Intracerebral Hemorrhage Management

University of Manitoba Stroke Day

October 27th, 2017

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Northern Stroke Lead CV/S SCN, AHS

Faculty/Presenter Disclosure

Faculty: Thomas Jeerakathil

Relationships with commercial interests:

Grants/Research Support: None

Speakers Bureau/Honoraria: Honoraria for 2 advisory board meetings for Bayer

Consulting Fees: None

Other: None

Mitigating Potential Bias

The advisory board meeting was to obtain my perspective on DOACs

There are no ongoing relationships or contracts with any company

Objectives

- To understand the burden of intracerebral hemorrhage
- To understand prognostic factors in ICH
- To understand management strategies in intracerebral hemorrhage

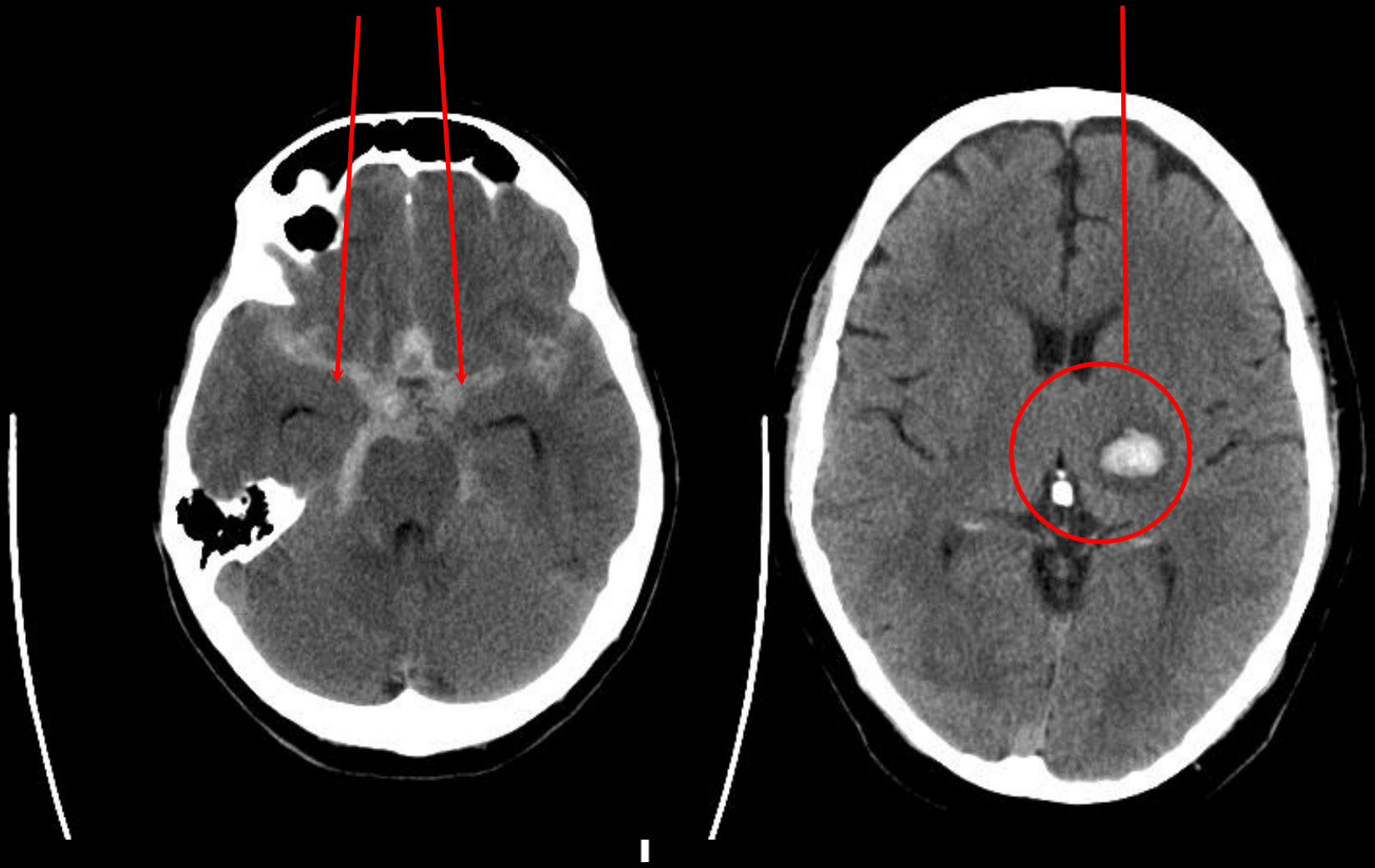
Joanne

- 50 year old lady, accountant
- History of hypertension, degree of control unclear
- Sudden onset left hemisensory loss
- Collapse with left hemiparesis
- Decreased level of consciousness
- Headache

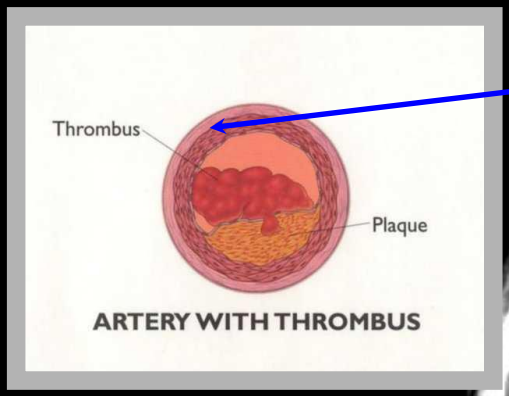
2 kinds of hemorrhagic stroke 10-20% of all stroke:

Aneurysmal Subarachnoid

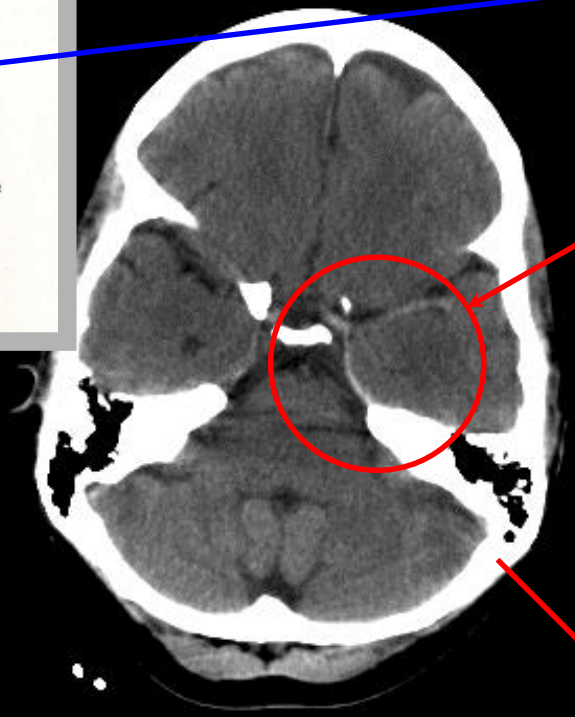
Intracerebral hematoma

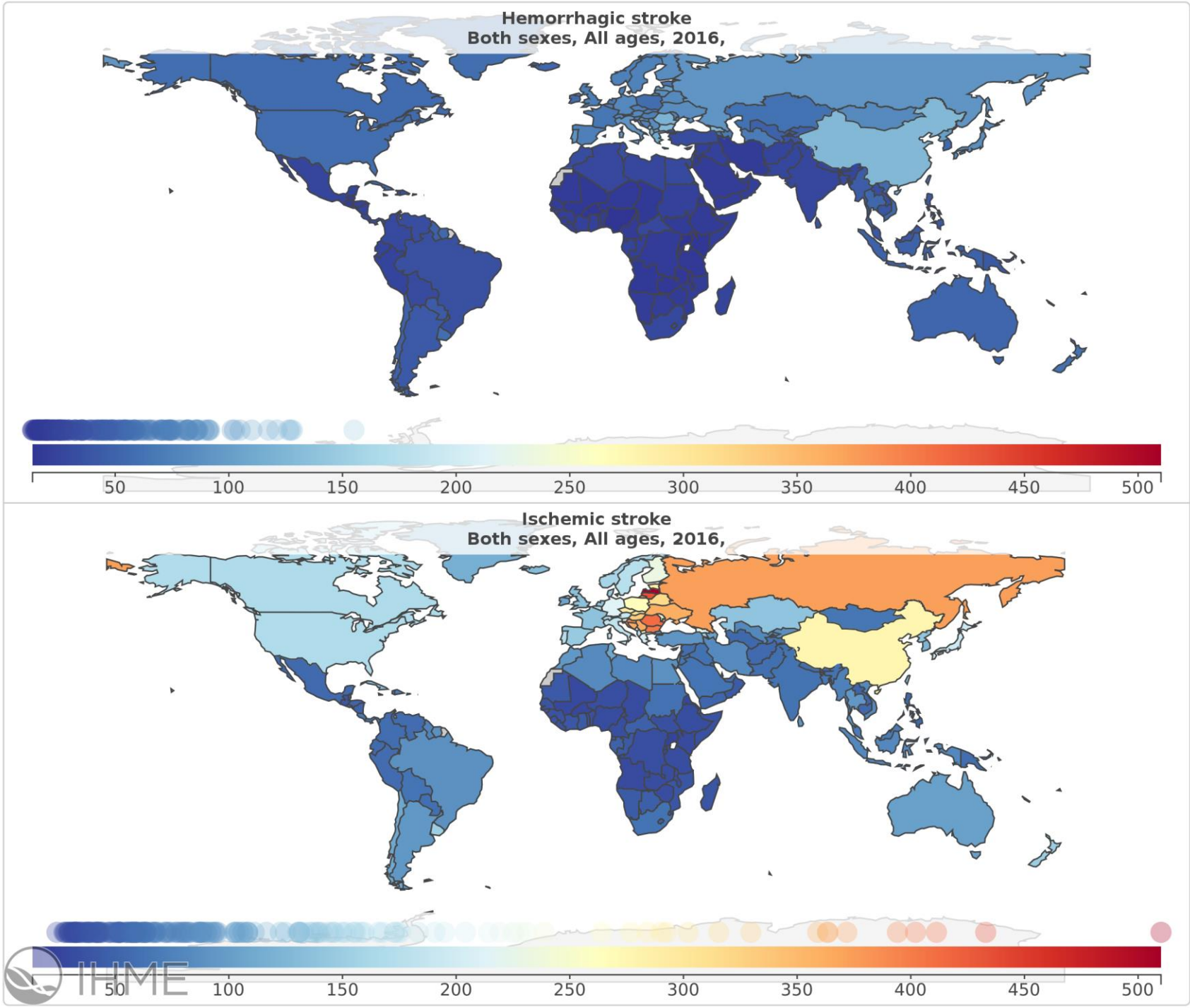


Ischemic Stroke:

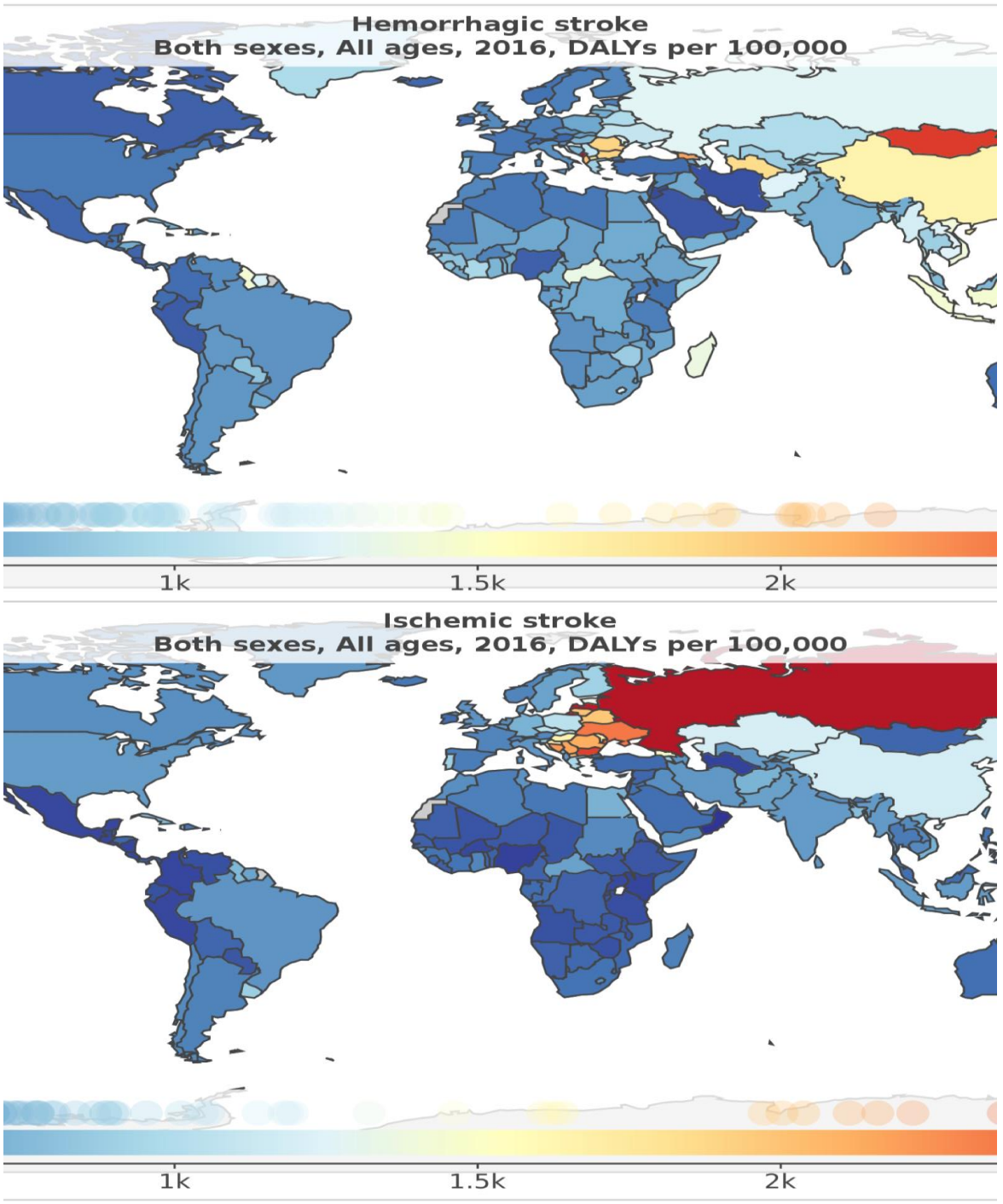


Clot visible blocking the middle cerebral artery (inside artery)



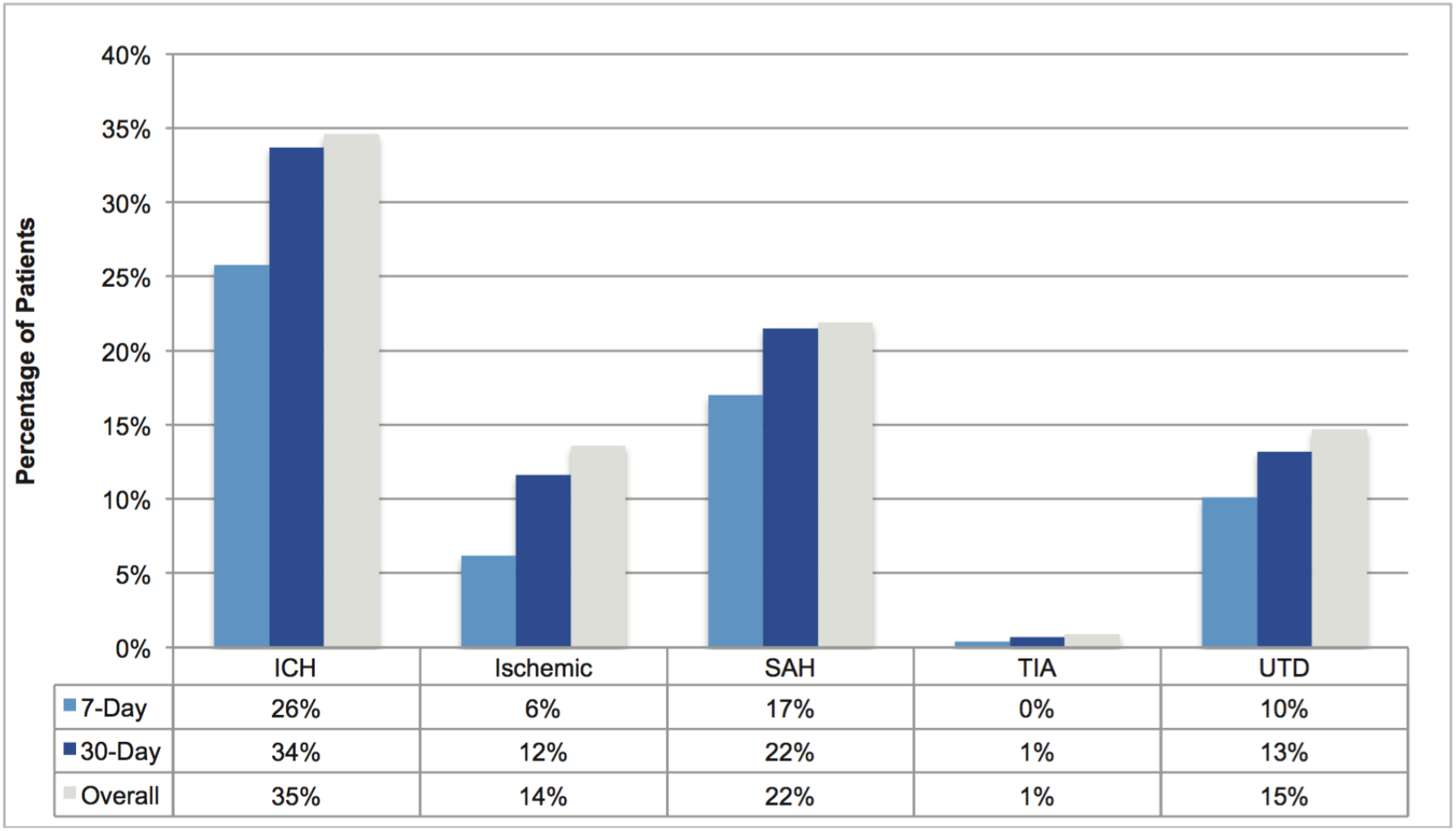

Hemorrhagic stroke
Both sexes, All ages, 2016,
50
100
150
200
250
300
350
400
450
500
Ischemic stroke
Both sexes, All ages, 2016,
50
100
150
200
250
300
350
400
450
500
IHME

Global Burden of Disease Study: Ischemic vs Hemorrhagic Stroke re DALYs



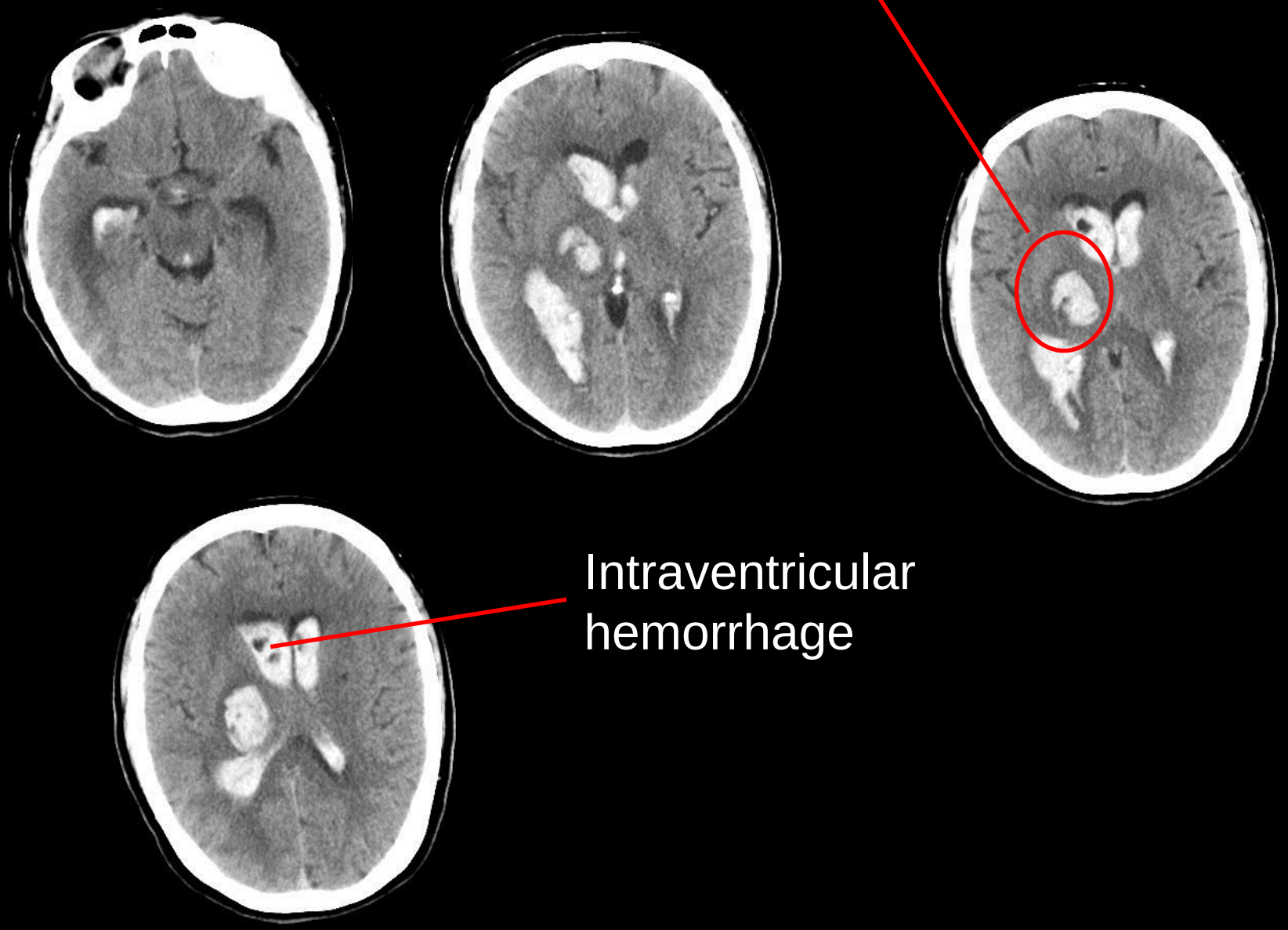
ICH – comparative mortality

Figure 4. In-Hospital Mortality Rates of Audit Patients by Stroke Type, Canada 2008/2009



