Intracerebral Hemorrhage

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Disclosures

- I have no commercial interests or disclosures
- I will not receive any payment for this presentation

Objectives

- Causes of ICH
  - Hypertension
  - CAA
- Initial management of ICH
  - Imaging
  - Coagulopathy
  - BP control
  - Surgery
- ICH course and prognosis

Intracerebral Hemorrhage: Background

- Despite much research and numerous clinical trials, ICH morbidity and mortality remains dismal
- In Canada, about 15% of all strokes are due to intracerebral hemorrhage, with a mortality of 40%

ICH: Causes

- About 70-80% of all ICH is primary hemorrhage, usually caused by hypertension or cerebral amyloid angiopathy
  - The incidence of CAA rises to over 50% in ICH patients over 80 years old

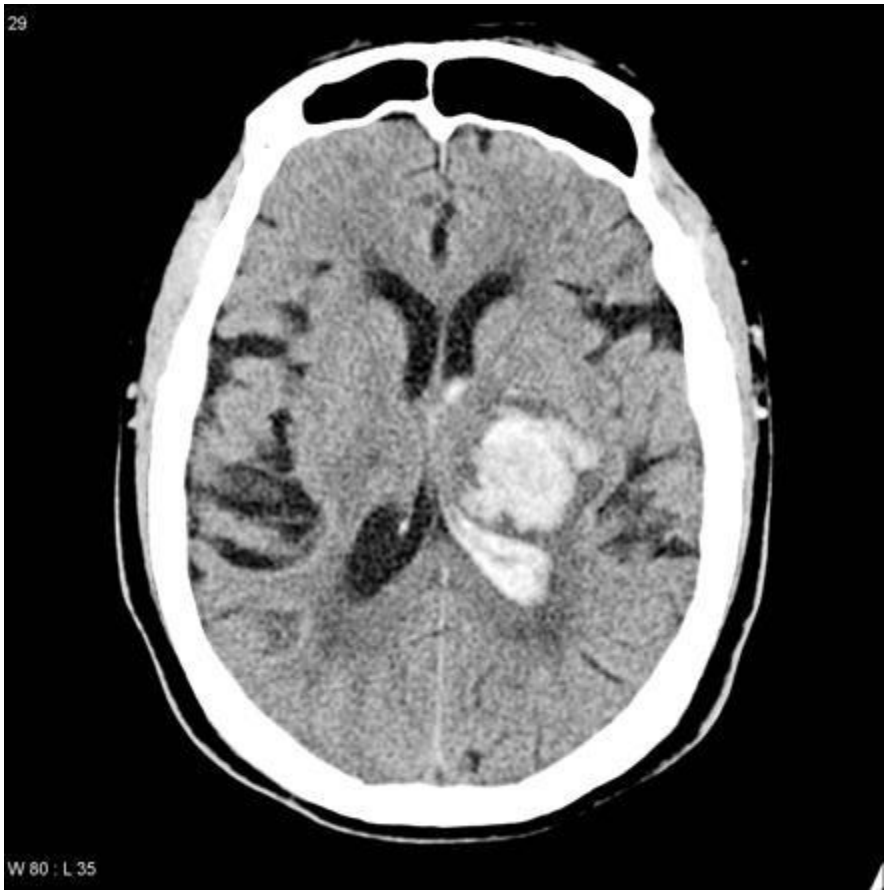
- About 15 to 20% is caused by a macrovascular etiology such as arteriovenous malformation, cerebral venous sinus thrombosis or cavernous malformation

Hypertension in Primary ICH

- Hypertension can be relevant for both deep and lobar ICH

- In patients under 70, HTN is the most common cause of ICH
  - Even in patients < 45 yo, HTN is still the most common cause of ICH, outpacing other causes such as vascular malformations

Deep ICH



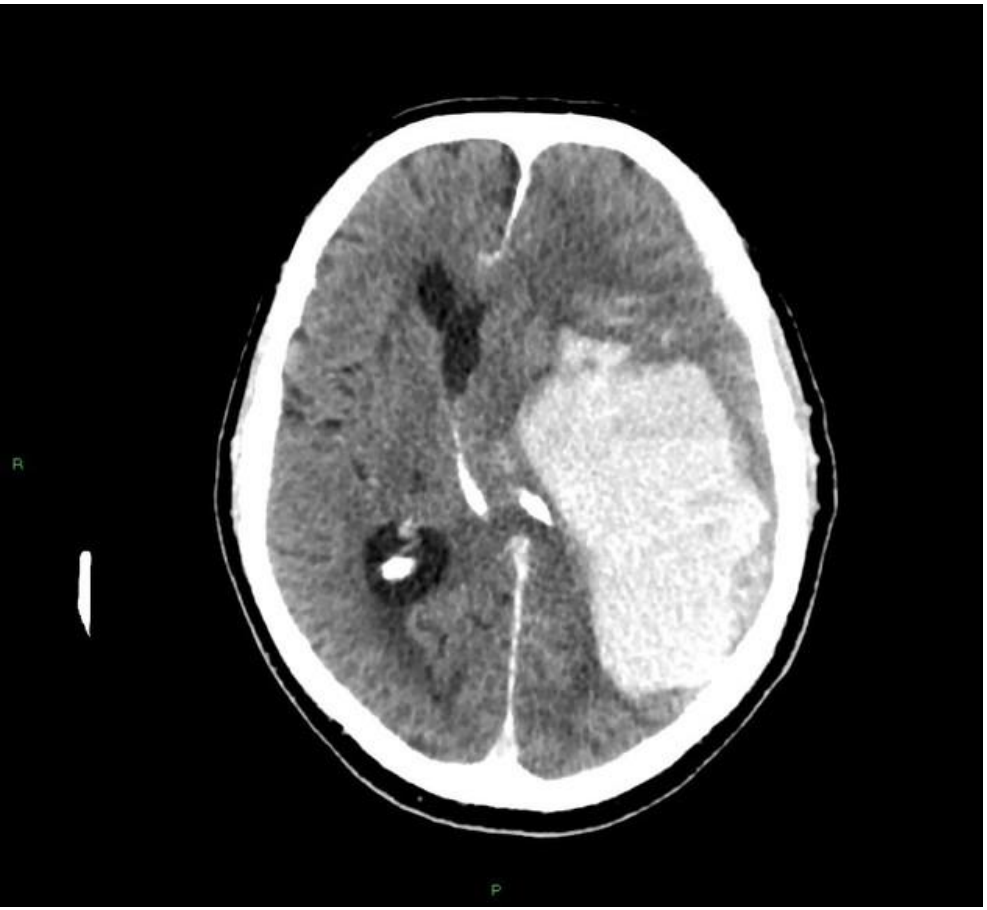
- Typical locations for hemorrhage include: thalamus, putamen, pons and cerebellum
- Associated with increased sBP (154 ± 26 mmHg) vs controls (143 ± 22 mmHg) (p = 0.008)
- Hypertension **not** more prevalent than in controls in the study by Lioutas et al., but small sample

Lioutas et al. JAMA Neurol. 2020; 77(10):1252-60

Active bleeding, deep ICH

Dowlatshahi et al Lancet 2013;381:152

Lobar ICH



- These can be due to both HTN and/or CAA
- Associated with higher sBP (148 ± 26 mmHg) vs controls (138 ± 23 mmHg) (p = 0.002)
- History of hypertension more prevalent than in controls (79.2% vs 61.1%, p=0.009)

Lioutas et al. JAMA Neurol. 2020; 77(10):1252-60

How long does someone have to have hypertension before ICH?

Acute post-stroke blood pressure relative to premorbid levels in intracerebral haemorrhage versus major ischaemic stroke: a population-based study

Urs Fischer, Marie Therese Cooney*, Linda M Bull, Louise E Silver, John Chalmers, Craig S Anderson, Ziyah Mehta, Peter M Rothwell*

Background It is often assumed that blood pressure increases acutely after major stroke, resulting in so-called post-stroke hypertension. In view of evidence that the risks and benefits of blood pressure-lowering treatment in acute stroke might differ between patients with major ischaemic stroke and those with primary intracerebral haemorrhage, we compared acute-phase and premorbid blood pressure levels in these two disorders.

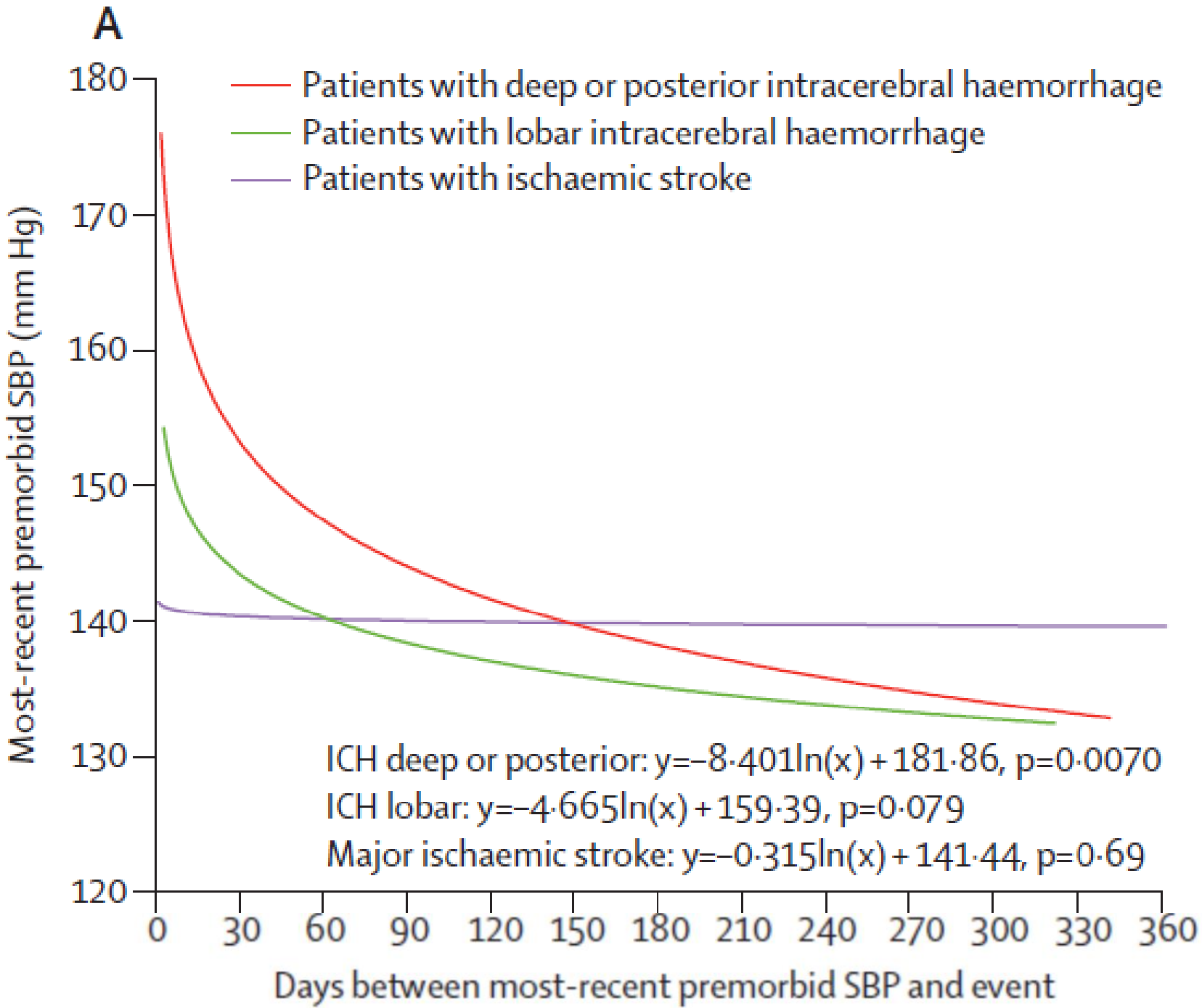
Lancet Neurol 2014

Published Online
February 28, 2014

Acute post-stroke blood pressure relative to premorbid levels in intracerebral haemorrhage versus major ischaemic stroke: a population-based study

