University of Nottingham
UK | CHINA | MALAYSIA

Investigator Meeting

Targeting the patients most at risk of haematoma expansion

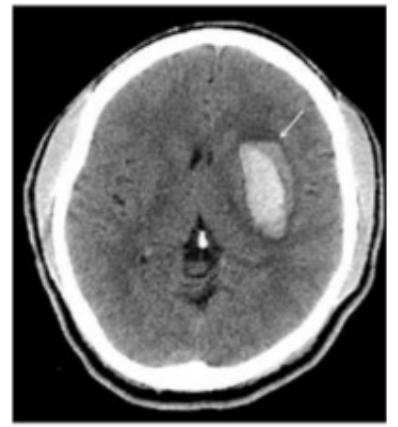
21/11/24

Stroke Trials Unit, Nottingham

TARGET PATIENTS MOST LIKELY TO BENEFIT

Please remember we want to target participants that are most likely to benefit from treatment intervention. Patients at the greatest risk are

- If they present very early after the onset of symptoms
- Larger haemotoma volumes
- On antiplatelet therapy or anticoagulants
- CT markers of haemotoma expansion such as black hole or blend sign https://doi.org/10.1161/STROKEAHA.119.026128

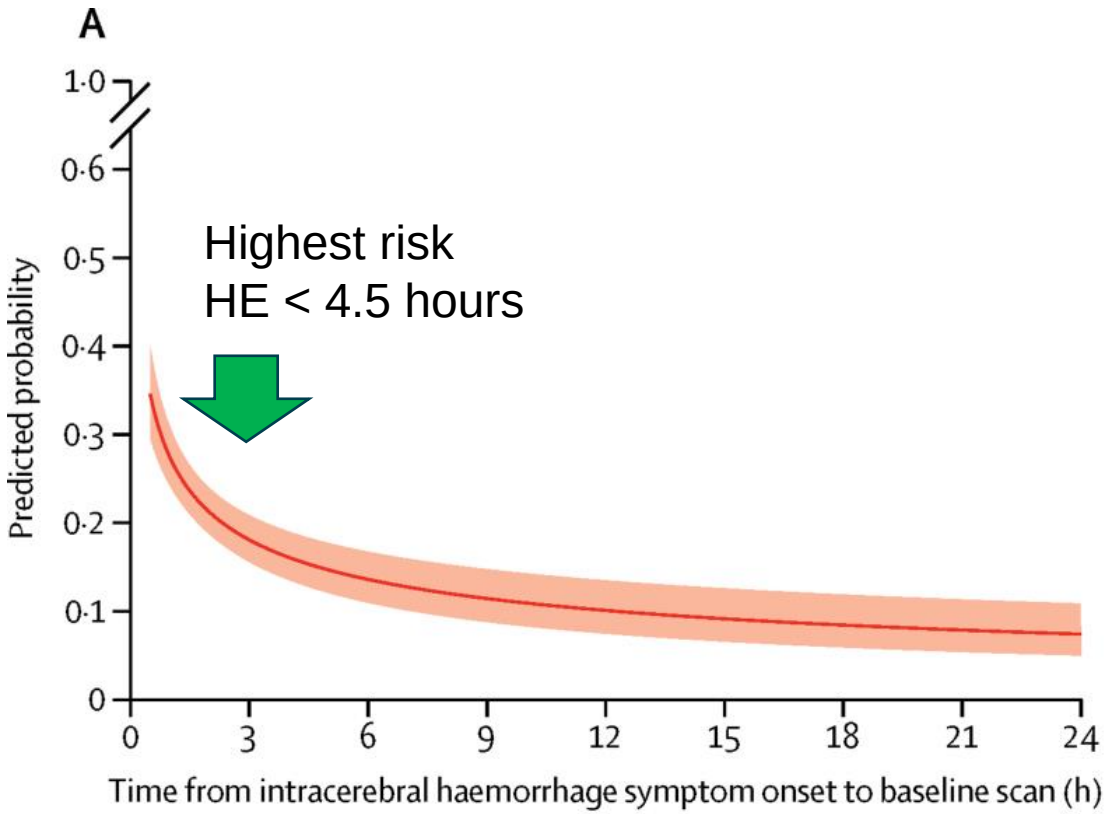


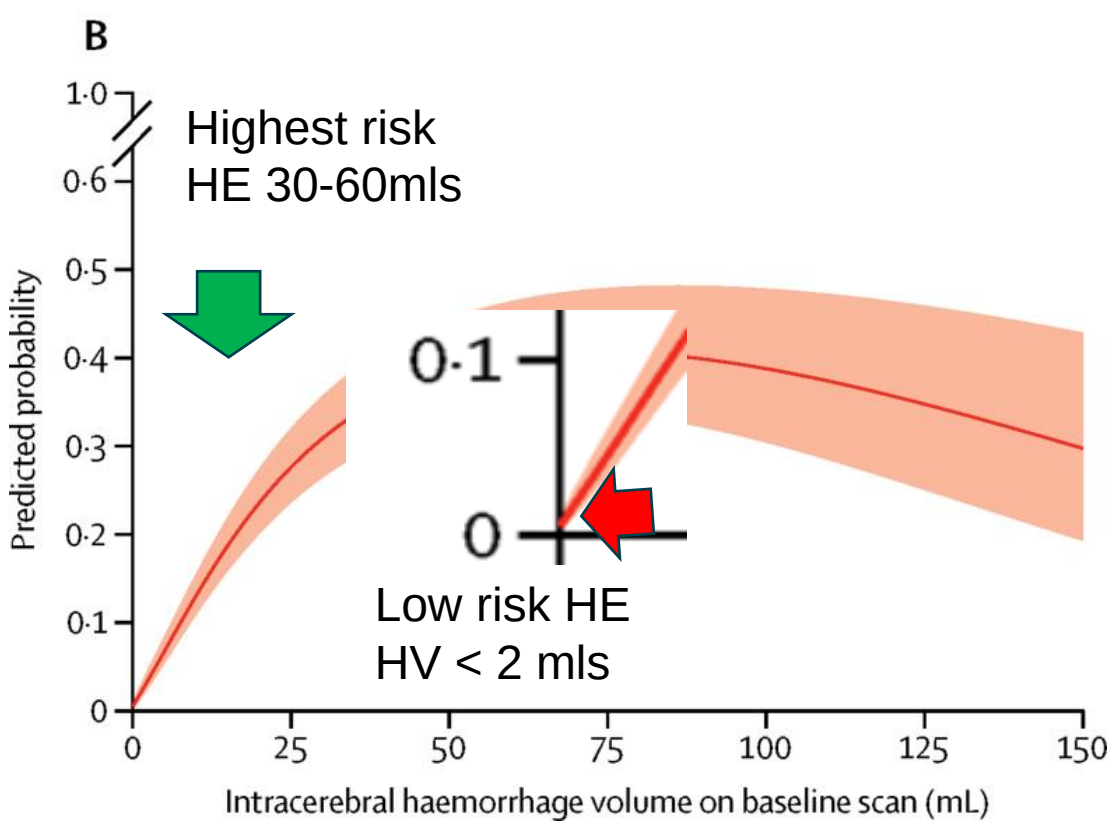
Objectives of TICH 3

Investigate whether tranexamic acid improves early death in those presenting with a spontaneous ICH with in 4.5 hours

