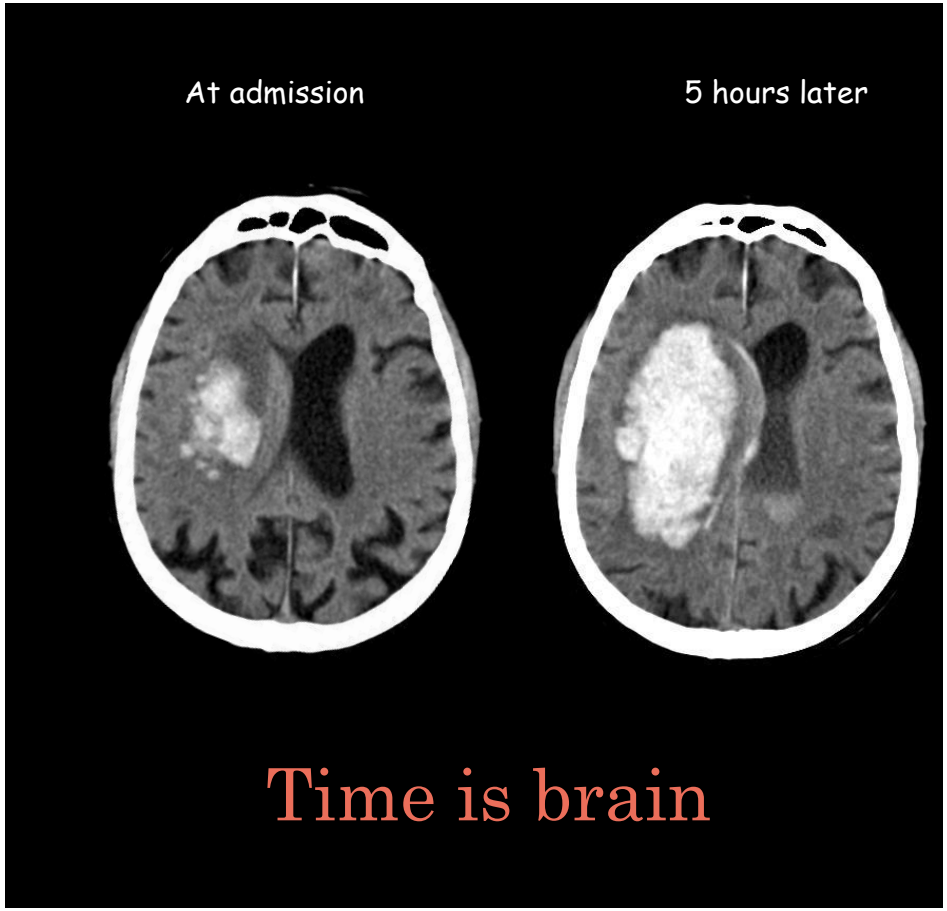
Hanley D et al. Lancet 2019

Why did every ICH trials fail?

- Wrong strategy?



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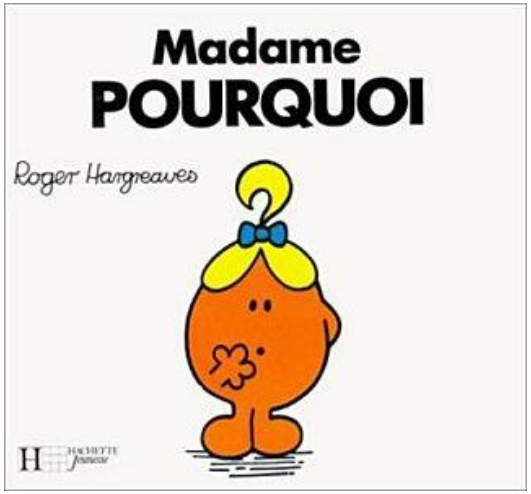
Pourquoi est-ce que le patient saigne?



Quelle est la cause?