Urs Fischer, Marie Therese Cooney*, Linda M Bull, Louise E Silver, John Chalmers, Craig S Anderson, Ziyah Mehta, Peter M Rothwell*

- Ischemic stroke: N = 523 (40% cardioembolic)
  - Previous HTN: 67%
- Hemorrhage: N = 113 (58% deep or posterior)
  - Previous HTN: 59%
- OXVASC, Oxfordshire Community Stroke Project
- Premorbid BP obtained from primary care records

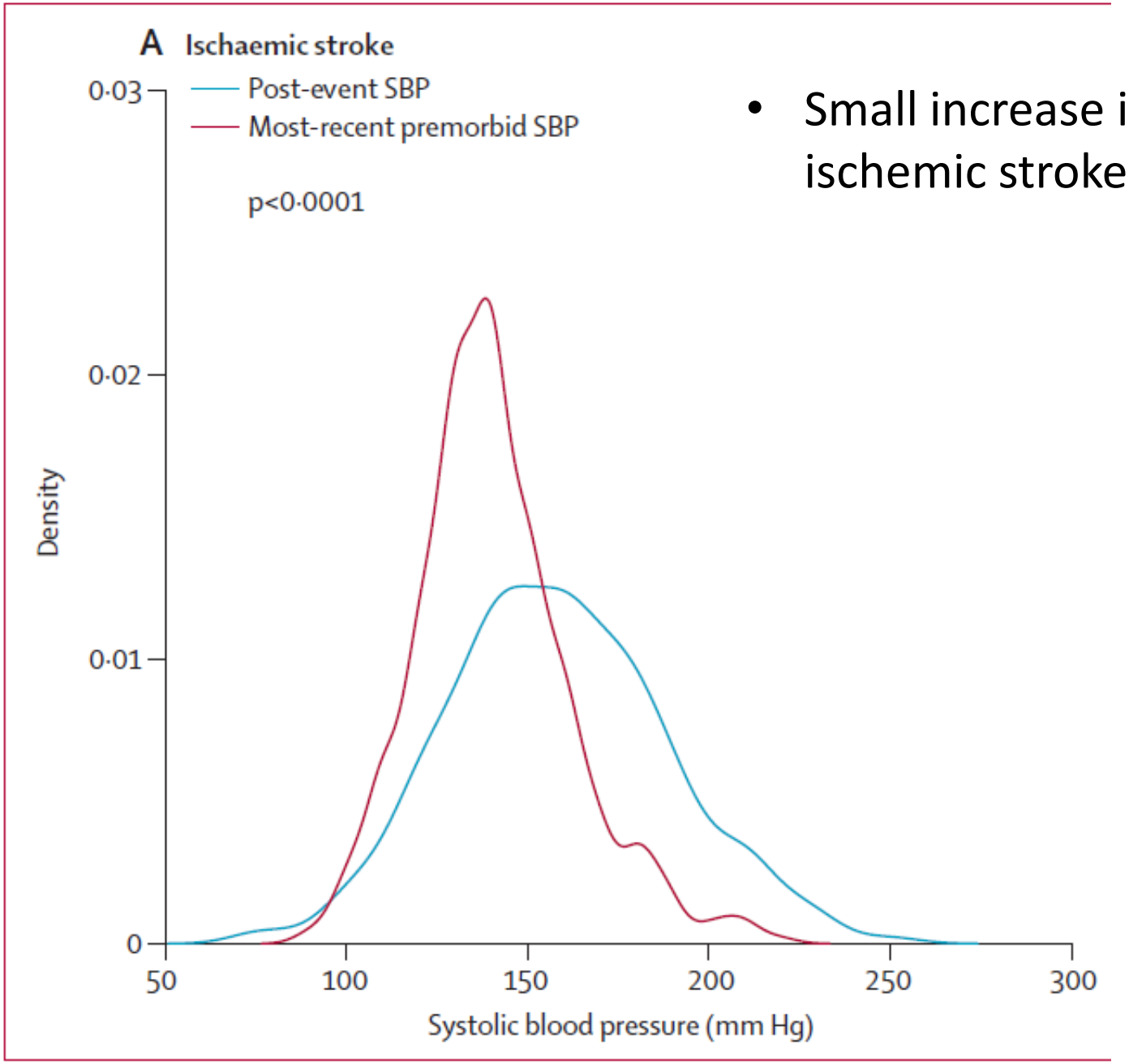

A
Patients with deep or posterior intracerebral haemorrhage
Patients with lobar intracerebral haemorrhage
Patients with ischaemic stroke
Most-recent premorbid SBP (mm Hg)
180
170
160
150
140
130
120
ICH deep or posterior: y=–8·401ln(x)+181·86, p=0·0070
ICH lobar: y=–4·665ln(x)+159·39, p=0·079
Major ischaemic stroke: y=–0·315ln(x)+141·44, p=0·69
0
30
60
90
120
150
180
210
240
270
300
330
360
Days between most-recent premorbid SBP and event

- You don’t have to have a longstanding history of hypertension to be at risk for ICH

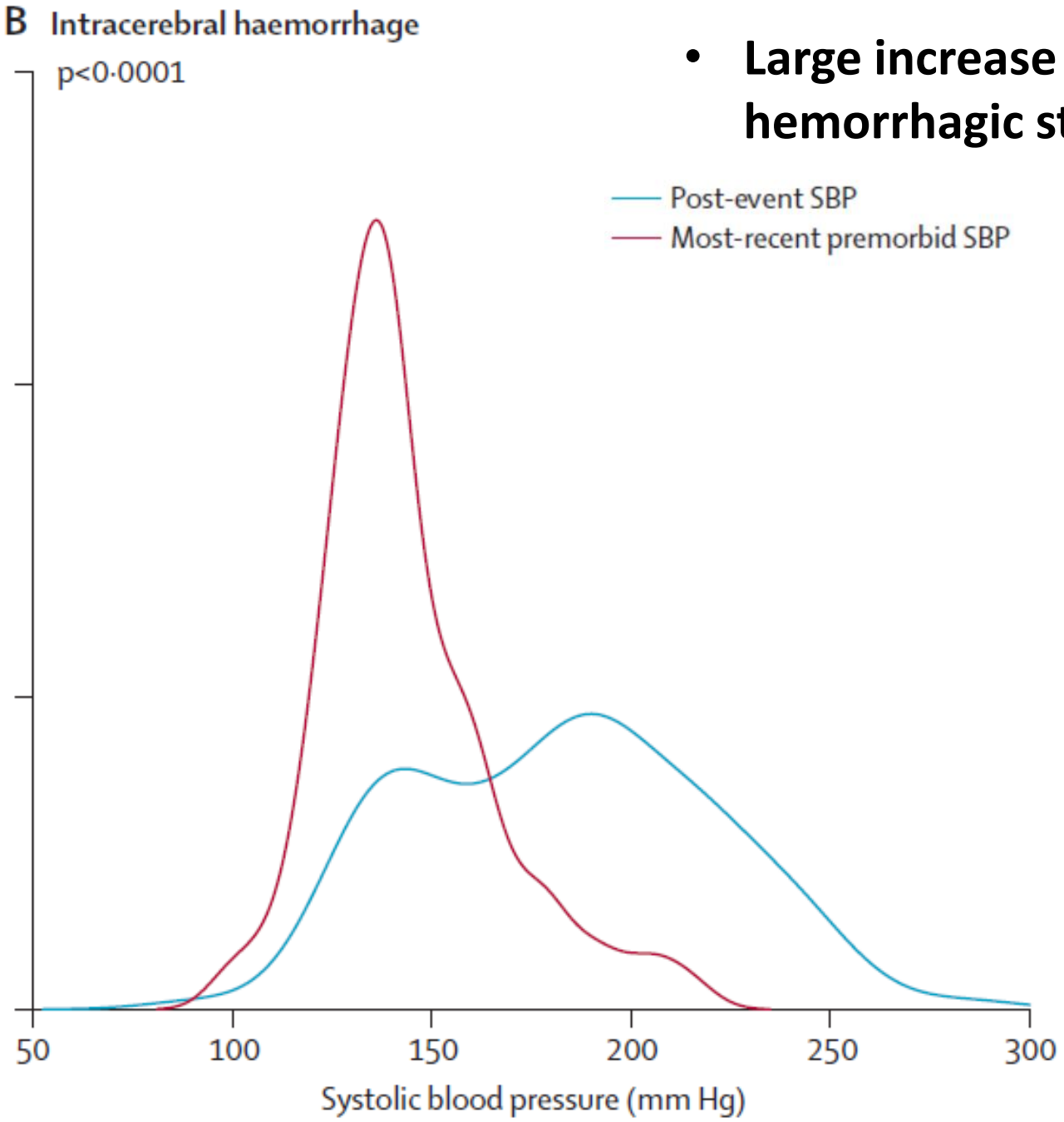
- Many patients in the Oxfordshire study had premorbid elevated BP for just a few months, or even less before they had ICH

BP goes up after ICH

- Many factors at play, including:
  - Neuroendocrine changes (altered levels of norepinephrine, catecholamines, and dysfunction of pituitary-hypothalamic-adrenocortical axis)
  - Autonomic dysfunction
  - Disturbed autoregulation
  - Urinary retention, infection, psychological stress



- Small increase in BP with ischemic stroke



- **Large increase in BP with hemorrhagic stroke**

	0–15 min	>24 h
Mean post-event SBP (mm Hg)		
Intracerebral haemorrhage	204·4 (31·5); 8	168·7 (43·3); 10
Ischaemic stroke	155·0 (29·2); 42	158·8 (31·1); 76

So is BP lowering in ICH safe?