Tranexamic acid plays a role in halting haematoma expansion

Haemorrhage growth by time and volume

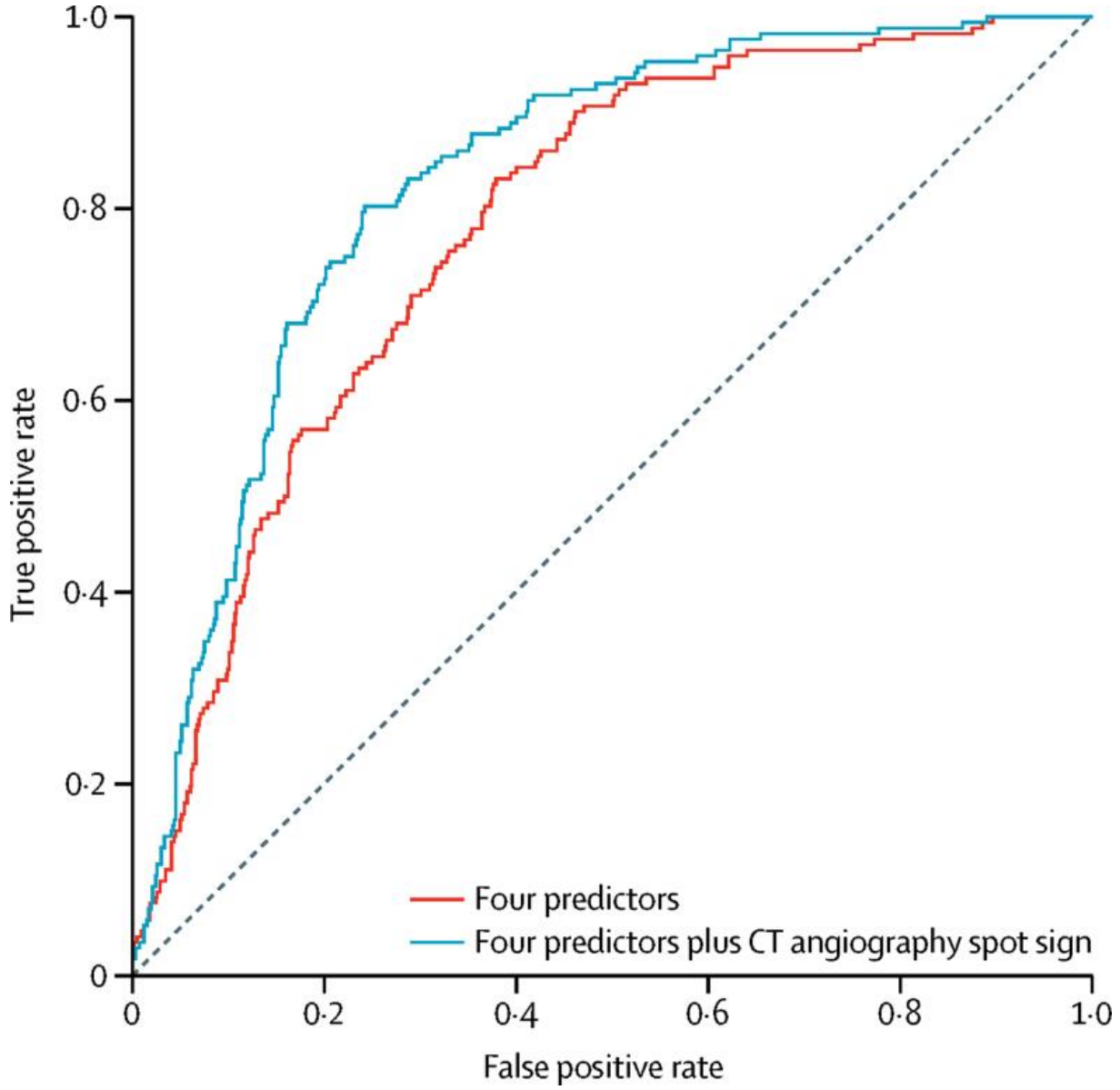




Predicted probability of intracerebral haemorrhage growth >6 mL

Al-Shahi Salman R et al Neurol. 2018. doi: 10.1016/S1474-4422(18)30354-5..

CTA spot sign and haematoma expansion

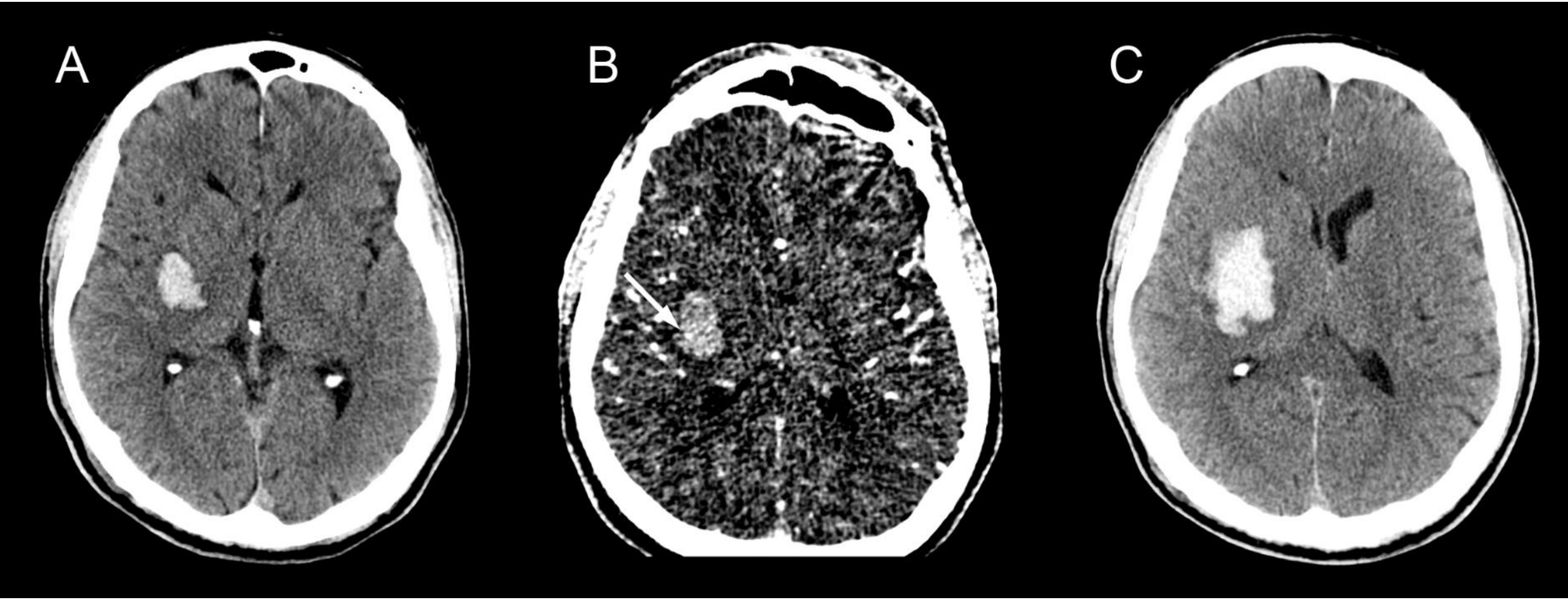


Characteristic curves for the predicted probability of intracerebral haemorrhage growth >6 mL

- Time from symptom onset to baseline imaging [h]
- Intracerebral haemorrhage volume on baseline imaging [ml]
- Antiplatelet therapy at symptom onset
- Anticoagulant therapy at symptom onset
- CT spot sign positive