Forget '*primary*'

Forget Primary

Deep perforating vasculopathy
- Haematoma located in the basal ganglia or brainstem; microbleeds or old intracerebral haemorrhage in the basal ganglia or brainstem; white matter lesions; lacunes

Cerebral amyloid angiopathy
- Lobar intracerebral haemorrhage; cortico-subcortical microbleeds; cortical superficial siderosis; apolipoprotein E ε4; cognitive decline; transient focal neurological episodes

Brain arteriovenous malformation
- Extension to other brain compartments; flow voids; calcification

Intracranial arterial aneurysm
- Disproportionate subarachnoid extension

Cavernous malformation
- Small, homogeneous intracerebral haemorrhage with no extension to other brain compartments

Intracranial venous thrombosis
- Headaches preceding intracerebral haemorrhage onset; intracerebral haemorrhage close to sinuses or veins; high relative oedema volume; onset in pregnancy or postpartum

Dural arteriovenous fistula
- Subarachnoid or subdural extension; abnormal dilated cortical vessels

Haemorrhagic transformation of cerebral infarction
- Substantial areas of acute ischaemic lesions adjacent to the intracerebral haemorrhage or diffuse acute ischaemic lesions in other arterial territories

Severe clotting factor deficiency such as haemophilia
- Abnormal coagulation tests

Tumour (primary/metastasis)
- Large perihaematomal oedema

Vasculitis
- Headaches; small acute ischaemic lesions in different arterial territories; focal diffuse arterial stenosis

Infective endocarditis
- Acute ischaemic lesions in different arterial territories; small irregular arterial aneurysms; diffuse brain microbleeds

Posterior reversible encephalopathy syndrome
- Thunderclap headaches; parietal and occipital asymmetrical oedematous lesions

Cordonnier C et al. Lancet 2018

En urgence

- Existe-t-il une malformation vasculaire à très haut risque de récidive précoce?
- Existe-t-il une thrombose veineuse cérébrale?
- On regarde
  - le parenchyme
  - les artères
  - les veines

- IRM + TOF ou ARM – séquence de flux si suspicion TVC
- CT + CTA

- Gold standard reste l'artériographie

Take home message

- ICH is a medical emergency
- Time is Brain
- Stroke unit care
- Blood pressure management is important!
- Correct haemostasis disorders
- Surgical indication are exceptionnal (cortical ICH in young patients who deteriorate)

- ICH remains the deadliest form of stroke in 2019
  - Time to look beyond blood - Think about edema
  - Tailor your strategy:

    Why did your patient bleed?

    What is the underlying vessel disease?