	ICH	Ischemic	SAH	TIA	UTD
7-Day	26%	6%	17%	0%	10%
30-Day	34%	12%	22%	1%	13%
Overall	35%	14%	22%	1%	15%

The quality of stroke care in Canada - CSN 2011


Intracerebral hematoma
Intraventricular hemorrhage

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

The ICH Score: A Simple, Reliable Grading Scale for Intracerebral Hemorrhage

J. Claude Hemphill III, David C. Bonovich, Lavrentios Besmertis, Geoffrey T. Manley and S. Claiborne Johnston

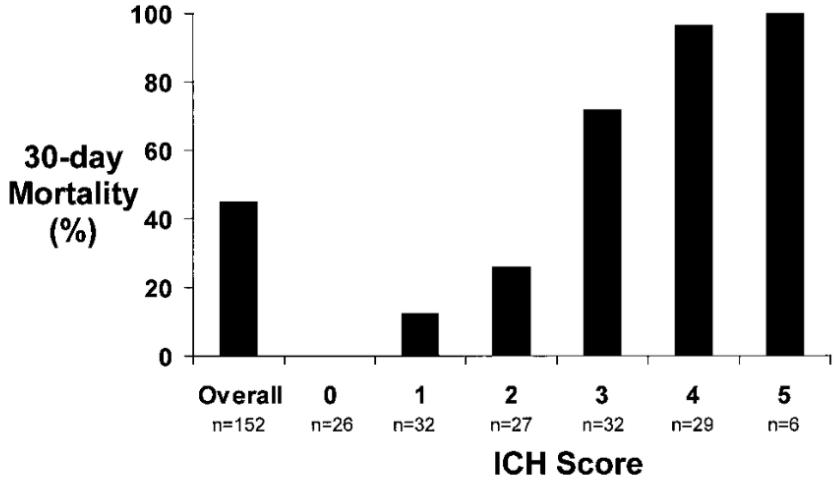
Stroke. 2001;32:891-897
doi: 10.1161/01.STR.32.4.891
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

TABLE 3. Determination of the ICH Score

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, y	
≥80	1
<80	0
Total ICH Score	0–6

GCS score indicates GCS score on initial presentation (or after resuscitation); ICH volume, volume on initial CT calculated using *ABC*/2 method; and IVH, presence of any IVH on initial CT.



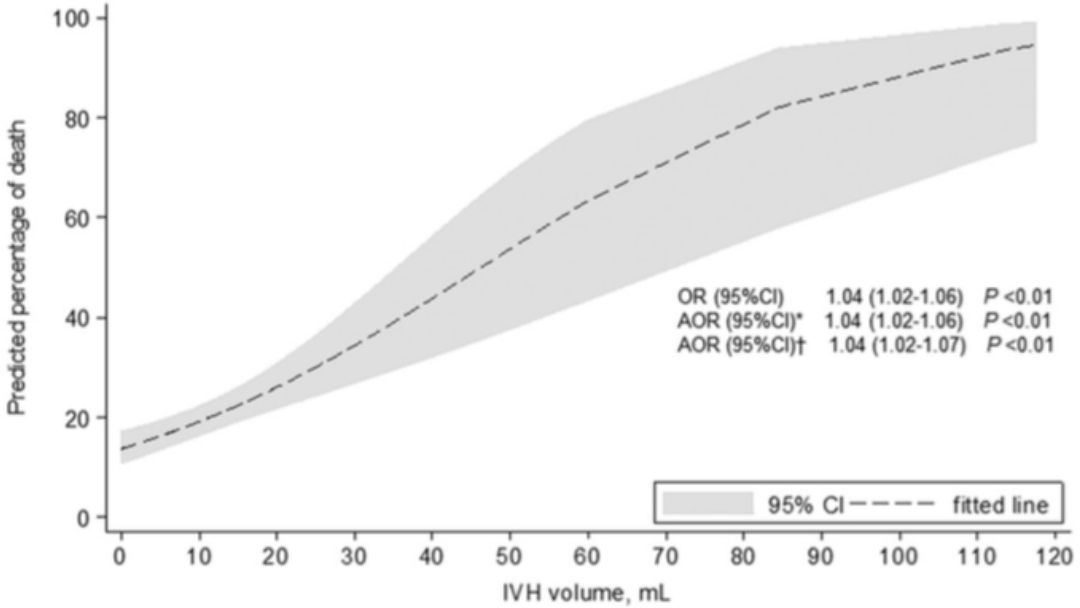
The ICH Score and 30-day mortality. Thirty-day mortality increases as ICH Score increases. No patient with an ICH Score of 0 died. All patients with an ICH Score of 5 died. No patient in the UCSF ICH cohort had an ICH Score of 6, although this would be expected to be associated with mortality.

Significance of Intraventricular Hemorrhage in Acute Intracerebral Hemorrhage

Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial Results

Edward Chan, BSc (Adv); Craig S. Anderson, MD, PhD; Xia Wang, MMed; Hisatomi Arima, MD, PhD; Anubhav Saxena, BSc (Adv); Tom J. Moullaali, MD; Emma Heeley, PhD; Candice Delcourt, MD; Guojun Wu, MD; Jinchao Wang, MD; Guofang Chen, MD; Pablo M. Lavados, MD; Christian Stapf, MD; Thompson Robinson, MD; John Chalmers, MD, PhD; Yining Huang, MD; the INTERACT2 Investigators

(*Stroke*. 2015;46:653-658. DOI: 10.1161/STROKEAHA.114.008470.)


Predicted percentage of death
100
80
60
40
20
0
0 10 20 30 40 50 60 70 80 90 100 110 120
IVH volume, mL
OR (95%CI) 1.04 (1.02-1.06) P <0.01
AOR (95%CI)* 1.04 (1.02-1.06) P <0.01
AOR (95%CI)† 1.04 (1.02-1.07) P <0.01
95% CI
fitted line

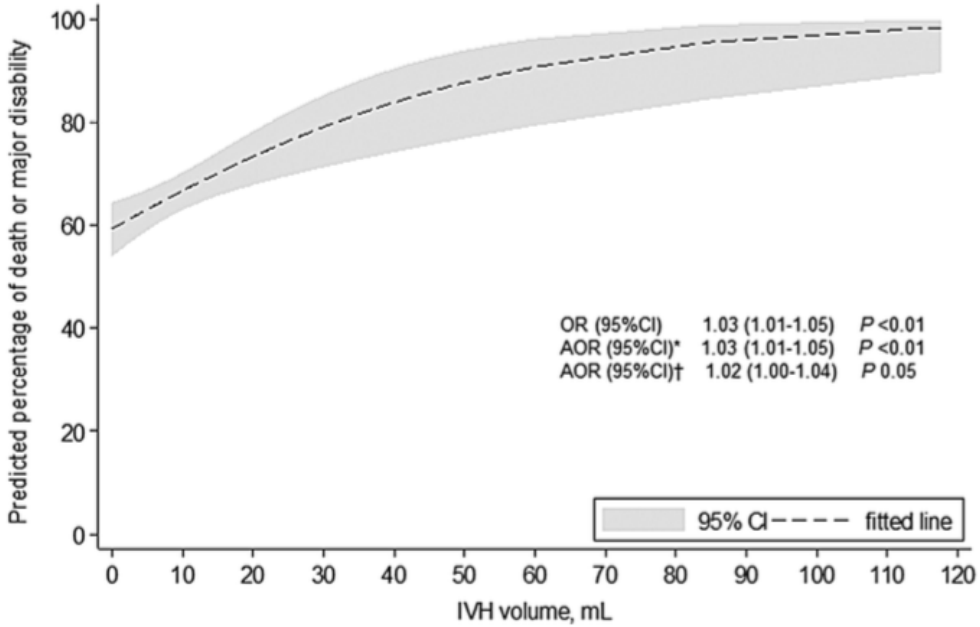

Predicted percentage of death or major disability
100
80
60
40
20
0
0 10 20 30 40 50 60 70 80 90 100 110 120
IVH volume, mL
OR (95%CI) 1.03 (1.01-1.05) P <0.01
AOR (95%CI)* 1.03 (1.01-1.05) P <0.01
AOR (95%CI)† 1.02 (1.00-1.04) P 0.05
95% CI
fitted line

Table 4. Relationship of Baseline Intraventricular Hemorrhage Volume and Outcome

Outcome/IVH Volume	n (%)	OR (95% CI)	*P* Trend	AOR (95% CI)*	*P* Trend	AOR (95% CI)†	*P* Trend
Death or major disability	…	…	<0.01	…	0.03	…	0.16
0–2.99	144 (59)	1.0	…	1.0	…	1.0	…
3.01–10.14	159 (65)	1.29 (0.89–1.86)	…	1.32 (0.86–2.02)	…	1.24 (0.80–1.93)	…
10.15–117.55	178 (73)	1.88 (1.28–2.76)	…	1.62 (1.04–2.53)	…	1.40 (0.88–2.23)	…
Death		…	<0.01	…	<0.01	…	0.02
0–2.99	31 (13)	1.0	…	1.0	…	1.0	…
3.01–10.14	49 (20)	1.72 (1.05–2.81)	…	1.84 (1.06–3.22)	…	1.62 (0.83–3.17)	…
10.15–117.55	63 (26)	2.39 (1.49–3.84)	…	2.46 (1.44–4.22)	…	2.13 (1.10–4.10)	…
Major disability	…	…	0.04	…	0.07	…	0.21
0–2.99	113 (53)	1.0	…	1.0	…	1.0	…
3.01–10.14	110 (56)	1.13 (0.77–1.68)	…	1.22 (0.79–1.91)	…	1.23 (0.78–1.94)	…
10.15–117.55	115 (64)	1.55 (1.03–2.33)	…	1.52 (0.96–2.42)	…	1.35 (0.84–2.18)	…

Data are n (%) unless otherwise stated.