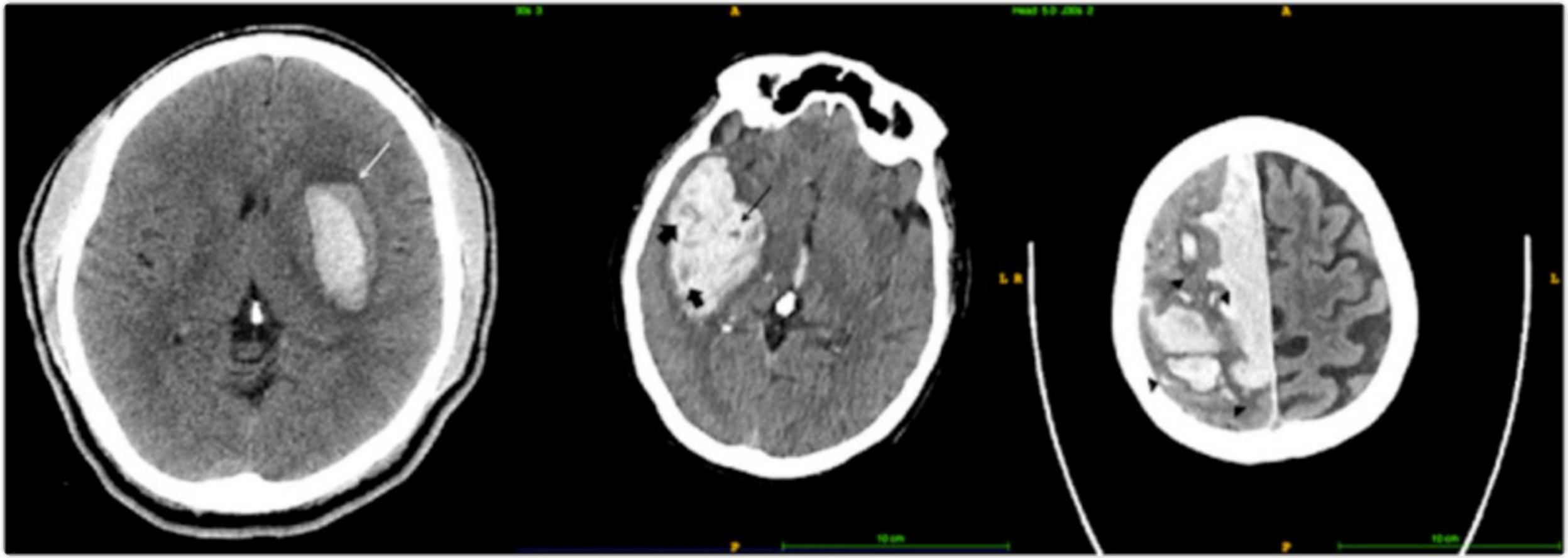
Al-Shahi Salman R et al Neurol. 2018. doi: 10.1016/S1474-4422(18)30354-5..

CTA Spot Sign



Case courtesy of Christen Barras, Radiopaedia.org, rID: 24481

Non-contrast CT markers



BLEND SIGN

BLACK HOLE SIGN
HYPODENSITIES

ISLAND SIGN

Law ZK, et al Stroke. 2020 Jan;51(1):121-128. doi: 10.1161/STROKEAHA.119.026128.

Baseline Differences

Hematoma location	Total	HE (+)	HE(-)	P Value
Supratentorial lobar	688 (29.6%)	206 (36.3%)	396 (26.4%)	<0.001
Supratentorial deep	1451 (62.4%)	332 (58.6%)	1011 (67.5%)	<0.001
Infratentorial	145 (6.2%)	29 (5.1%)	91 (6.1%)	0.41
Previous antiplatelet therapy	611 (26.3%)	164 (28.8%)	357 (23.7%)	0.016
Onset-to-CT time (median, h)	1.9 (1.4–2.8)	1.8 (1.3–2.5)	2	
Onset-to-CT time (mean, h)	2.3 (1.3)	2.0 (1.1)		
Hematoma volume, mL				
ICH only (median, IQR)	13.3 (5.5–32.4)	21.4 (7.7–44.2)	10	
ICH only, categorical				
<30 mL	1651 (72.6%)	345 (60.5%)	1	
30–60 mL	365 (16.1%)	143 (25.1%)	1	
>60 mL	257 (11.3%)‡	82 (14.4%)		
ICH+IVH (median, IQR)	16.3 (6.3–37.4)	23.8 (9.1–50.8)	13.2 (5.3–29.1)	<0.001
Blend sign	366 (16.1%)	133 (23.3%)	180 (11.9%)	<0.001
Black hole sign	414 (18.2%)	130 (22.8%)	218 (14.5%)	<0.001
Hypodensities	701 (30.2%)	225 (39.5%)	365 (24.3%)	<0.001
Island sign	200 (8.8%)	65 (11.4%)	102 (6.8%)	0.001

Haematoma Expansion is more likely to occur in:

Lobar bleeds

Prev antiplatelet therapy

Volumes of 30-60ml

Radiological Markers of HE

Outcomes

Relationship to Haematoma Expansion

	Unadjusted OR	P value
Blend sign	2.25 (1.75–2.88)	<0.001
Black hole sign	1.75 (1.37–2.23)	<0.001
Hypodensities	2.04 (1.66–2.51)	<0.001
Island sign	1.77 (1.28–2.46)	0.001