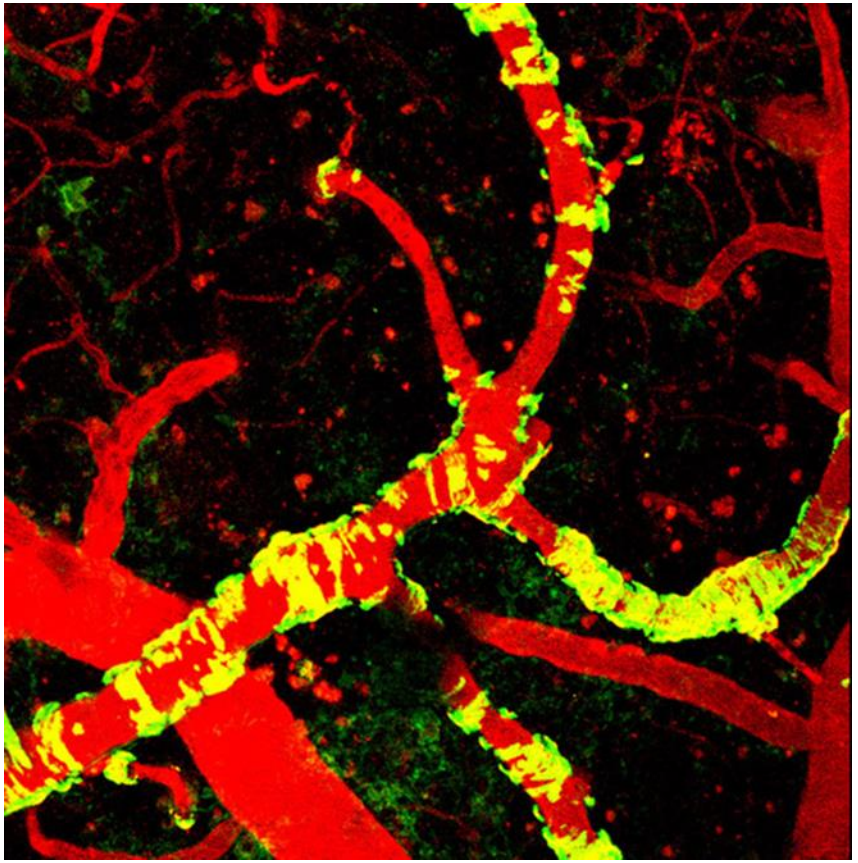
- Trials such as INTERACT 2 and ATACH-2 have shown that lowering sBP to 140 mmHg is safe
- But no clear clinical benefit shown
- Although BP lowering tends to lead to less frequent hematoma expansion, is that enough?

Canadian Stroke Best Practice Recommendation

- Systolic blood pressure lowering to a target of < 140 mmHg systolic does not worsen neurological outcomes (relative to a target of 180 mmHg systolic) [Evidence level A]; however, clinical benefit has yet to be established [Evidence level A].
- There is a lack of strong evidence to guide choice of initial blood pressure lowering agents.
- Parenteral labetalol, hydralazine, nicardapine and/or enalapril (oral or intravenous) may be considered for acute blood pressure reduction.

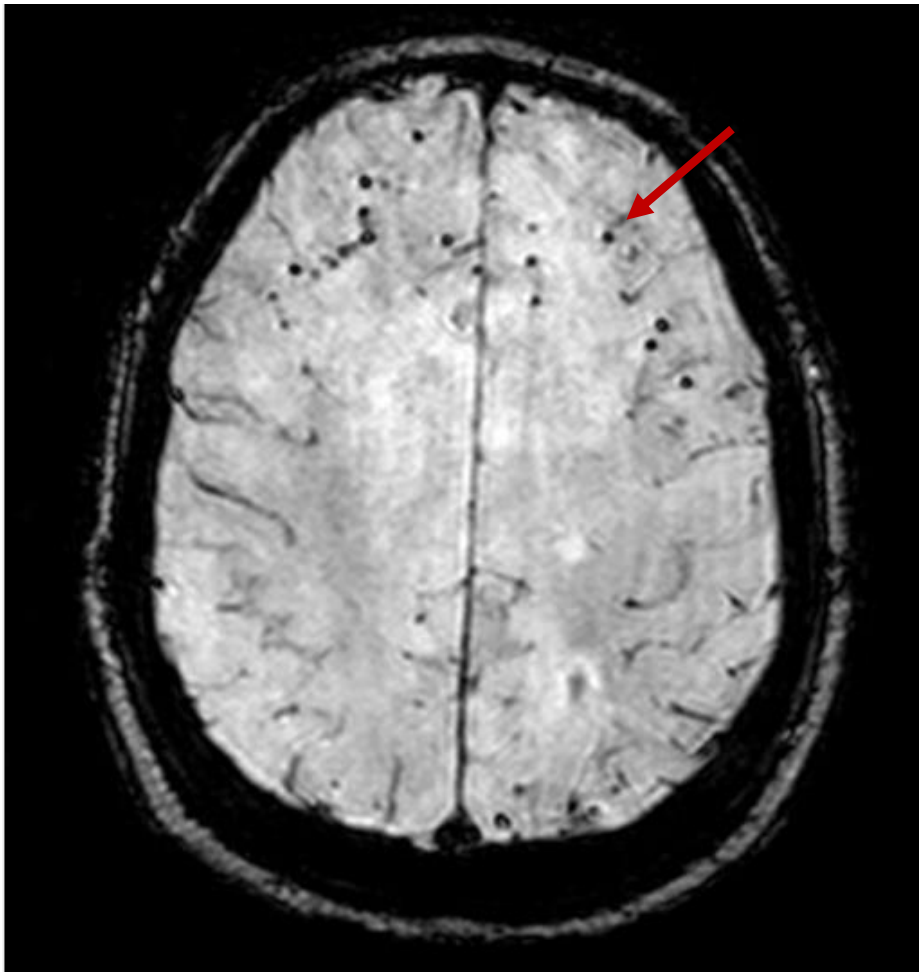
ICH and Cerebral Amyloid Angiopathy

- Deposition of amyloid protein in media/adventitia of small cortical arteries, arterioles and capillaries



Cerebral microbleeds (CMBs)

- Seen on GRE or SWI MRI sequences
- Focal accumulations of hemosiderin-laden macrophages
- Can occur in a variety of conditions including: CAA, chronic hypertensive encephalopathy, CADASIL, vasculitis, PRES, radiation-induced vasculopathy



Modified Boston Criteria for hemorrhage related to CAA

1) Definite CAA (full postmortem examination demonstrating:)
   - Lobar, cortical, or corticosubcortical hemorrhage
   - Severe CAA with vasculopathy
   - Absence of other diagnostic lesion

2) Probable CAA with supporting pathology (clinical data and pathologic tissue demonstrating:)
   - Lobar, cortical, or corticosubcortical hemorrhage
   - Some degree of CAA in specimen
   - Absence of other diagnostic lesion

3) Probable CAA (clinical data and MRI or CT demonstrating:)
   - Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed) or
   - Single lobar, cortical, or corticosubcortical hemorrhage and focal (≤ 3 sulci) or disseminated (≥ 4 sulci) superficial hemosiderosis
   - Age ≥ 55 years
   - Absence of other cause of hemorrhage or superficial siderosis

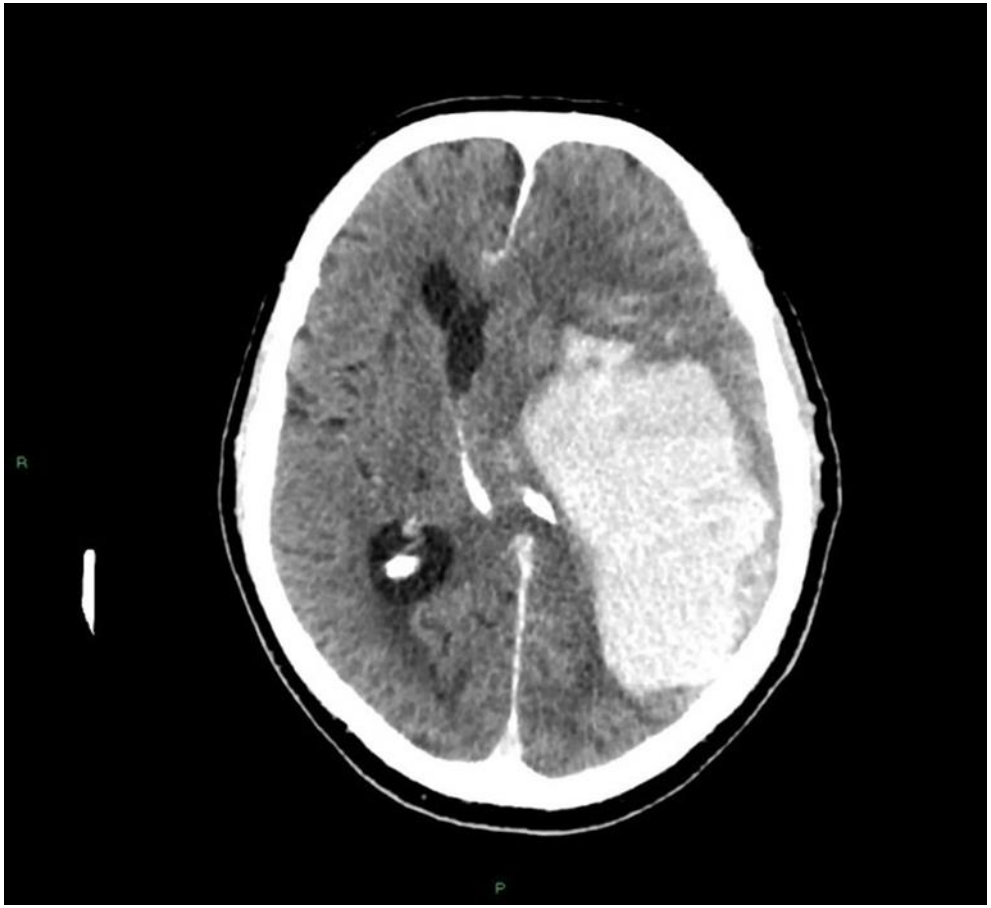
4) Possible CAA (clinical data and MRI or CT demonstrating:)
   - Single lobar, cortical, or corticosubcortical hemorrhage or
   - Focal (≤ 3 sulci) or disseminated (≥ 4 sulci) superficial hemosiderosis
   - Age ≥ 55 years
   - Absence of other cause of hemorrhage or superficial siderosis