AOR indicates adjusted odds ratio; CI, confidence intervals; IVH, intraventricular hemorrhage; and OR, odds ratio.

*Adjusted factors are age, sex, China region, time to computed tomographic scan, baseline blood pressure, history of heart disease, history of ischemic stroke or undifferentiated stroke, prior use of warfarin/aspirin, baseline hematoma volume and location, randomized treatment, and interaction between baseline hematoma volume and location.

†Additional adjustment for all baseline characteristics in model 1 together with and significant management variables including the use of intubation, admission to an intensive care unit, use of any hemostatic therapy, any neurosurgical intervention, a decision to withdraw active treatment and care and interactions of baseline hematoma volume and location, baseline hematoma volume and intubation, baseline hematoma volume and any neurosurgical intervention, and intubation and any neurosurgical intervention.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 20, 2013 VOL. 368 NO. 25

Rapid Blood-Pressure Lowering in Patients with Acute Intracerebral Hemorrhage

Craig S. Anderson, M.D., Ph.D., Emma Heeley, Ph.D., Yining Huang, M.D., Jiguang Wang, M.D., Christian Stapf, M.D., Candice Delcourt, M.D., Richard Lindley, M.D., Thompson Robinson, M.D., Pablo Lavados, M.D., M.P.H., Bruce Neal, M.D., Ph.D., Jun Hata, M.D., Ph.D., Hisatomi Arima, M.D., Ph.D. Mark Parsons, M.D., Ph.D., Yuechun Li, M.D., Jinchao Wang, M.D., Stephane Heritier, Ph.D., Qiang Li, B.Sc. Mark Woodward, Ph.D., R. John Simes, M.D., Ph.D., Stephen M. Davis, M.D., and John Chalmers, M.D., Ph.D. for the INTERACT2 Investigators*

N Engl J Med 2013;368:2355-65.
DOI: 10.1056/NEJMoa1214609

INTERACT 2: Randomized open blinded endpoint trial

2839 patients; primary outcome available for 2794

Similar baseline characteristics between groups

Multicentre/international

Target of <140mmHg within 1 hour in intensive group vs <180 mmHg in the comparison group

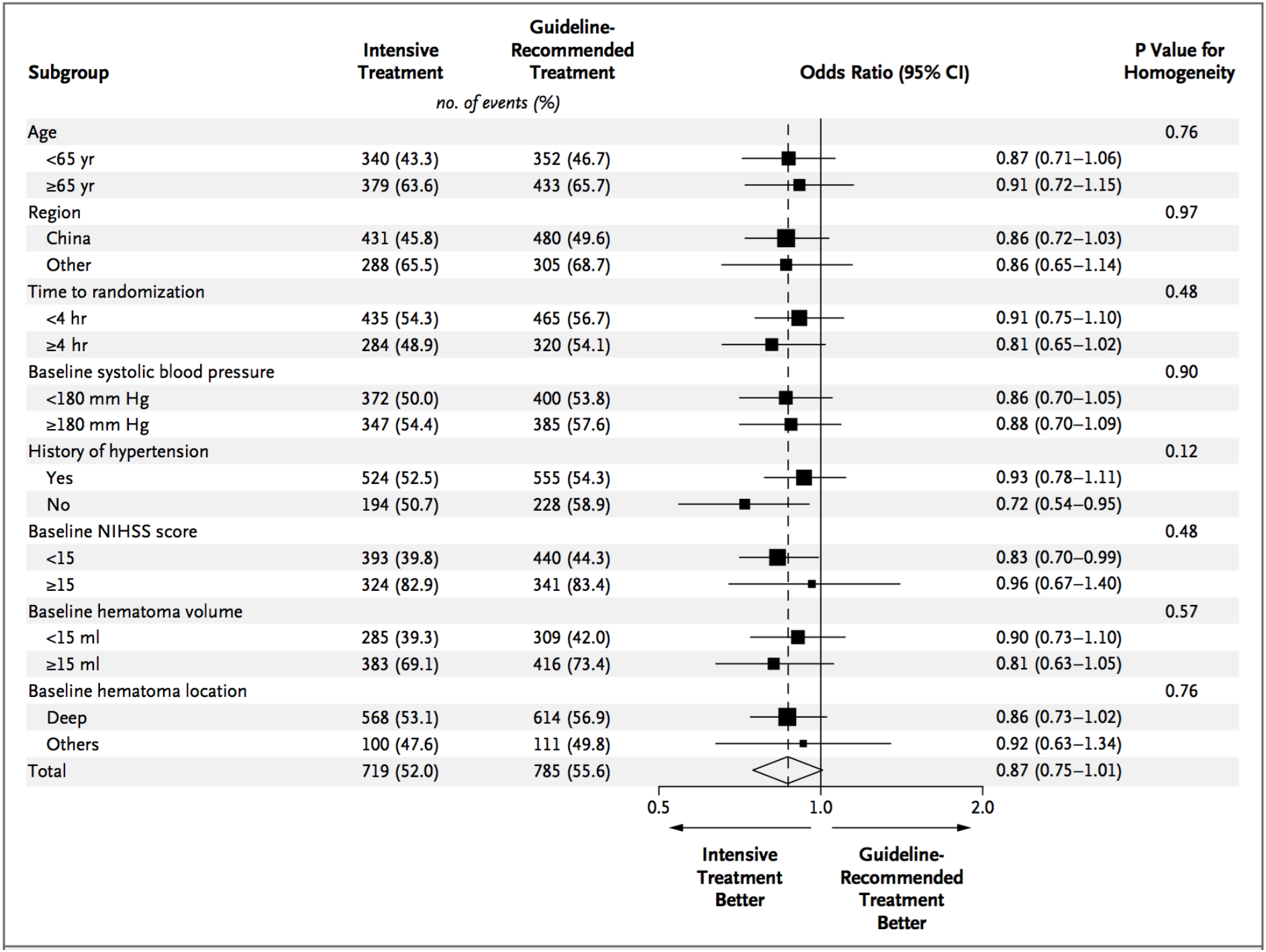
Table 2. Treatment of Patients with Intracerebral Hemorrhage.

Variable	Intensive Blood-Pressure Lowering (N=1399)	Guideline-Recommended Blood-Pressure Lowering (N=1430)	P Value
Time from ICH to start of treatment — hr			<0.001
Median	4.0	4.5	
Interquartile range	2.9–5.1	3.0–7.0	
Time from randomization to start of treatment — hr			<0.001
Median	0.1	0.3	
Interquartile range	0.0–0.39	0.0–2.8	
Blood-pressure–lowering treatment during first 24 hr — no. (%)			
Any intravenous treatment	1260 (90.1)	613 (42.9)	<0.001
Use of a single intravenous agent	849 (60.7)	421 (29.4)	<0.001
Type of intravenous agent used			
Alpha-adrenergic antagonist, such as urapidil	454 (32.5)	191 (13.4)	
Calcium-channel blocker, such as nicardipine or nimodipine	227 (16.2)	122 (8.5)	
Combined alpha- and beta-blocker, such as labetalol	202 (14.4)	83 (5.8)	
Nitroglycerin	209 (14.9)	59 (4.1)	
Diuretic, such as furosemide	174 (12.4)	94 (6.6)	
Nitroprusside	169 (12.1)	28 (2.0)	
Hydralazine	82 (5.9)	50 (3.5)	
Other	85 (6.1)	44 (3.1)	

Table 3. Primary, Secondary, and Safety Outcomes at 90 Days.*

Variable	Intensive Blood-Pressure Lowering (N=1399)	Guideline-Recommended Blood-Pressure Lowering (N=1430)	Odds Ratio (95% CI)	P Value
Primary outcome: death or major disability — no./total no. (%)†	719/1382 (52.0)	785/1412 (55.6)	0.87 (0.75–1.01)	0.06
Secondary outcomes				
Score on the modified Rankin scale — no./total no. (%)‡			0.87 (0.77–1.00)	0.04
0: No symptoms at all	112/1382 (8.1)	107/1412 (7.6)		
1: No substantive disability despite symptoms	292/1382 (21.1)	254/1412 (18.0)		
2: Slight disability	259/1382 (18.7)	266/1412 (18.8)		
3: Moderate disability requiring some help	220/1382 (15.9)	234/1412 (16.6)		
4: Moderate–severe disability requiring assistance with daily living	250/1382 (18.1)	268/1412 (19.0)		
5: Severe disability, bed-bound and incontinent	83/1382 (6.0)	113/1412 (8.0)		
6: Death by 90 days	166/1382 (12.0)	170/1412 (12.0)		
Death — no./total no. (%)	166/1394 (11.9)	170/1421 (12.0)	0.99 (0.79–1.25)	0.96

Health-related quality of life§				
Problems with mobility — no./total no. (%)	767/1203 (63.8)	821/1231 (66.7)	0.88 (0.74–1.04)	0.13
Problems with self-care — no./total no. (%)	563/1202 (46.8)	635/1230 (51.6)	0.83 (0.70–0.97)	0.02
Problems with usual activities — no./total no. (%)	731/1203 (60.8)	814/1231 (66.1)	0.79 (0.67–0.94)	0.006
Problems with pain or discomfort — no./total no. (%)	477/1197 (39.8)	552/1227 (45.0)	0.81 (0.69–0.95)	0.01
Problems with anxiety or depression — no./total no. (%)	406/1192 (34.1)	463/1220 (38.0)	0.84 (0.72–1.00)	0.05
Overall health utility score	0.60±0.39	0.55±0.40		0.002
Living in residential care facility — no./total no. (%)	108/1222 (8.8)	114/1248 (9.1)	0.96 (0.73–1.27)	0.80
Duration of initial hospitalization — days				0.43
Median	20	19		
Interquartile range	12–35	11–33		