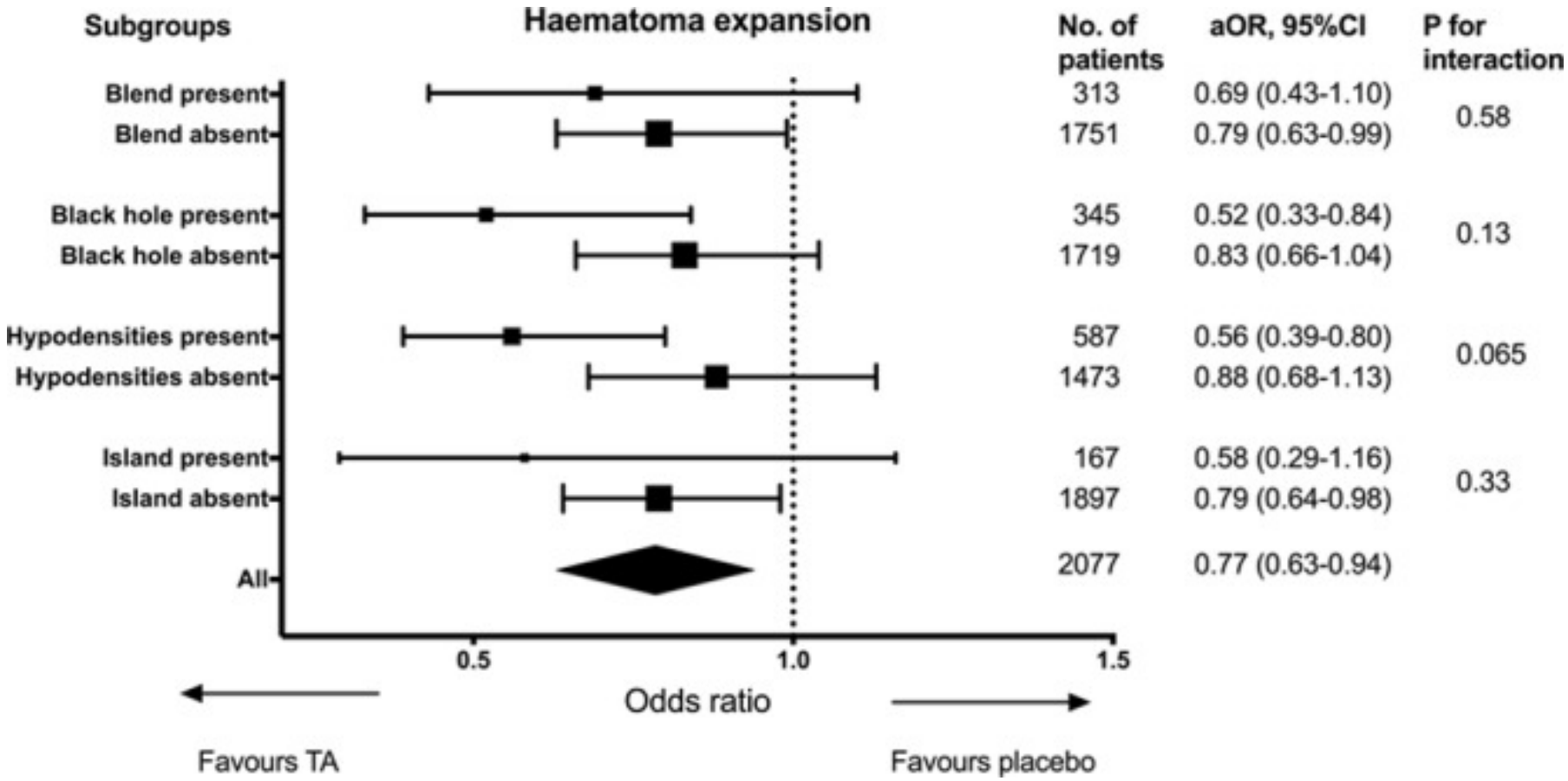
Relationship to Death and Dependency (mRS>=4)

	Unadjusted OR	P value
Blend sign	1.95 (1.54–2.47)	<0.001
Black hole sign	2.49 (1.97–3.15)	<0.001
Hypodensities	2.50 (2.07–3.03)	<0.001
Island sign	7.29 (4.68–11.35)	<0.001

Plain CT markers have been associated to greater risk of haematoma expansion and worse functional outcomes at 90 days.