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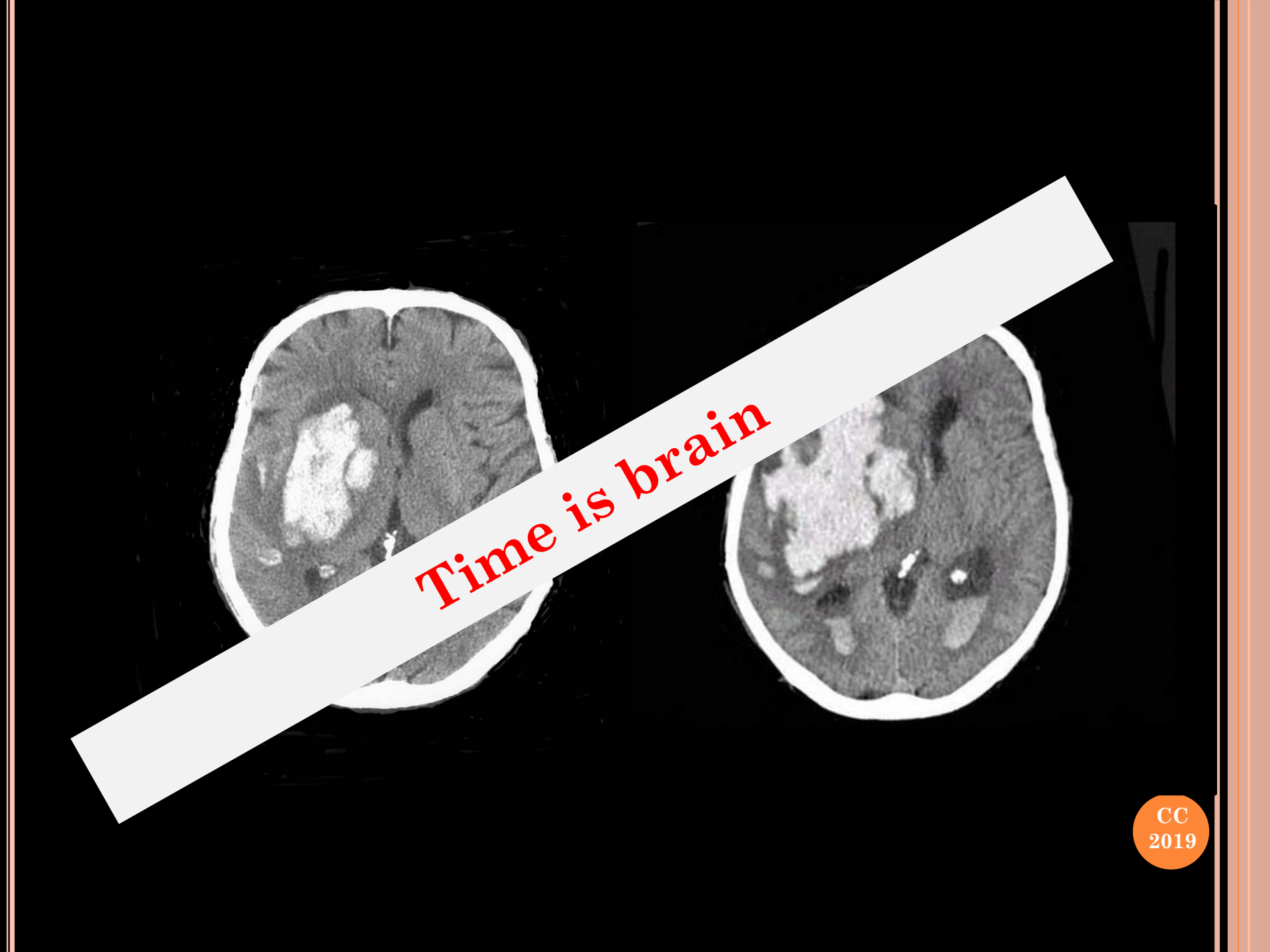

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2019

Panel 1: Key management steps in intracerebral haemorrhage

Brain and vascular imaging

- Imaging should be done to detect an underlying cause that requires early intervention—eg, vascular malformation, cerebral venous thrombosis, vasculitis, reversible cerebral vasoconstrictor syndrome where the likelihood of diagnosis is higher on the basis of patient age (>50 years), intracerebral haemorrhage location (peripheral or cortical), history of hypertension (absent), and presence of cerebral small vessel disease (imaging features)
- CT angiography spot sign predicts haematoma growth but whether this improves upon established clinical and haematoma predictive markers is still to be defined
- MRI can detect chronic microhaemorrhaging and cerebral superficial siderosis, which is helpful for the diagnosis of cerebral amyloid angiopathy

Stroke unit care

Lowering of blood pressure (systolic target <140 mm Hg over 1–2 h)

Correction of haemostatic abnormalities

- Consider whether there is a specific disease (eg, haematological disorder)
- Consider whether this disease is due to a specific anticoagulant drug and whether a reversal agent or antidote is required

Prevention of complications

- Careful identification of deteriorating patients requiring neurosurgical intervention
- Use of intermittent pneumatic compression therapy for venous thromboembolism prophylaxis
- Management of seizures

Search for the cause of the intracerebral haemorrhage

Prevention

- Lower blood pressure to prevent recurrent intracerebral haemorrhage and other serious vascular events
- Consider whether there is a high risk of recurrent intracerebral haemorrhage to prevent starting or restarting antithrombotic treatment to prevent ischaemic events
- Screen for cognitive impairment during follow-up

Cordonnier C. Lancet 2018