Subgroup
Intensive Treatment
Guideline-Recommended Treatment
Odds Ratio (95% CI)
P Value for Homogeneity
no. of events (%)
Age 0.76
<65 yr 340 (43.3) 352 (46.7) 0.87 (0.71–1.06)
≥65 yr 379 (63.6) 433 (65.7) 0.91 (0.72–1.15)
Region 0.97
China 431 (45.8) 480 (49.6) 0.86 (0.72–1.03)
Other 288 (65.5) 305 (68.7) 0.86 (0.65–1.14)
Time to randomization 0.48
<4 hr 435 (54.3) 465 (56.7) 0.91 (0.75–1.10)
≥4 hr 284 (48.9) 320 (54.1) 0.81 (0.65–1.02)
Baseline systolic blood pressure 0.90
<180 mm Hg 372 (50.0) 400 (53.8) 0.86 (0.70–1.05)
≥180 mm Hg 347 (54.4) 385 (57.6) 0.88 (0.70–1.09)
History of hypertension 0.12
Yes 524 (52.5) 555 (54.3) 0.93 (0.78–1.11)
No 194 (50.7) 228 (58.9) 0.72 (0.54–0.95)
Baseline NIHSS score 0.48
<15 393 (39.8) 440 (44.3) 0.83 (0.70–0.99)
≥15 324 (82.9) 341 (83.4) 0.96 (0.67–1.40)
Baseline hematoma volume 0.57
<15 ml 285 (39.3) 309 (42.0) 0.90 (0.73–1.10)
≥15 ml 383 (69.1) 416 (73.4) 0.81 (0.63–1.05)
Baseline hematoma location 0.76
Deep 568 (53.1) 614 (56.9) 0.86 (0.73–1.02)
Others 100 (47.6) 111 (49.8) 0.92 (0.63–1.34)
Total 719 (52.0) 785 (55.6) 0.87 (0.75–1.01)
0.5
1.0
2.0
Intensive Treatment Better
Guideline-Recommended Treatment Better

INTERACT 2 Summary

- Failed to show an effect of BP lowering in preventing death or disability in it's primary outcome
- However mRS ordinal shift analysis was positive for a benefit (modest)
- Some improvements in HRQOL (approx 5% better)
- Treatment group attained only mean 150mmg at 1 hour (33% achieve <140mmHg) vs 164mmHg in the comparison group

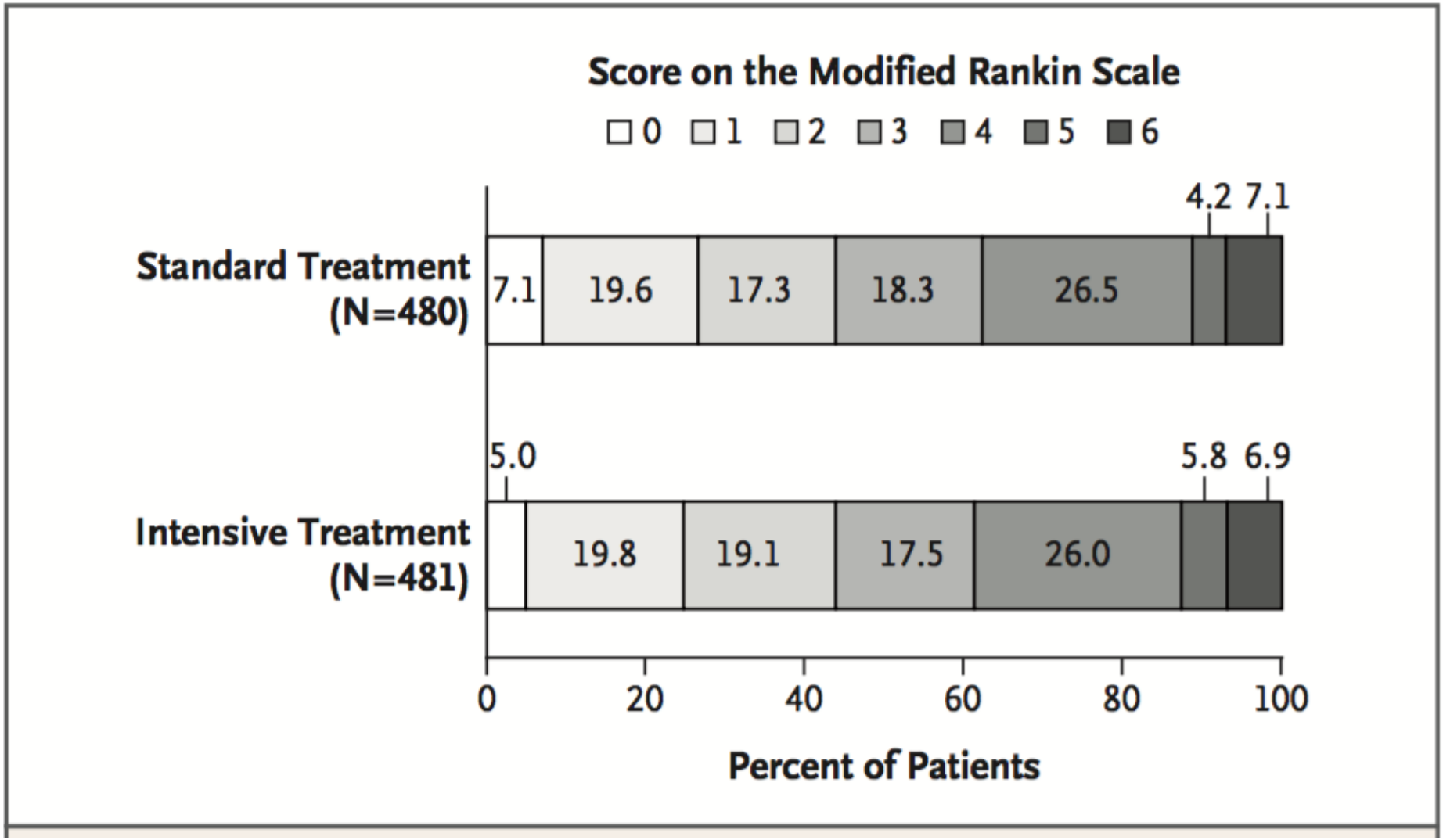
ORIGINAL ARTICLE

Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage

Adnan I. Qureshi, M.D., Yuko Y. Palesch, Ph.D., William G. Barsan, M.D., Daniel F. Hanley, M.D., Chung Y. Hsu, M.D., Renee L. Martin, Ph.D., Claudia S. Moy, Ph.D., Robert Silbergleit, M.D., Thorsten Steiner, M.D., Jose I. Suarez, M.D., Kazunori Toyoda, M.D., Ph.D., Yongjun Wang, M.D., Haruko Yamamoto, M.D., Ph.D., and Byung-Woo Yoon, M.D., Ph.D., for the ATACH-2 Trial Investigators and the Neurological Emergency Treatment Trials Network*

N Engl J Med 2016;375:1033-43.
DOI: 10.1056/NEJMoa1603460

- Randomized open two group blinded outcome trial
- 1000 patients; IV BP lowering with nicardipine based regimen
- Target blood pressure 110-139mmHg vs 140-179 mmHg



No significant benefit nor a trend

Table 2. Primary, Secondary, and Safety Outcomes, According to Treatment Group.*

Outcome	Intensive Treatment (N=500)	Standard Treatment (N=500)
Primary outcome: death or disability — no./total no. (%)‡	186/481 (38.7)	181/480 (37.7)
Hematoma expansion — no./total no. (%)§	85/450 (18.9)	104/426 (24.4)
Neurologic deterioration within 24 hr — no. (%)¶	55 (11.0)	40 (8.0)
Treatment-related serious adverse event within 72 hr — no. (%)‖	8 (1.6)	6 (1.2)
Any serious adverse event within 3 mo — no. (%)	128 (25.6)	100 (20.0)