Ideal candidates for TICH 3

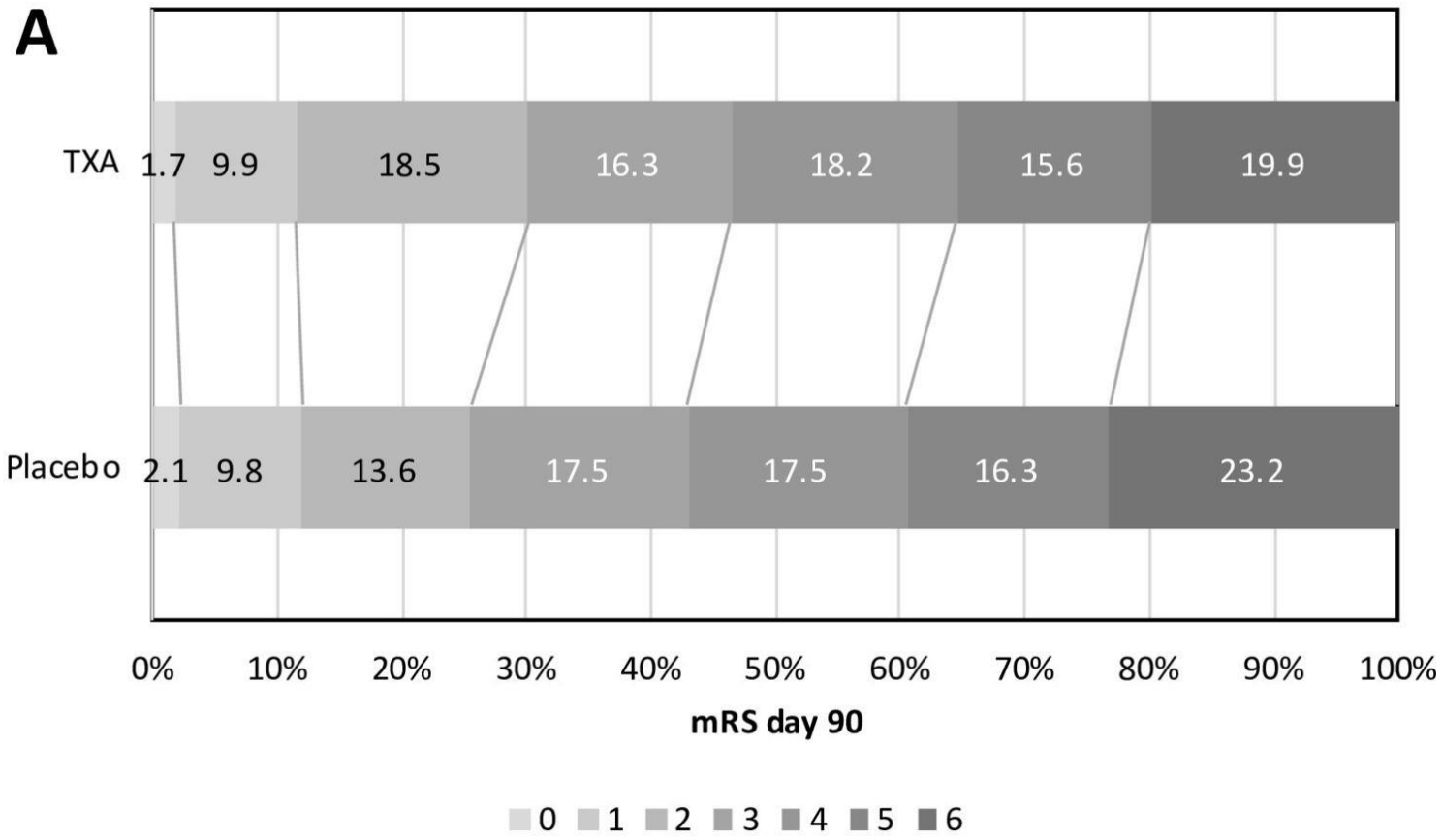
NCCT signs and haematoma expansion



Tranexamic acid reduced haematoma expansion significantly if they had NCCT markers

Law ZK, et al Stroke. 2020 Jan;51(1):121-128. doi: 10.1161/STROKEAHA.119.026128.