CAA clinical presentation

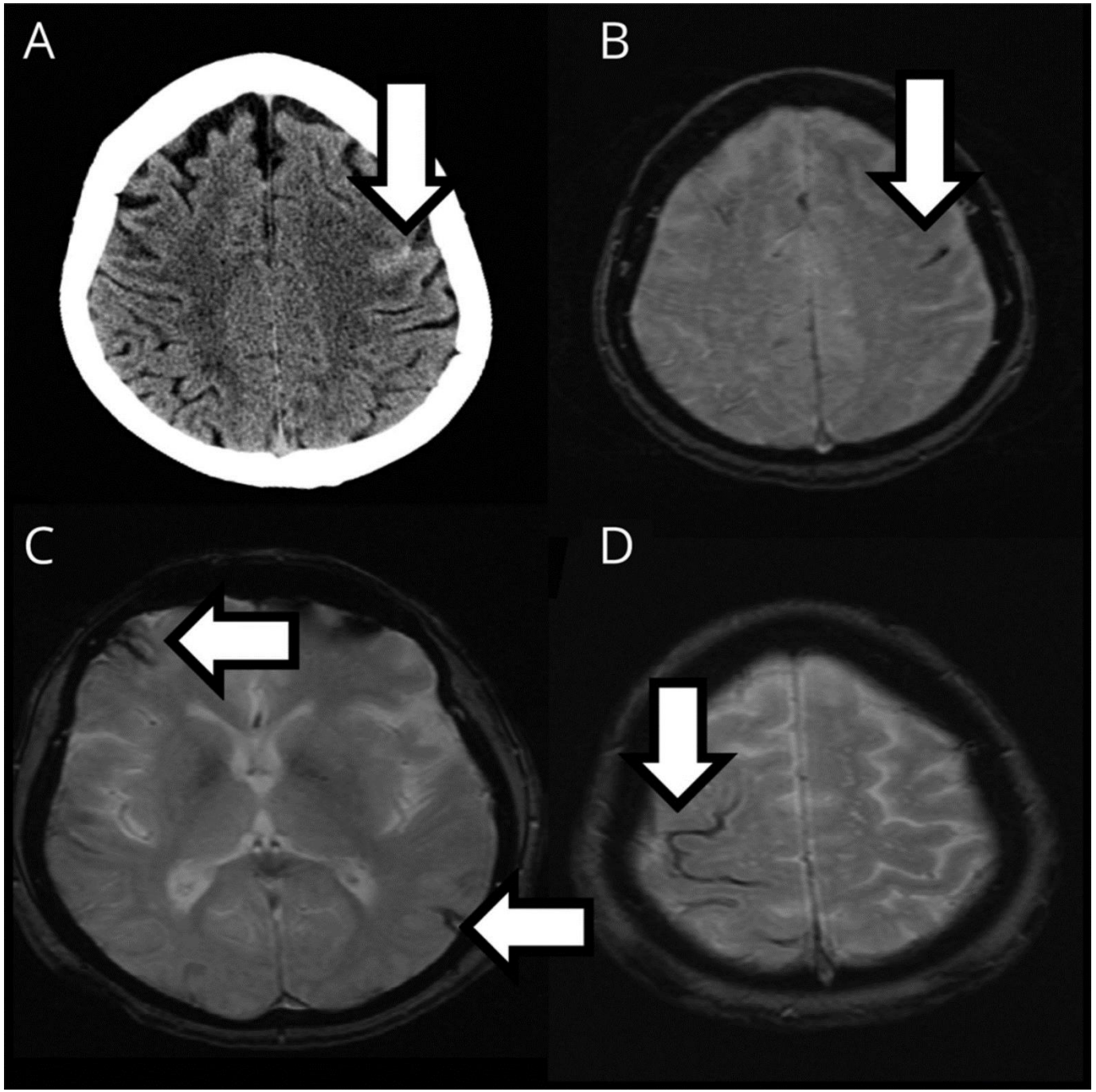
- Lobar hemorrhage is the most well known presentation
- CAA can also present with TIA/minor stroke-like episodes
- CAA can also present with neuroinflammation and even angiitis

CAA-related lobar hemorrhage

- Probability of CAA as the cause of a lobar hemorrhage is 30-70%, with higher probability in older patients
- Multiple lobar hemorrhages or the presence of **cortical superficial siderosis** are strong indicators of CAA



Cortical superficial siderosis is associated with Transient Focal Neurological Episodes (TFNE)



Cortical superficial siderosis and recurrent ICH risk

- In a recent meta-analysis of ICH patients with CAA, the presence of cSS was associated with an **annual risk of recurrent ICH of 11.1%** vs 3.9% in ICH patients without CAA, over 3.1 years of follow up.
  - Charidimou et al. Neurology.2019;93(24):e2192-e2202

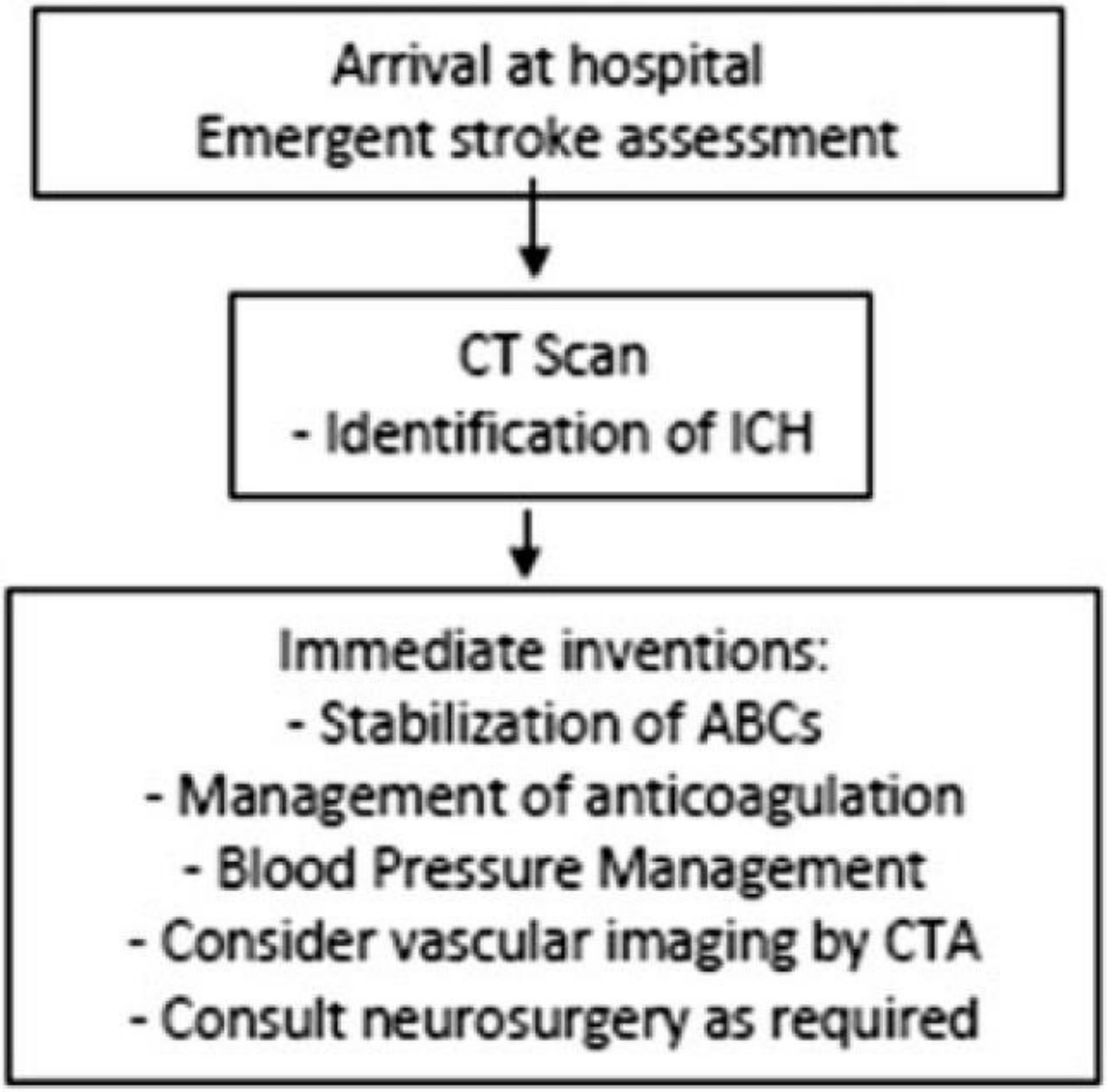
Other causes of ICH that could be considered

- RCVS
- Cocaine, methamphetamine
- AVM or cavernous malformation
- Neoplasm
- Reperfusion syndrome after carotid revascularization
- Anticoagulants

ICH initial management

- Assess GCS, ABCs. Rapid neurological examination (usually based on NIHSS) and note if any indication of herniation
- NCCT and CTA
- Blood pressure management and reversal of coagulopathy
- Should I call Neurosurgery?

- https://www.strokebestpractices.ca/recommendations/management-of-intracerebral-hemorrhage


Arrival at hospital
Emergent stroke assessment
CT Scan
- Identification of ICH
Immediate inventions:
- Stabilization of ABCs
- Management of anticoagulation
- Blood Pressure Management
- Consider vascular imaging by CTA
- Consult neurosurgery as required