Non significant trend towards reduced hematoma expansion

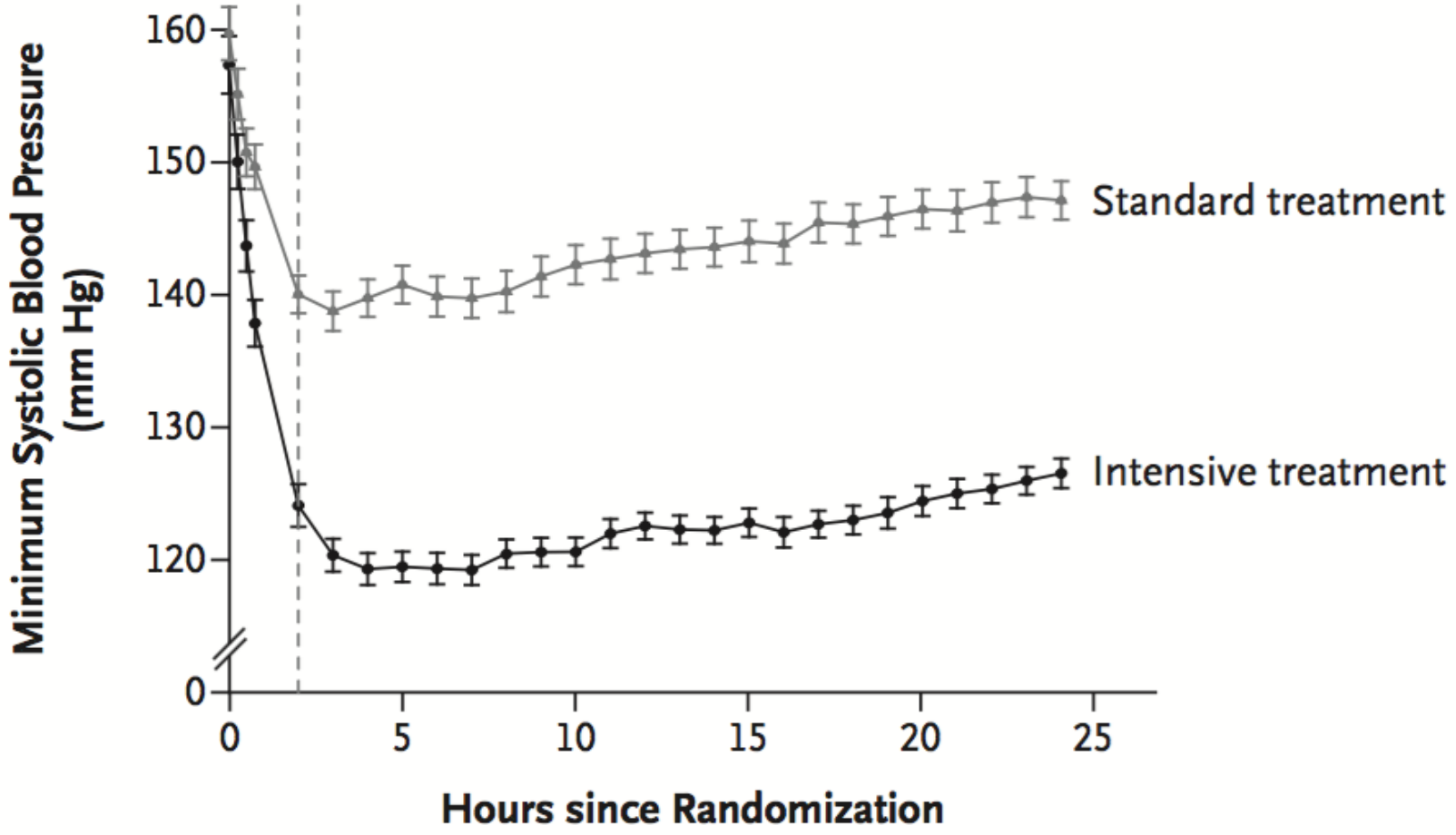
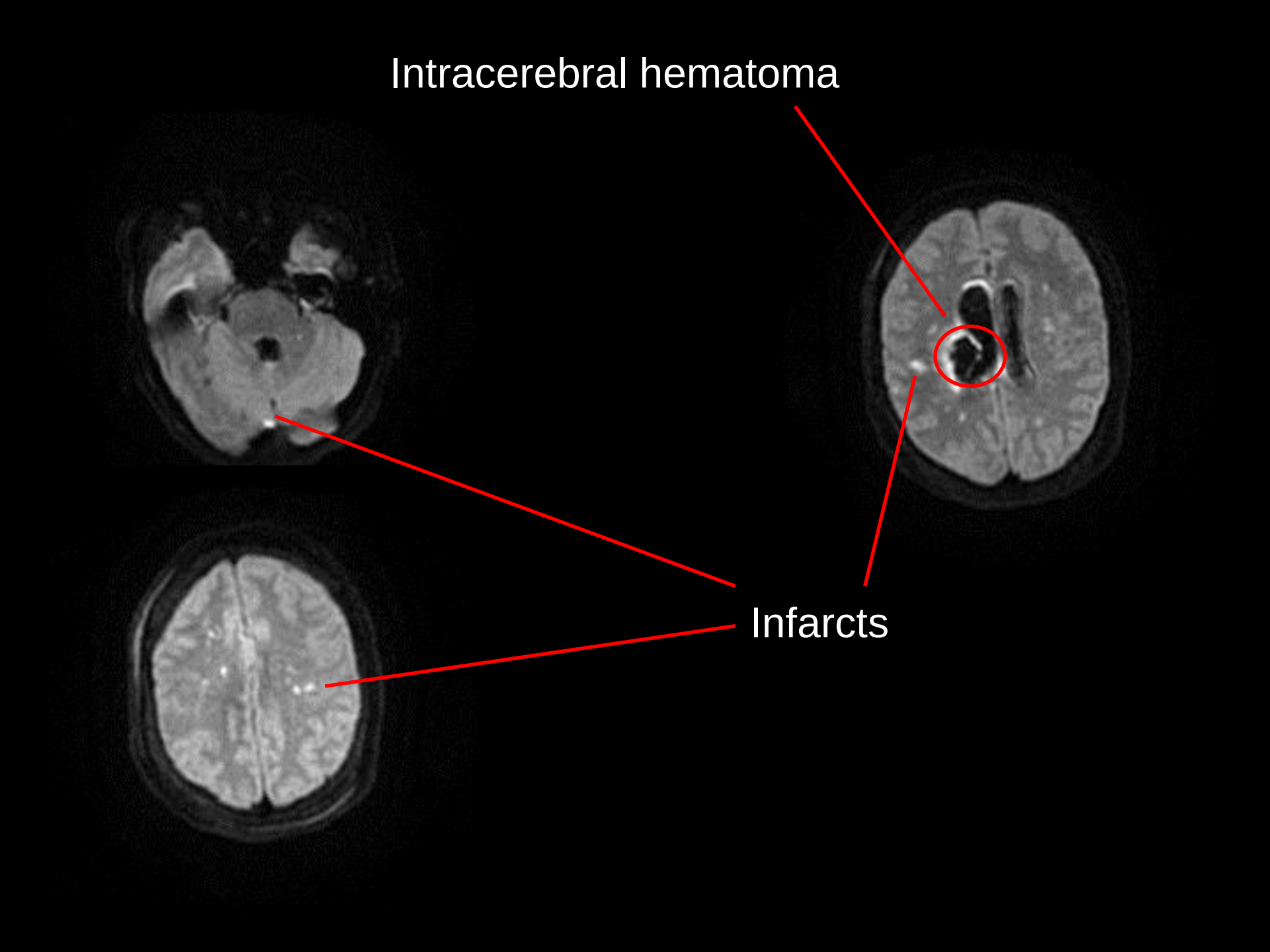


Figure 1. Mean Hourly Minimum Systolic Blood Pressure during the First 24 Hours after Randomization, According to Treatment Group.

The dashed vertical line indicates 2 hours, and I bars 95% confidence intervals.

Joanne

- An EVD was placed
- Blood pressure spiked to extremely high levels (>240 systolic)
- Aggressive antihypertensive therapy initiated
- WBCs in CSF (? ventriculitis)
- Antibiotics started
- Some decreased movement of right arm
- MRI obtained