Remember to treat BP



In the subgroup of patients who received TXA and had BP <170 had better functional outcomes compared to placebo.

cOR 0.73, 95% CI 0.59 to 0.91, p=0.005

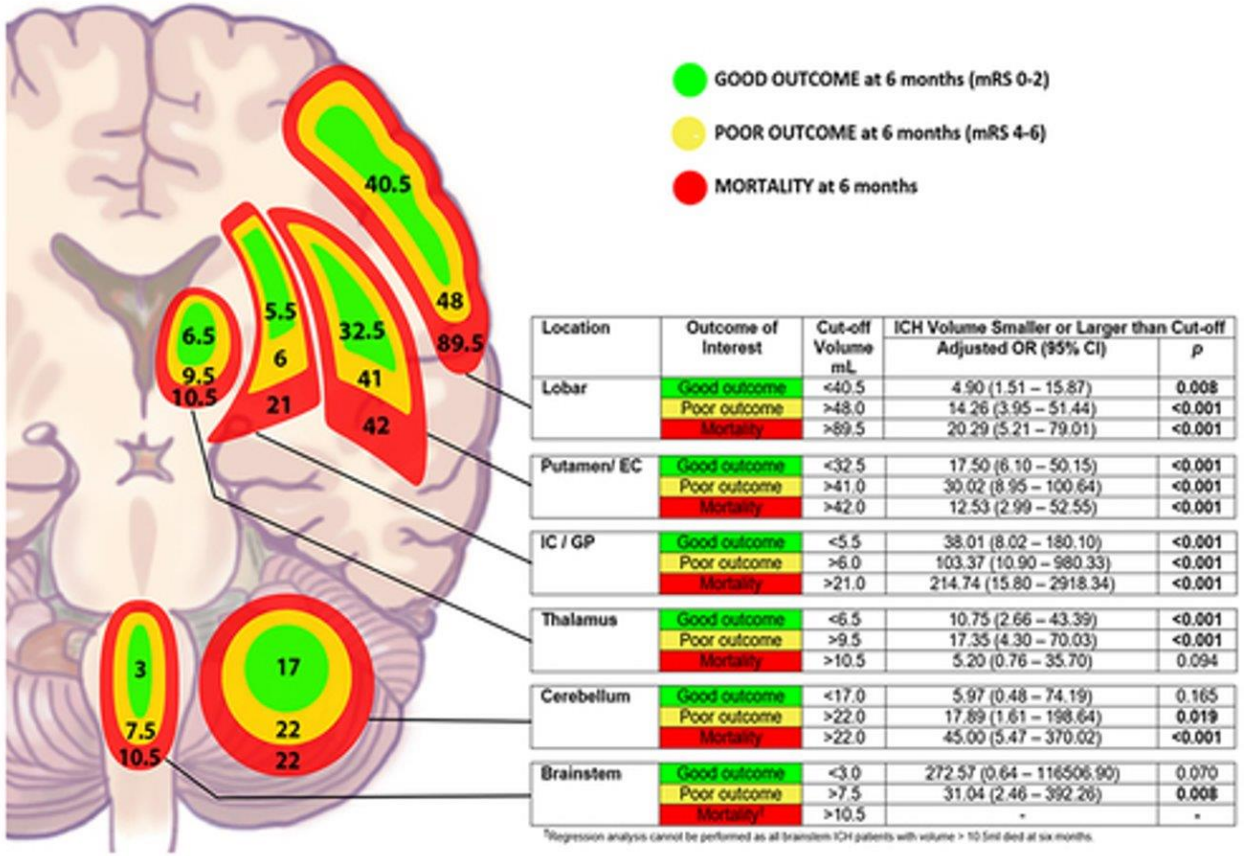
J P Appleton et al BMJ Neurology Open 2023;5:e000423.