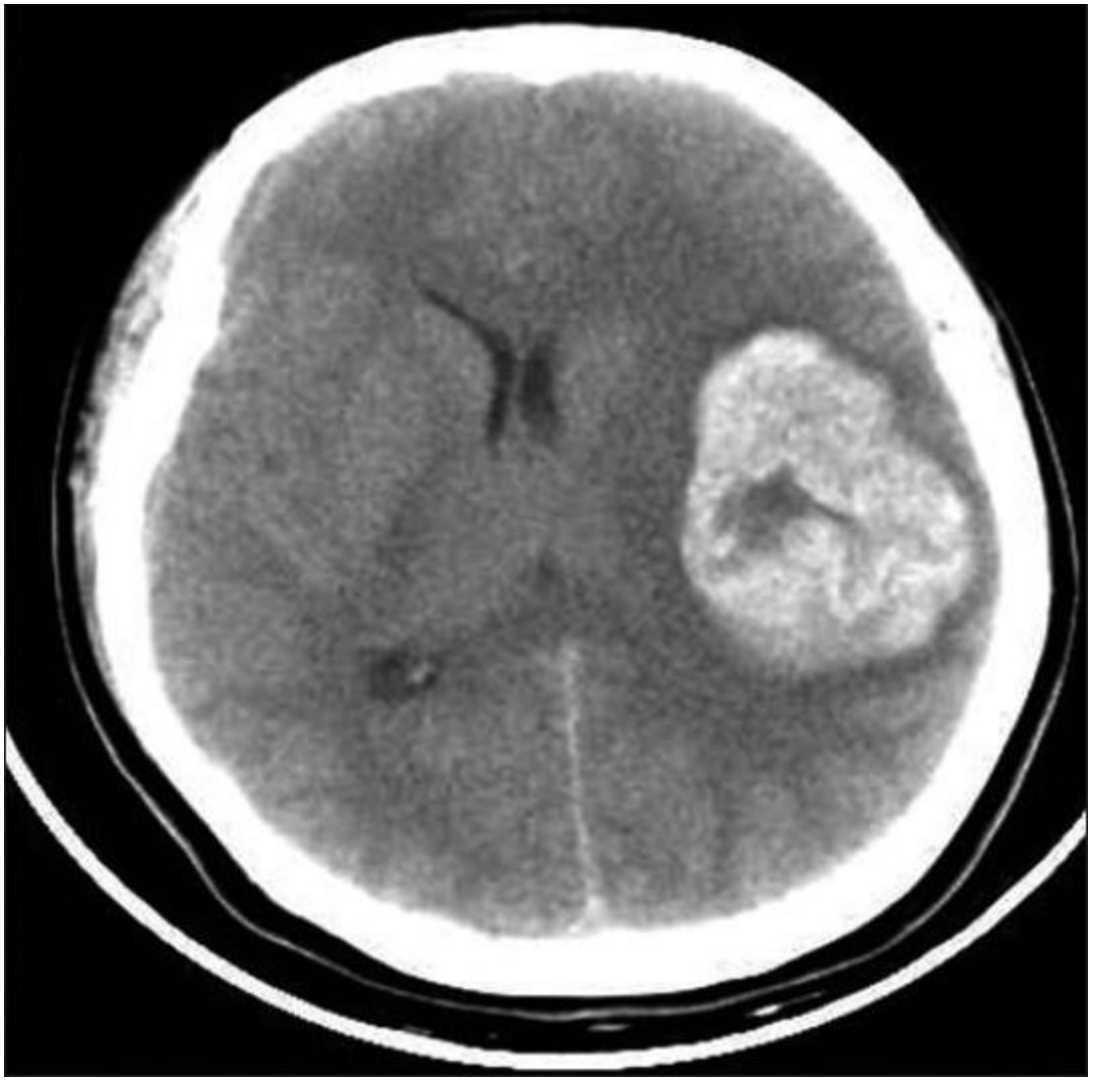
Imaging studies

- About 15 to 25% of all ICH has an underlying macrovascular etiology such as an arteriovenous malformation, cavernous malformation, or cerebral venous sinus thrombosis

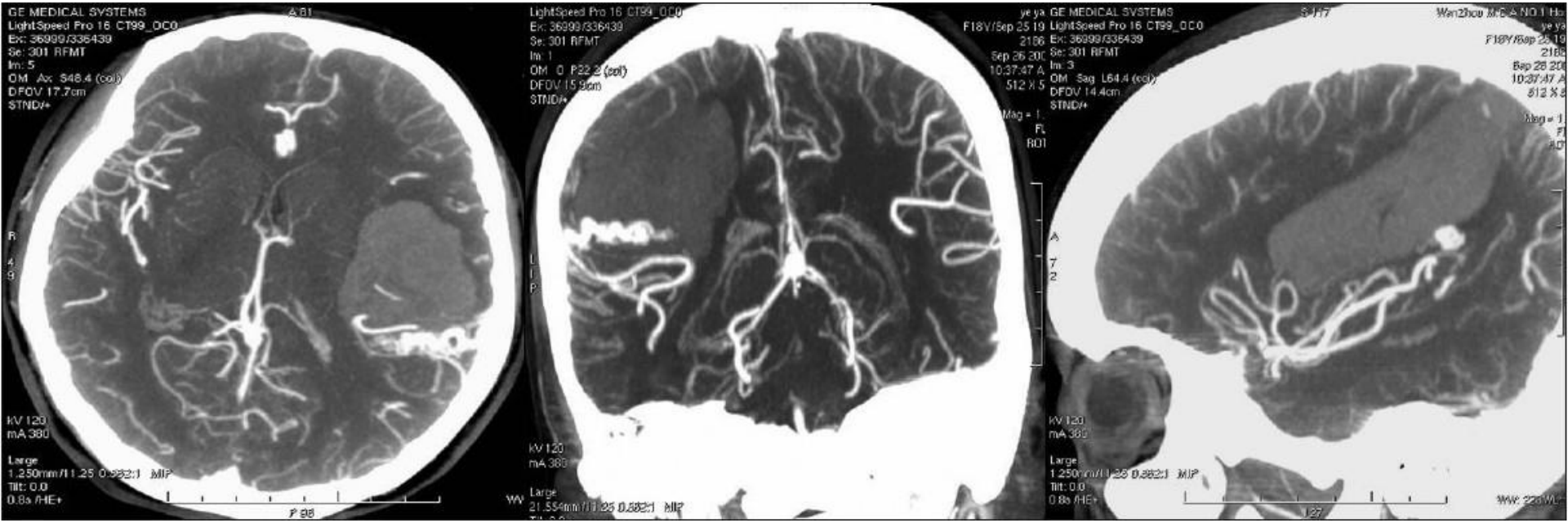
- **CT angiography from the Circle of Willis to the vertex is the preferred vascular imaging modality**

Who is more likely to have a macrovascular cause of ICH?

- Female
- Under 70 years old
- No hypertension or coagulopathy
- NCCT shows calcification or enlarged vessels at the borders of the ICH
- NCCT shows hyperattenuation in a dural venous sinus or cortical vein near the ICH



Tan XX, Zhong M, Zheng K, Zhao B. Computed tomography angiography based emergency microsurgery for massive intracranial hematoma arising from arteriovenous malformations. Neurol India 2011;59:199-203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LightSpeed Pro 16 CT99_0C0
Ex: 36999/336439
Se: 301 RFMT
Im: 5
OM Ax 548.4 (col)
DFOV 17.7cm
STND/+
kV 120
mA 380
Large
1.250mm/1.25 0.562:1 MIP
Tilt: 0.0
0.8s /HE+
LightSpeed Pro 16 CT99_0C0
Ex: 36999/336439
Se: 301 RFMT
Im: 1
OM 0 P32.2 (col)
DFOV 15.9cm
STND/+
kV 120
mA 380
Large
21.554mm/11.25 0.562:1 MIP
GE MEDICAL SYSTEMS
LightSpeed Pro 16 CT99_0C0
Ex: 36999/336439
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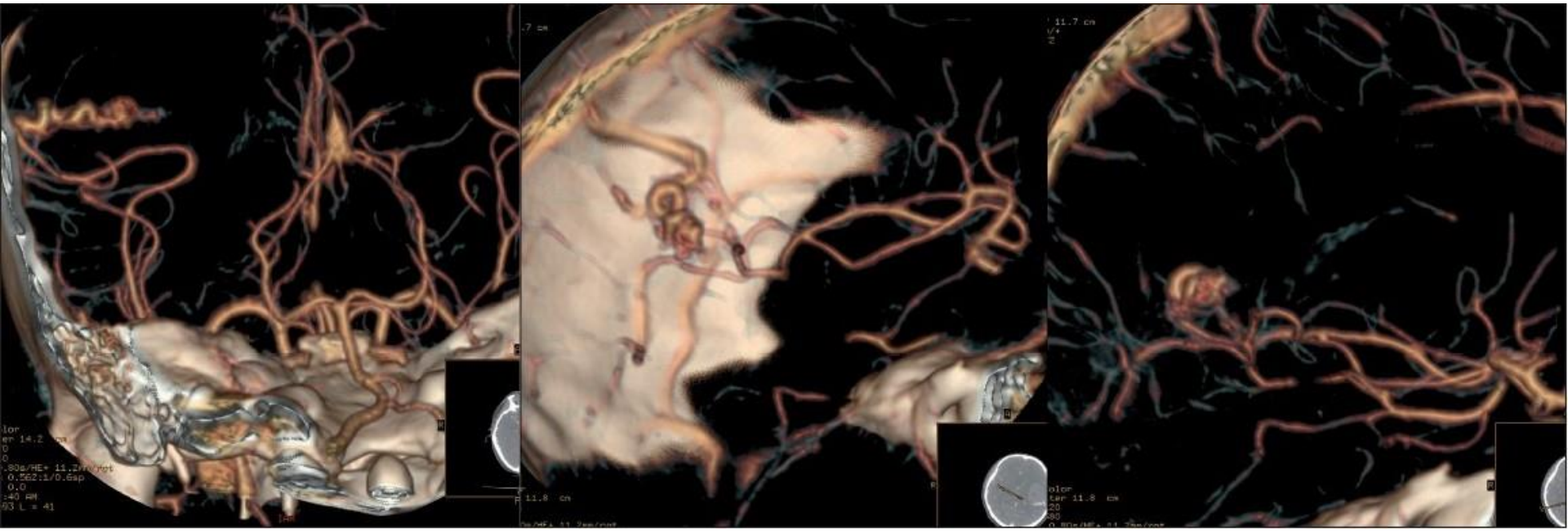
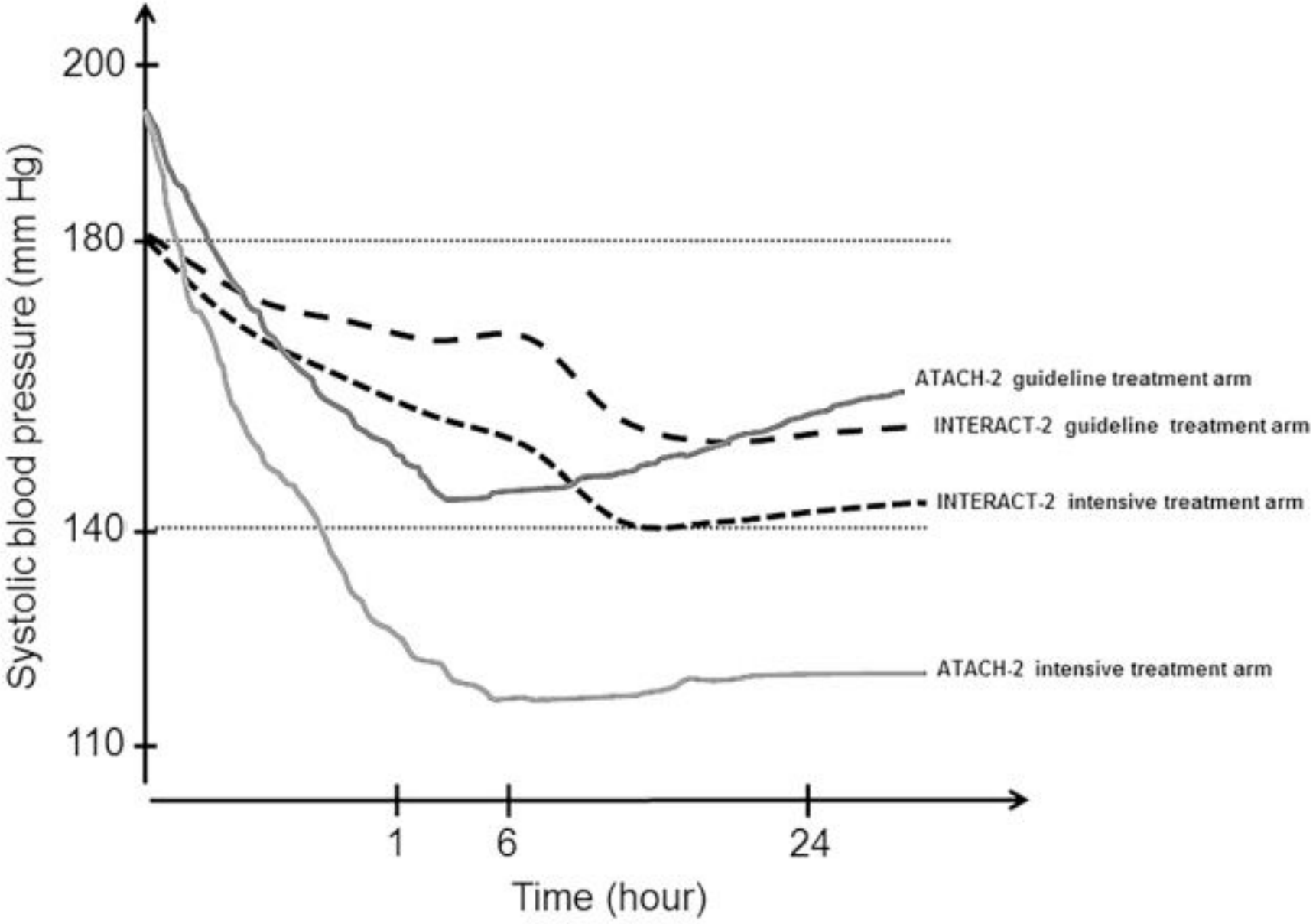