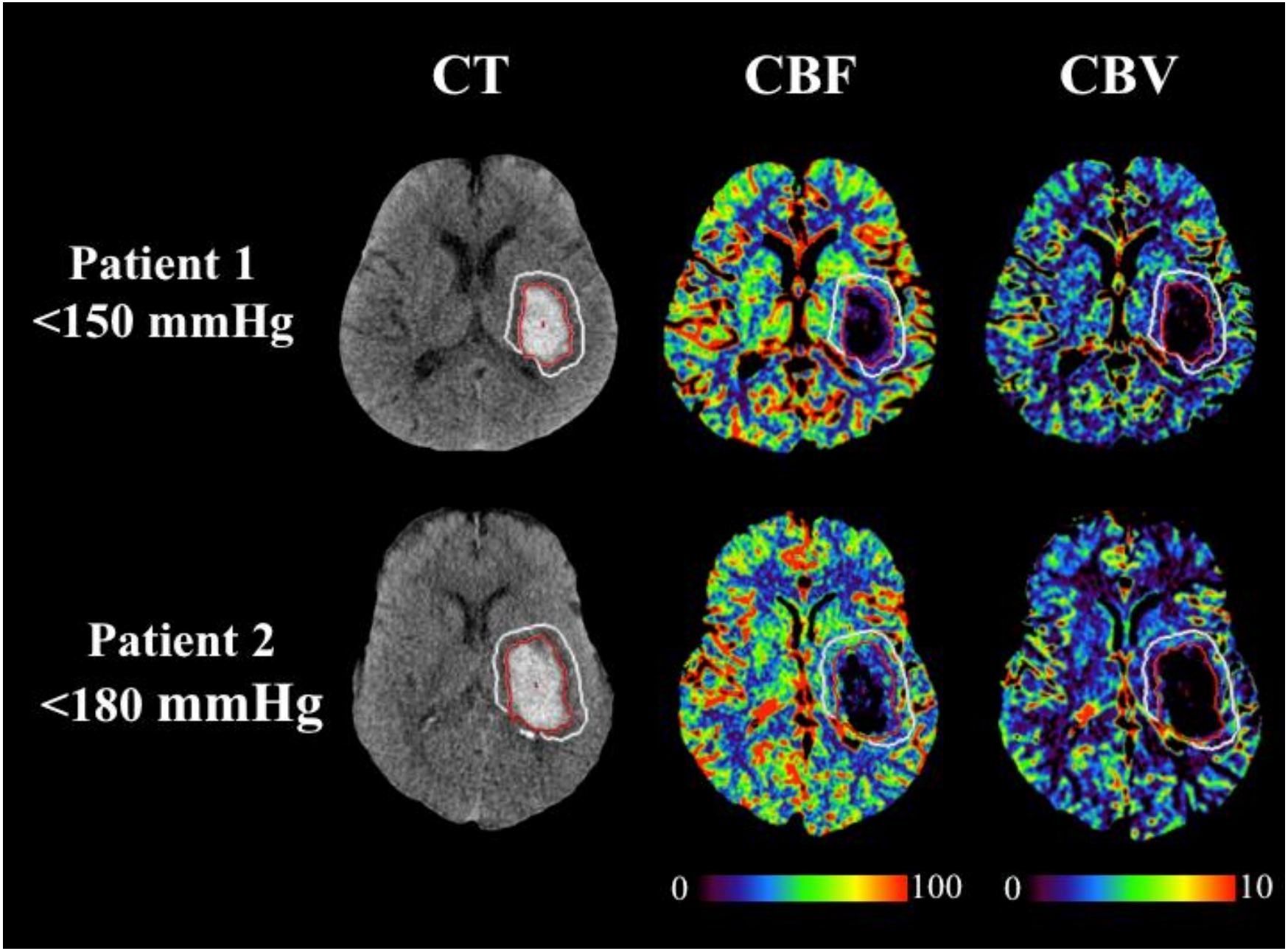

Intracerebral hematoma
Infarcts

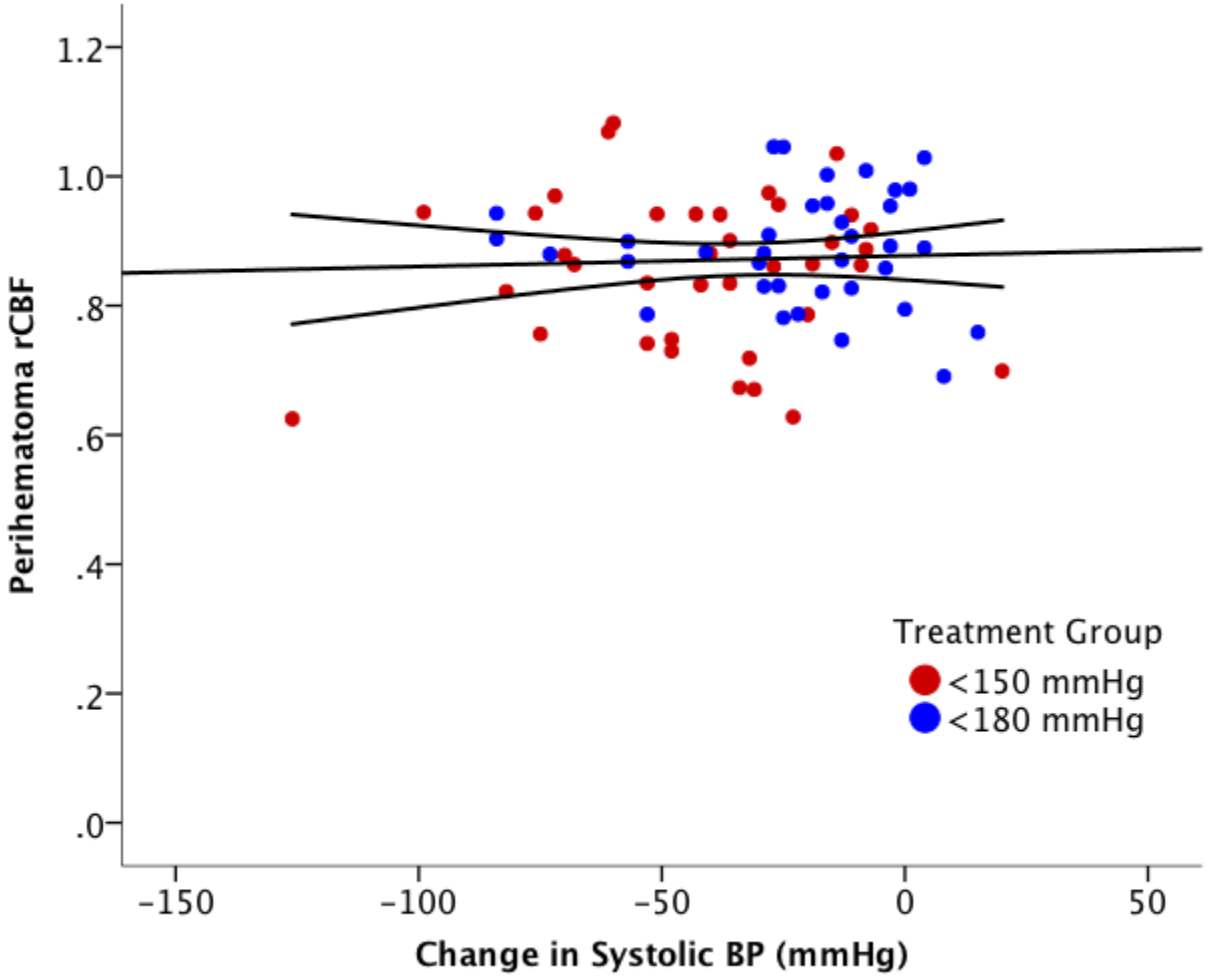
Ischemic lesions in ICH

- Small
- Often remote from ICH
- Origin unclear (arterial narrowing in response to hemorrhage? hemodynamic?)
- May predict a worse prognosis

The Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial: ICH ADAPT

	<150 mmHg Target (n=39)	<180 mmHg Target (n=36)	p
IV Antihypertensive Therapy Administered	100%	44 %	<0·0001
Mean Labetalol Dose (mg)	33·9 ± 26·5	11·4 ± 21·7	<0·0001
Mean Hydralazine Dose (mg)	10·3 ± 14·6	1·5 ± 4·9	0·0006
Enalapril Administered	8 (21 %)	1 (3 %)	0·03
Systolic BP at time of CTP (mmHg)	140 ± 19	162 ± 12	<0·0001
Diastolic BP at time of CTP (mmHg)	71 ± 14	83 ± 12	<0·0001
MAP at time of CTP (mmHg)	94 ± 14	109 ± 10	<0·0001

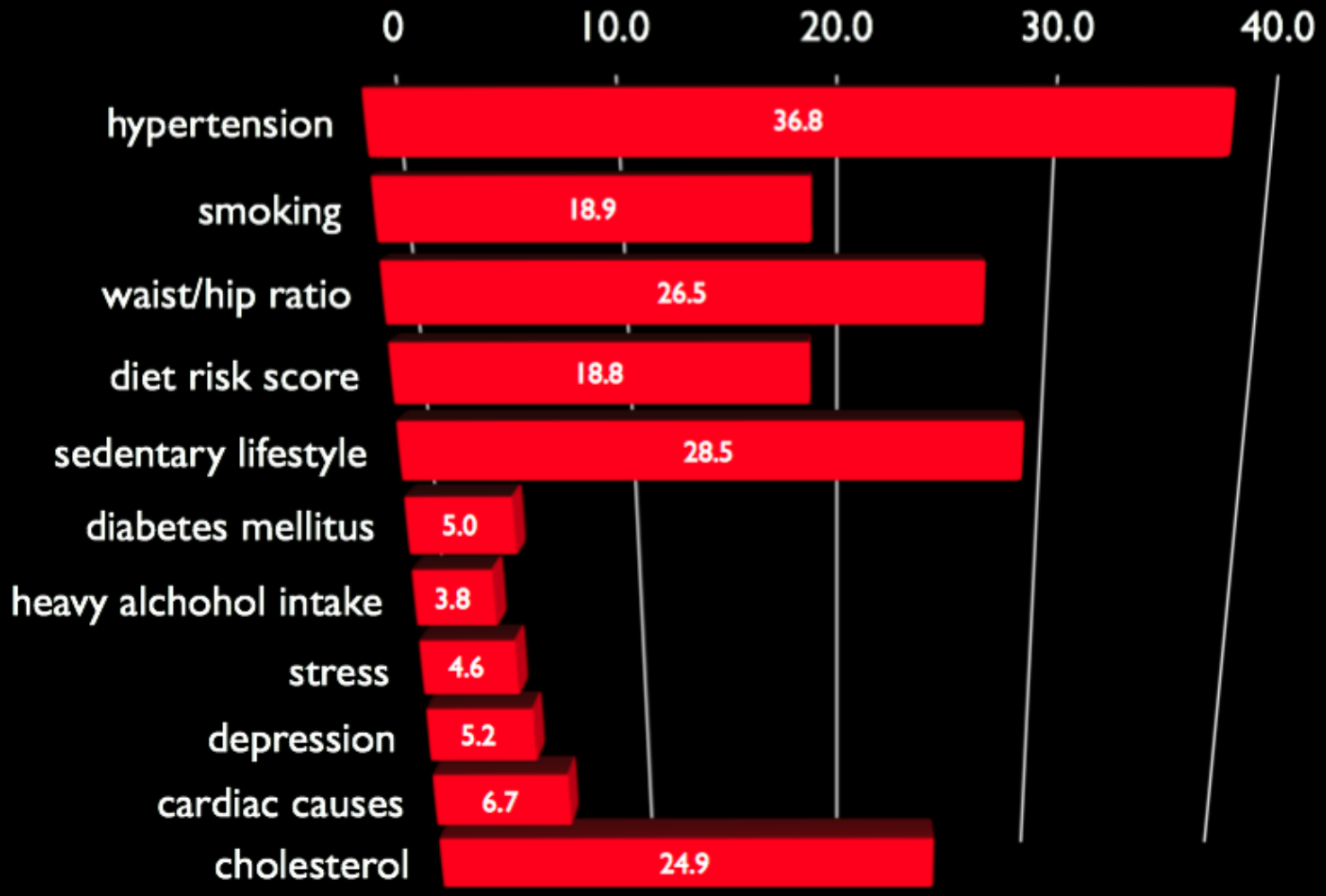

CT
CBF
CBV
Patient 1
<150 mmHg
Patient 2
<180 mmHg
0
100
0
10


1.2
1.0
.8
.6
.4
.2
.0
Perihematoma rCBF
−150
−100
−50
0
50
Change in Systolic BP (mmHg)
Treatment Group
<150 mmHg
<180 mmHg

Ineffective therapies in primary ICH

- Surgical evacuation
  - Can be life saving – lobar hemorrhages
  - No reductions in disability
- Hemostatic therapy
  - Factor 7a
- Steroids

10 Risk Factors Explain 90% of Stroke Risk



Interstroke O'Donnell et al;
Lancet 2010: 376; 112–23

Cholesterol Levels and Risk of Hemorrhagic Stroke

A Systematic Review and Meta-Analysis

Xiang Wang, MD*; Yan Dong, MD*; Xiangqian Qi, MD*; Chengguang Huang, MD; Lijun Hou, MD

- Background of increased ICH risk with low serum cholesterol levels in past epidemiological studies
- SPARCL Trial showed that patients with ICH who received statin therapy had an increased risk of recurrent ICH
- Meta-analysis of over 23 prospective studies; 1.4 million patients
- Examined serum cholesterol concentrations and risk for hemorrhagic stroke

(*Stroke*. 2013;44:1833-1839.)

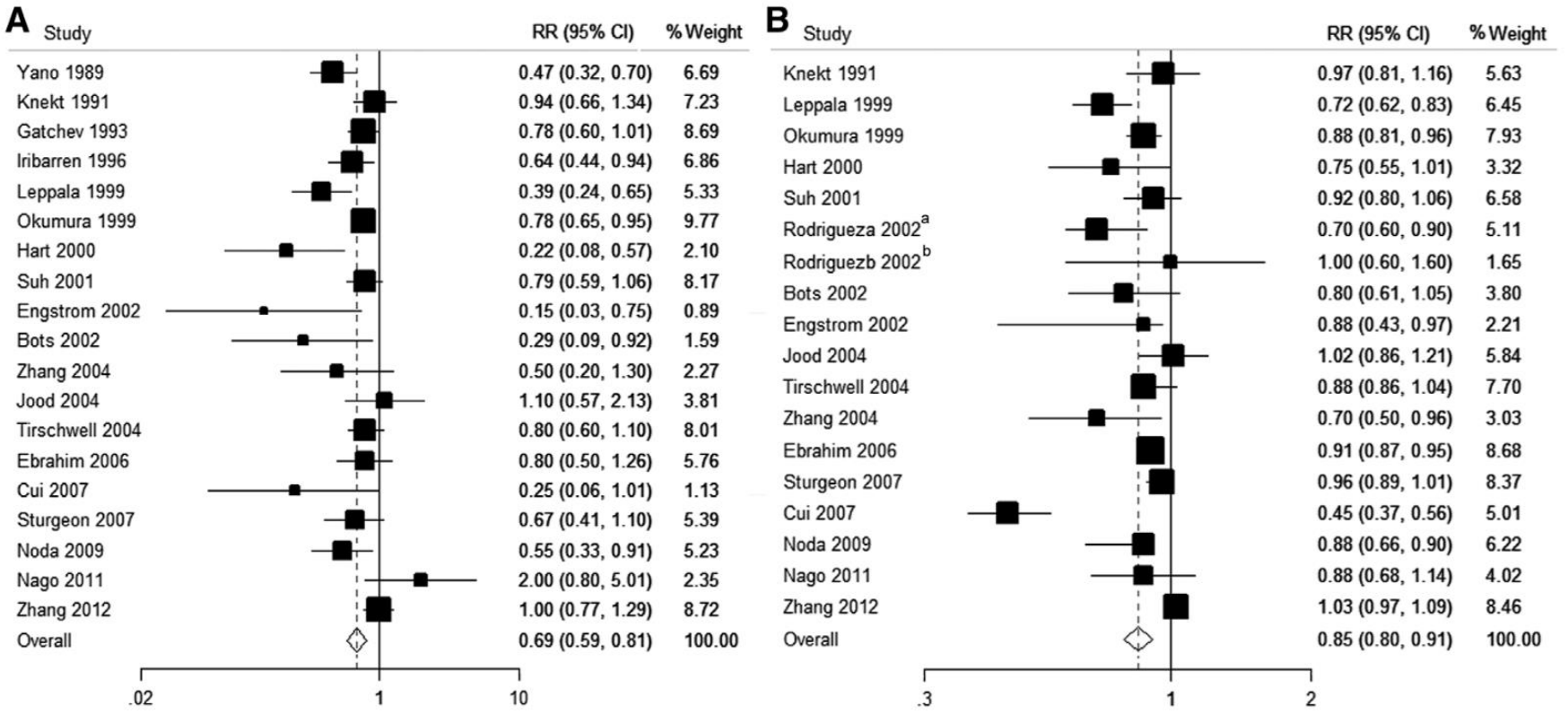


Figure 2. Forest plots of total cholesterol levels and risk of hemorrhagic stroke. **A**, High vs low analysis. **B**, Per 1 mmol/L increment. CI indicates confidence interval; and RR, risk ratio.