Why haematoma location matters

Location-specific Hematoma Volume Cut-off and Clinical Outcomes in Intracerebral Hemorrhage

STUDY QUESTION: What are the hematoma volume cut-offs in predicting neurological outcomes for different ICH locations?

POPULATION : 533 consecutive ICH patients from the University of Hong Kong stroke registry
Patients with pre-morbid mRS >2 or who underwent neurosurgical treatment were excluded



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	-	-

[†]Regression analysis cannot be performed as all brainstem ICH patients with volume > 10.5ml died at six months.

CONCLUSION : ICH outcomes differed significantly with location-specific hematoma size. Location-specific volume cut-off should be considered in patient selection for ICH trials.

- Tolerability of haematoma volumes is also dependent on location

- This study showed that lobar bleeds can tolerate much larger volumes compared to deeper bleeds such as brainstem

Teo KC Stroke. 2023
doi: 10.1161/STROKEAHA.122.041246.

TICH 3 Haematoma Volumes <5ml

Haematoma Volumes	/1324
<0.5 ml	14 (0.1%)
<1 ml	37 (2.8%)
<5ml	340 (25.7%)

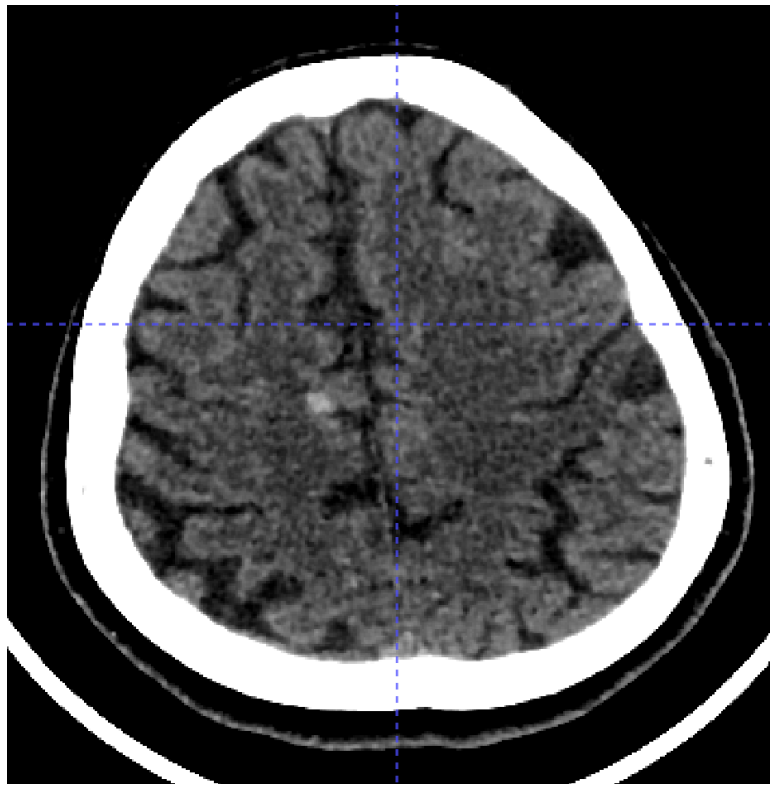
Clinical Characteristics at Randomisation in UK