BP management

- It’s safe to treat sBP to a target of 140 mm Hg
- But all trials of intensive BP treatment for ICH have failed to show benefit!
- So why make any recommendations at all?


200
180
140
110
Systolic blood pressure (mm Hg)
ATACH-2 guideline treatment arm
INTERACT-2 guideline treatment arm
INTERACT-2 intensive treatment arm
ATACH-2 intensive treatment arm
1
6
24
Time (hour)

BP management

- Although INTERACT-2 failed to show benefit with intensive treatment, the treatment arm didn’t actually get to target BP until several hours
- Although ATACH-2 failed to show benefit, the control arm was also treated quite intensively and the treatment arm was probably treated a little too aggressively

Reversal of coagulopathy

- **PCC** is superior to FFP to reverse warfarin (INR ≤ 1.2)
- Apixaban, rivaroxaban, edoxaban: **PCC** 50 U/kg to a maximum dose of 3000 U
- Dabigatran: **Idarucizumab** 2.5 g given twice IV within 15 minutes of each bolus
- Consider **protamine** to reverse LMWH or UFH

- **Tranexamic acid** 1g IV bolus then 1g over 8 hours may be useful, although there is no direct evidence

Surgery and ICH

- The STICH-2 trial failed to show benefit for “early” intervention for surgery
- **However, in this trial “early” intervention was done 26 hours after ictus**
  - Recall how quickly and frequently hematoma expansion occurs in the first 24 hours
  - “Early” intervention was probably not early enough
- **The population treated in clinical trials differs from what we often see in the ED**
  - Patients who were showing signs of herniation and diminished LOC were unlikely to have been randomized
  - Intraventricular hemorrhage was excluded

When should I call Neurosurgery?

- If Neurosurgery is not on site, it is recommended by CSBPR to initiate consultation by phone or Telemedicine
- **Decreased LOC** and signs of **herniation**
- **Intraventricular hemorrhage** or **mass effect** and **hydrocephalus**
- Age < 65 (but some patients older than that who are otherwise healthy could also be considered)
- **Hematoma is close to the cortical surface** (~1 cm) or is in the cerebellum

What to expect clinically with hemorrhagic stroke

- Deficits are based on the location of the hematoma

- But the clinical course can change very quickly if the hematoma expands

Intracerebral hemorrhage has high mortality

- About a third will die in the first month
- Age is a major factor with over 50% mortality in patients > 80 yo

Mortality after hemorrhagic stroke
Antonio González-Pérez, David Gaist, Mari-Ann Wallander, GillianMcFeat, Luis A. García-Rodríguez
Neurology Aug 2013, 81 (6) 559-565

Recovery is slow

Table 2 **Modified Rankin Scale (mRS) score at various timepoints (n = 243)**

	mRS score	Hospital discharge	30 d	3 mo	6 mo	12 mo
No deficit	0	3 (1)	3 (1)	5 (2)	4 (2)	5 (2)
	1	21 (9)	25 (10)	29 (12)	32 (13)	35 (14)
	2	13 (5)	15 (6)	17 (7)	21 (9)	16 (7)
Walking	3	31 (13)	27 (11)	31 (13)	29 (12)	31 (13)
	4	55 (23)	55 (23)	42 (17)	36 (15)	26 (11)
	5	25 (10)	18 (7)	8 (3)	7 (3)	13 (5)
Dead	6	95 (39)	100 (41)	111 (46)	114 (47)	117 (48)

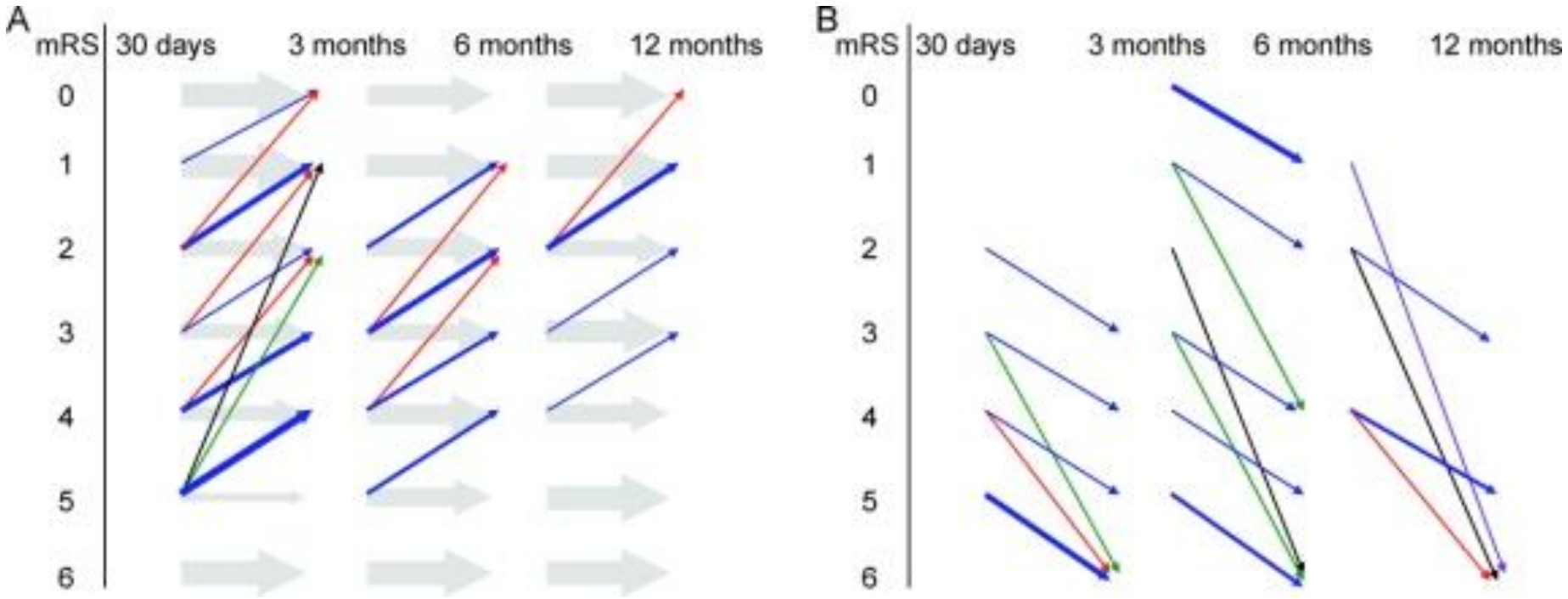
Values are expressed as n (%).

Hemphill JC 3rd, Farrant M, Neill TA Jr. Prospective validation of the ICH Score for 12-month functional outcome. Neurology. 2009 Oct 6;73(14):1088-94. doi: 10.1212/WNL.0b013e3181b8b332. Epub 2009 Sep 2. PMID: 19726752; PMCID: PMC2764394.

But many ICH patients change after hospital discharge

- 34% will improve by one point or more on mRS after hospital discharge
  - 13% will improve by 2 or more points

- 22% will deteriorate by one or more points
  - 10% will deteriorate by 2 or more points, often due to other conditions not related to ICH



- Grey: no improvement
- Blue: mRS changed by 1
- Line thickness reflects # patients

Be cautious when offering palliation based on ICH score

- One of the greatest predictors of in-hospital mortality is discussion of DNR within the first 24 hours

The ICH score has been used to grade the severity of ICH

Component	ICH Score Points
GCS score	
3–4	2
5–12	1
13–15	0
ICH volume (cm^3)	
≥ 30	1
< 30	0
IVH	
Yes	1
No	0
Infratentorial origin of ICH	
Yes	1
No	0
Age (year)	
≥ 80	1
< 80	0
Total ICH Score	0–6

The GCS score refers to the GCS score at initial presentation (or after resuscitation); ICH volume, volume on initial CT calculated using the ABC/2 method; IVH, presence of any IVH on the initial CT.

GCS, Glasgow coma scale; ICH, intracerebral hemorrhage; CT, computed tomography; IVH, intraventricular hemorrhage.

Adapted from Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke* 2001;32:891-897.

Severity assessment in maximally treated ICH patients

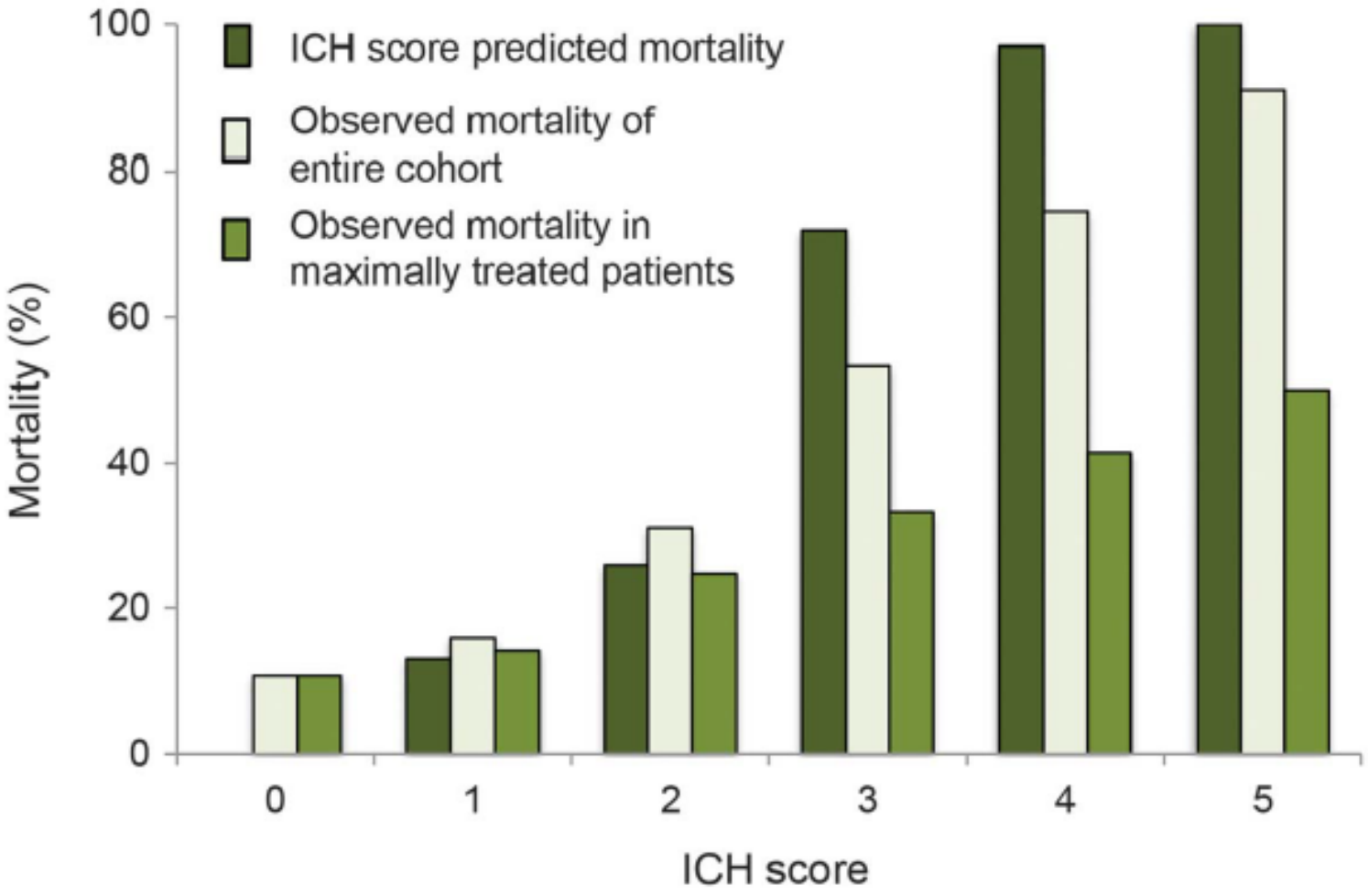
The max-ICH score

Conclusions: Care limitations significantly influenced the validity of common prognostication models resulting in overestimation of poor outcome. The max-ICH score demonstrated increased predictive validity with minimized confounding by care limitations, making it a useful tool for severity assessment in ICH patients. *Neurology*® 2017;89:423-431

Jochen A. Sembill, MD
Stefan T. Gerner, MD
Bastian Volbers, MD
Tobias Bobinger, MD
Hannes Lücking, MD
Stephan P. Kloska, MD
Stefan Schwab, MD
Hagen B. Huttner, MD
Joji B. Kuramatsu, MD

- **Early care limitations are a self-fulfilling prophecy**

Figure 1 **Comparison of mortality rates**

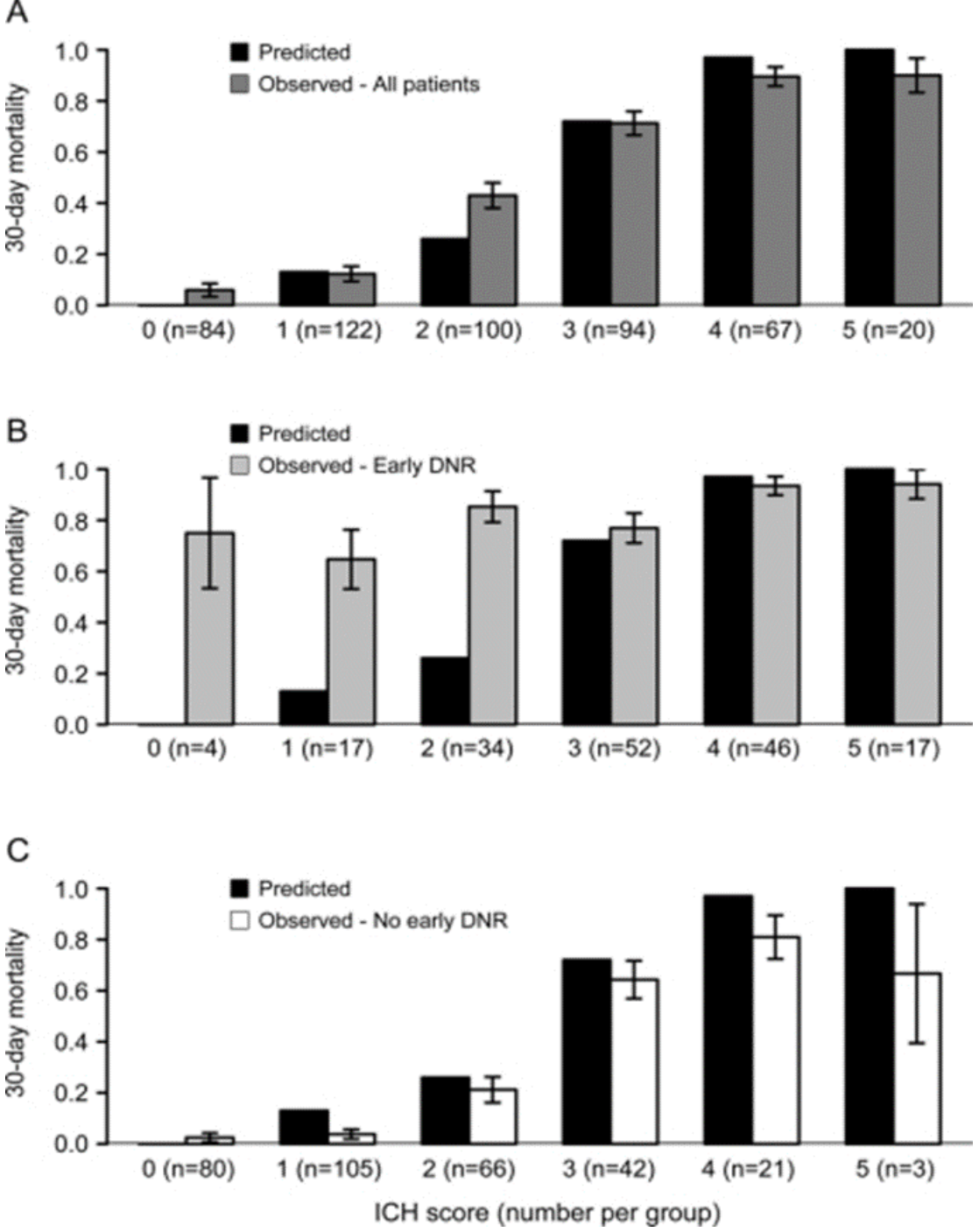


Observed short-term mortality rate in the entire intracerebral hemorrhage (ICH) cohort (n = 583) and in maximally treated patients (n = 471) in contrast to predicted short-term mortality rate by the ICH score.

- Prevalence of ECL 19.2% (n=112/583) and all of these patients died

- But propensity score matching showed that **50.7% theoretically could have survived** and **18.8% possibly reaching favorable outcome** (modified Rankin Scale score of 0 to 3).

Early DNR orders were associated with increased 30-day mortality higher than predicted by the ICH score



Summary: HTN and ICH

- Hypertension is a major cause of ICH especially in patients under 70 years old
- Hypertension is not always diagnosed before ICH
- Hypertension can be the cause of both deep and lobar ICH

Summary: CAA and ICH

- CAA is a major cause of ICH, especially in older patients
- CAA usually presents with lobar hemorrhage but can also present with small cortical hemorrhage
- Cortical superficial siderosis can be a manifestation of CAA and is associated with transient focal neurological episodes
- CSS is predictive of a high ICH recurrence rate

Summary: CTA and BP management

- CTA is useful to identify macrovascular causes of ICH
- Targeting sBP to 140 is safe
  - But clinical benefit was not demonstrated in trials
  - Trial results may not be definitive due to differences between trial methodology and real world scenarios

Summary: Coagulopathy and ICH

- PCC is effective to lower INR to < 1.2 in patients on warfarin
- PCC for apixaban, rivaroxaban, edoxaban
- Idarucizumab for dabigatran
- Tranexamic acid may be helpful
- Protamine for LMWH or UFH

Summary: Surgery and ICH

- Early neurosurgical consultation is recommended for cases in which life is threatened
  - Herniation, decreased LOC, mass effect, intraventricular extension of hematoma

Summary: ICH course and prognostication

- Slow recovery over many months

- Early care limitations and early DNR discussions seem to increase likelihood of in-hospital death, even after normalizing for case mix
  - Be cautious in discussing code status or ECL and consider delaying the discussion for the first 24 hours

Thanks for listening!

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Other issues that come up with ICH patients…

- How do I manage antithrombotic therapy if the patient has had ICH?

- Will my ICH patient go on to have epilepsy?

If my patient had a primary ICH, can I restart antiplatelet therapy at some point?

Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART): a randomised, open-label trial

*RESTART Collaboration**

Summary

Background Antiplatelet therapy reduces the risk of major vascular events for people with occlusive vascular disease, although it might increase the risk of intracranial haemorrhage. Patients surviving the commonest subtype of intracranial haemorrhage, intracerebral haemorrhage, are at risk of both haemorrhagic and occlusive vascular events, but whether antiplatelet therapy can be used safely is unclear. We aimed to estimate the relative and absolute effects of antiplatelet therapy on recurrent intracerebral haemorrhage and whether this risk might exceed any reduction of occlusive vascular events.