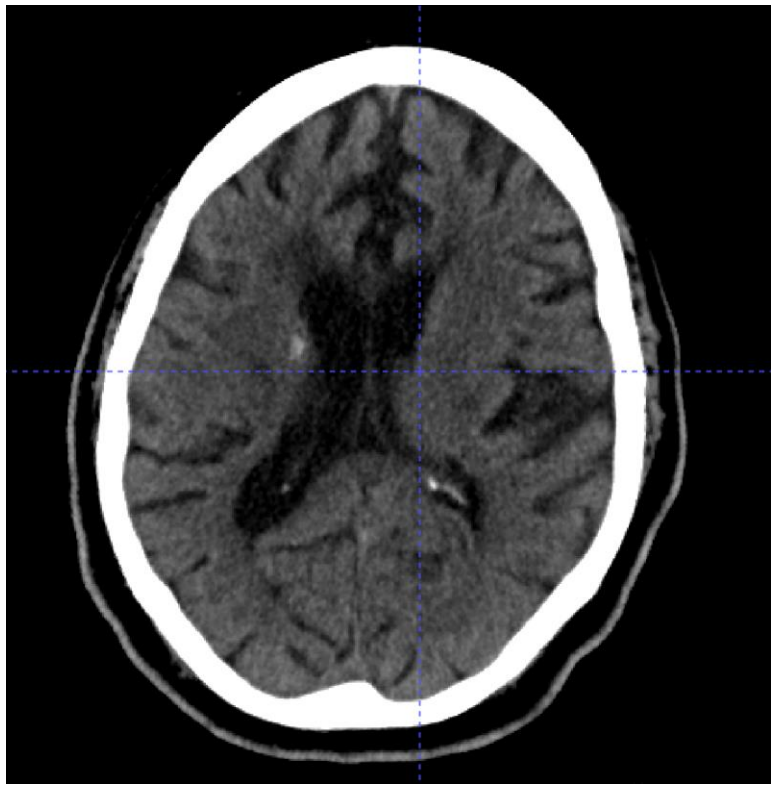
			Patients
Variable	**Statistic**	**N**	**All**
Number of patients randomised	**N**		**643**
Scan Details			
Haematoma location			
...Supra-tentorial Lobar	Yes (%)	643	162 (25.2)
...Supra-tentorial Deep	Yes (%)	643	418 (65.0)
...Infra-tentorial	Yes (%)	643	52 (8.1)
...Combination: All types	Yes (%)	643	11 (1.7)
Intraventricular Haemorrhage (IVH) present	Yes (%)	643	71 (11.0)
Haematoma volume	Mean (SD) {range}	638	17.2 (16.8) {0.1, 98.4}
...>66 mL, n (%)	n (%)	643	7 (1.1)
...<5 mL, n (%)	n (%)	643	177 (27.5)
...<4 mL, n (%)	n (%)	643	145 (22.6)
...<3 mL, n (%)	n (%)	643	97 (15.1)
...<2 mL, n (%)	n (%)	643	61 (9.5)

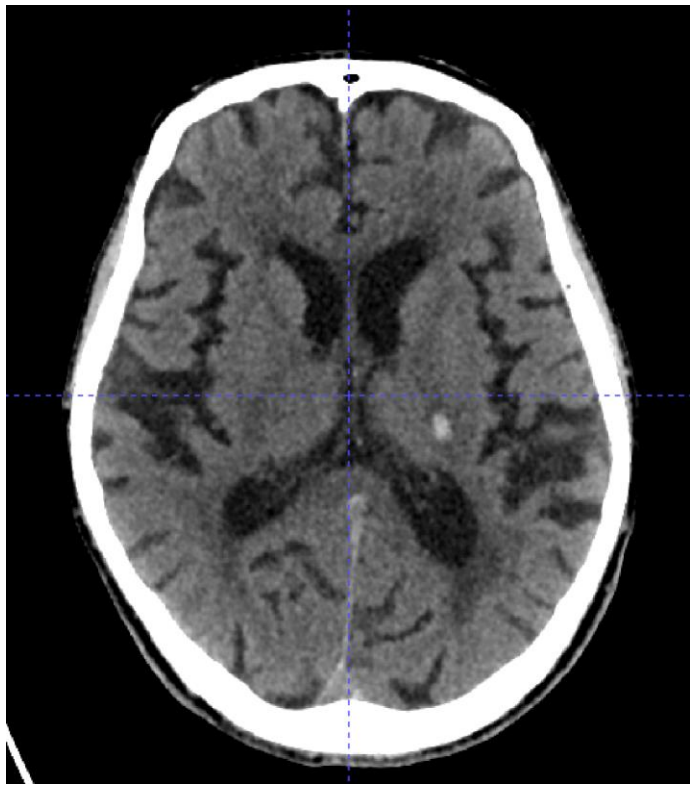
Deaths within patients with small haematoma<2ml

			Patients
Variable	**Statistic**	**N**	**All**
Patients randomised with haematoma< 2ml	**N**	**107**	**107**
Time to deaths (cumulative)			
Death by day 7	Yes, n(%)	107	2 (1.9)
Death by day 14	Yes, n(%)	107	2 (1.9)
Death by day 28	Yes, n(%	107	2 (1.9)
Death by day 180	Yes, n(%)	107	3 (2.8)

Some examples







Conclusions

There are predictors of haematoma expansion to look out for:

- **Lobar bleeds**
- **Prev antiplatelet therapy**
- **Volumes of 30-60ml**
- **Radiological Markers of HE on CT scans**

These are the patients that will be ideal recruits for the TICH 3 Trial

THANK YOU
ANY QUESTIONS