Methods The REstart or STop Antithrombotics Randomised Trial (RESTART) was a prospective, randomised, open-label, blinded endpoint, parallel-group trial at 122 hospitals in the UK. We recruited adults (≥18 years) who were taking antithrombotic (antiplatelet or anticoagulant) therapy for the prevention of occlusive vascular disease when they developed intracerebral haemorrhage, discontinued antithrombotic therapy, and survived for 24 h. Computerised randomisation incorporating minimisation allocated participants (1:1) to start or avoid antiplatelet therapy. We followed participants for the primary outcome (recurrent symptomatic intracerebral haemorrhage) for up to 5 years. We analysed data from all randomised participants using Cox proportional hazards regression, adjusted for minimisation covariates. This trial is registered with ISRCTN (number ISRCTN71907627).

Lancet 2019; 393: 2613–23

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See **Comment** page 2567

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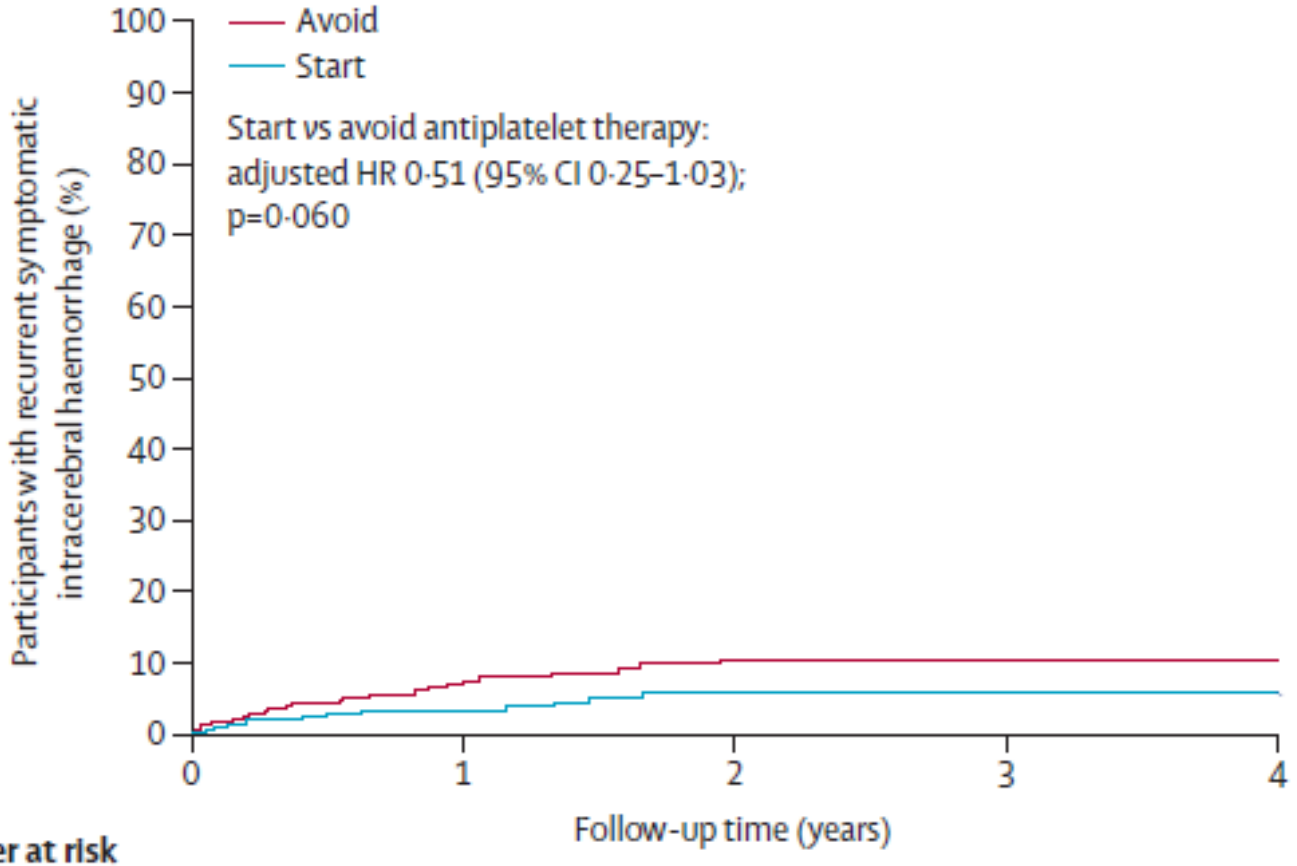


Number at risk (number of cumulative events)

Avoid	268 (0)	184 (18)	121 (23)	73 (23)	22 (23)
Start	268 (0)	190 (8)	122 (12)	72 (12)	25 (12)

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.

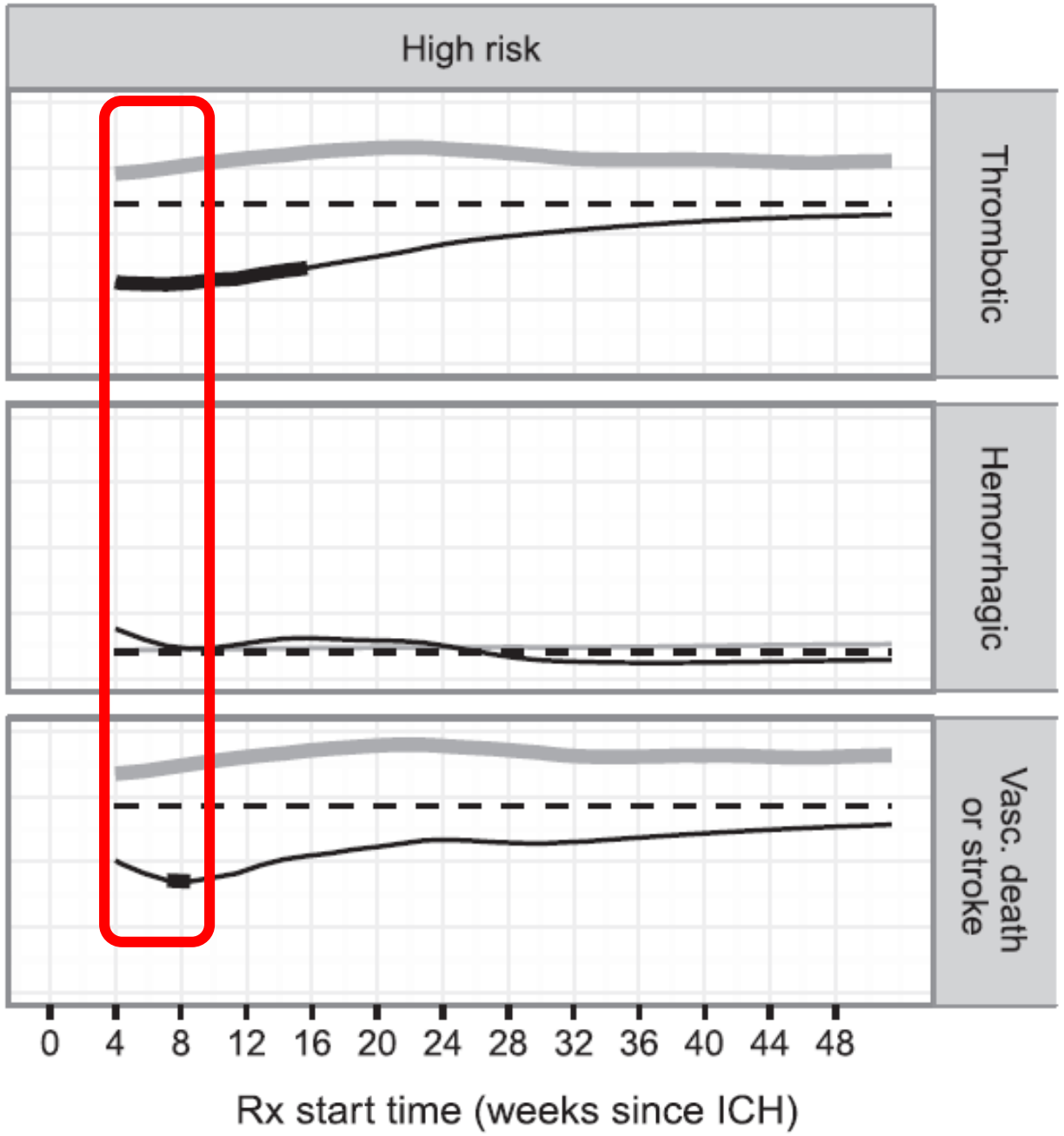
In summary, RESTART excluded all but a very modest increase in the risk of recurrent intracerebral haemorrhage with antiplatelet therapy, which seemed too small to exceed the established benefits of antiplatelet therapy for secondary prevention of major vascular events (video). Antiplatelet therapy might have reduced the recurrence of intracerebral haemorrhage. These findings provide reassurance about the use of antiplatelet therapy for similar patients in clinical practice. Ongoing randomised trials, their meta-analysis with RESTART, and an adequately powered definitive randomised trial should be done to strengthen the evidence.

Optimal Timing of Anticoagulant Treatment After Intracerebral Hemorrhage in Patients With Atrial Fibrillation

Johanna Pennlert, MD; Rosanna Overholser, PhD; Kjell Asplund, MD, PhD; Bo Carlberg, MD, PhD; Bart Van Rompaye, PhD; Per-Gunnar Wiklund, MD, PhD; Marie Eriksson, PhD

- Stroke 2017;48:314-320
- Observational study in Sweden with 2619 ICH survivors, 5759 person-years of follow-up

- Greatest benefit when anticoagulation was started 7 to 8 weeks after ICH
- Benefits similar for both men and women with high risk of cardioembolic stroke (i.e. CHA_2DS_2-VASc score of 6 for men and 7 for women)


High risk
Thrombotic
Hemorrhagic
Vasc. death or stroke
0
4
8
12
16
20
24
28
32
36
40
44
48
Rx start time (weeks since ICH)

The CAVE Score for Predicting Late Seizures After Intracerebral Hemorrhage

Elena Haapaniemi, MD; Daniel Strbian, MD; Costanza Rossi, MD; Jukka Putaala, MD; Tuulia Sipi, MB; Satu Mustanoja, MD; Tiina Sairanen, MD; Sami Curtze, MD; Jarno Satopää, MD; Reina Roivainen, MD; Markku Kaste, MD; Charlotte Cordonnier, MD; Turgut Tatlisumak, MD; Atte Meretoja, MD

(*Stroke*. 2014;45:1971-1976.)

CAVE score and risk of seizure >7 days after ICH

CAVE Score	Risk of late seizure
0	0.6%
1	3.6%
2	9.8%
3	34.8%
4	46.2%

1 point for: cortical involvement, age < 65 yrs, volume > 10 mL, early seizure within 7 days of ICH