- Across studies high vs low (on left) had lower risk
- Per every 1 mmol/L increase (on right) lower risk

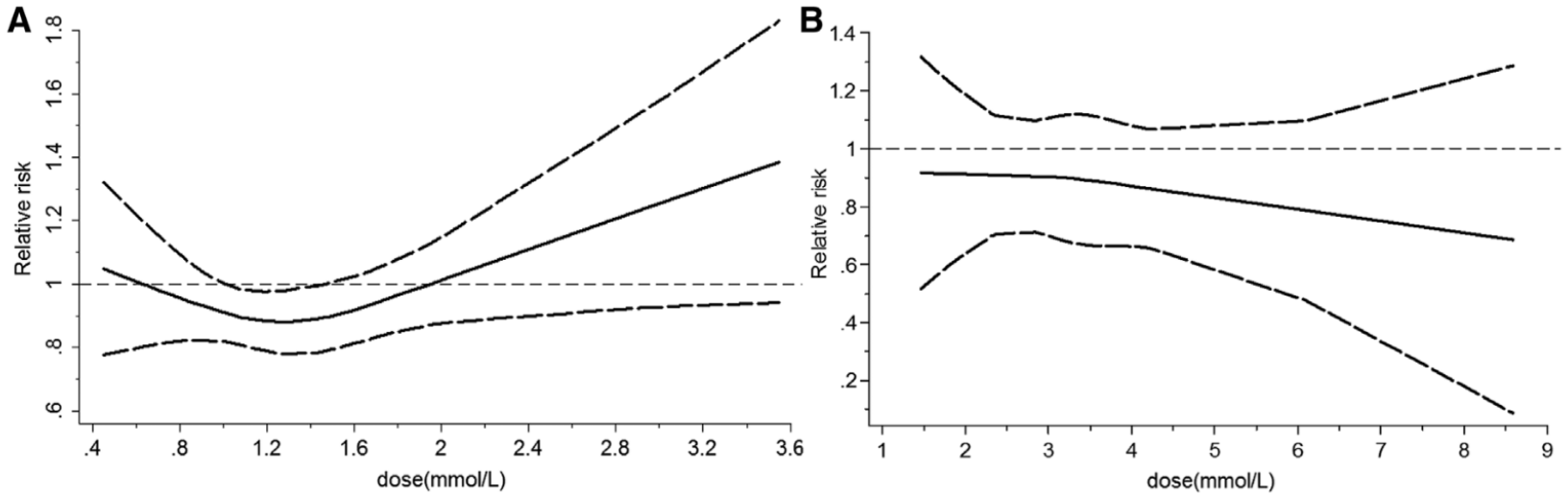


Figure 5. Relative risk (solid line) with 95% confidence interval (long dashed lines) for the associations of high-density lipoprotein cholesterol level (**A**) and low-density lipoprotein cholesterol level (**B**) with risk of hemorrhagic stroke in a restricted cubic spline random-effects model.

- Increased risk with lower LDL (inverse relationship)
- Incresed risk with higher HDL (direct relationship)

Take home for lipids and ICH

- There are substantial benefits from avoiding high LDL or low HDL for death, ischemic stroke and coronary disease which is 5-10 times as prevalent as ICH
- For patients with established atherosclerotic cardiovascular disease and past ICH you could still use statins
- For patients with ICH and no other vascular disease avoid statins in general

Background – what is a stroke unit?

- Stroke unit
  - Geographically clustered set of beds within a hospital
  - Staff/physician specialization and training in stroke
  - Multidisciplinary assessment/ communication
    - integration of care
  - Early access to rehabilitation services
  - Involvement of caregivers, family, and patients in the process of care delivery
  - Adherence to best medical practices in stroke care
    - Standardized ordersets

Is organized stroke care effective?

- Stroke unit vs alternative
  - Death –OR 0.82 (0.71-0.94; P< 0.005); 18 % RRR;
    - 4.1% ARR; NNT to prevent 1 death = 25
  - Death/institutional care – OR 0.80 (0.71, 0.90; p = 0.0002)
    - 4.1% ARR; NNT to prevent 1 death/inst care = 25
  - Death/dependency – OR 0.78 (0.68, 0.89; p = 0.0003)
    - 4.7% ARR; NNT to prevent 1 death/dep = 21
- Stroke unit vs gen medical wards
  - Death/dependency – OR 0.73 (0.63, 0.85)
    - 5.1% ARR; NNT to prevent 1 death/dep = 19.6
- Benefits may last out to 5 years (smaller #s analyzed)

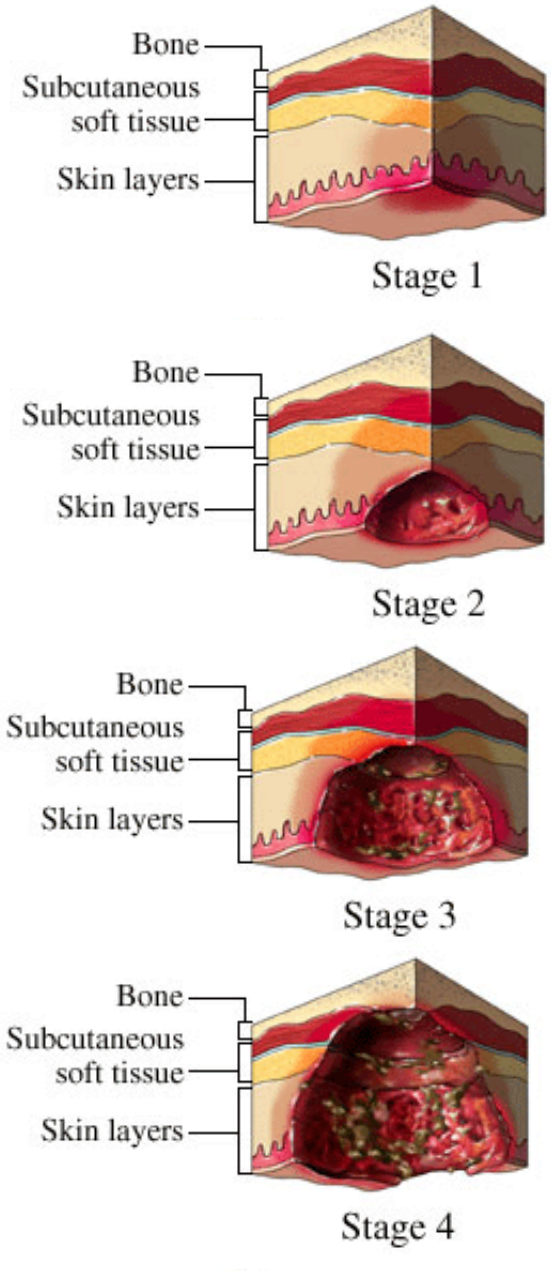
DVT/PE

- Common
- 10% of stroke fatalities due to PE
- Risk factors for DVT
  - Old age
  - Leg Paralysis
  - Atrial Fib
  - Hypercoagulable state/dehydration

SC Heparin/Enoxaparin (even 48 hours after stable ICH!), Compression Boots Mobilize

Aspiration Pneumonia

- Swallowing Dysfunction Common in Acute Stroke – pneumonia in 5%
- Bedside swallowing screens in anyone with any facial weakness or dysarthria or significant other neuro deficits (TORBSST or similar)
- Full swallowing assessments in those who fail the screening tests
- Head of bed to 30^{o}



Pressure ulcers

•A nasty complication best avoided

•Risk factors include malnutrition, incontinence, stroke severity, inability to ambulate, inability to shift in bed

•Start with reddish areas that resolve after pressure is relieved and then progressive skin breakdown occurs

Avoiding pressure ulcers

•Turning patient q 2 hours

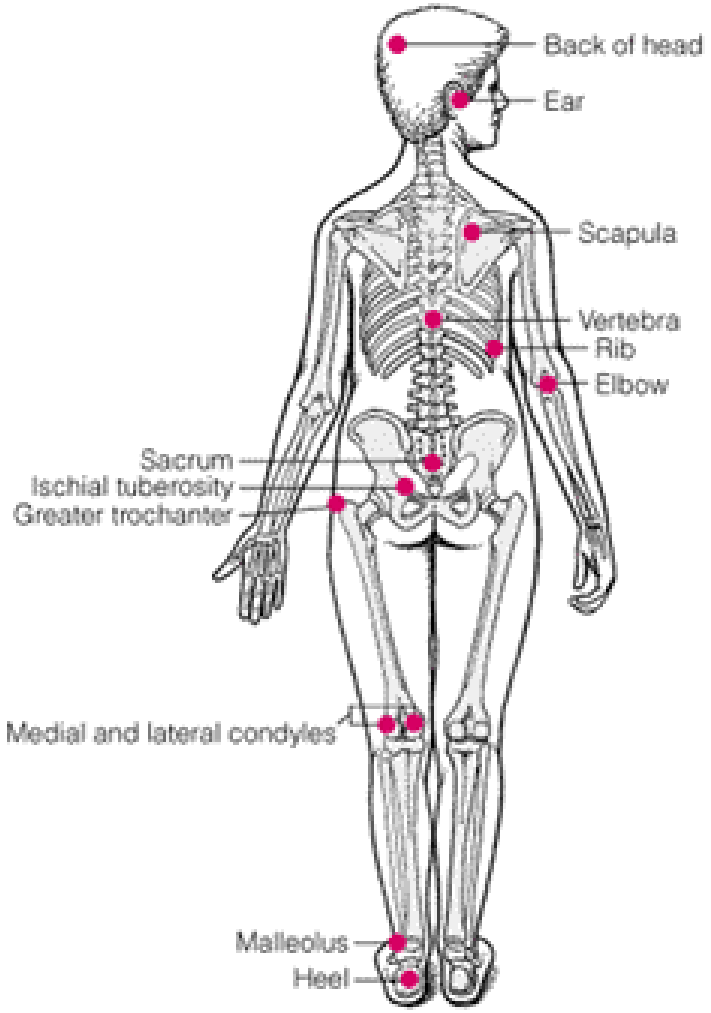
•Soft liners or air mattresses for early skin changes

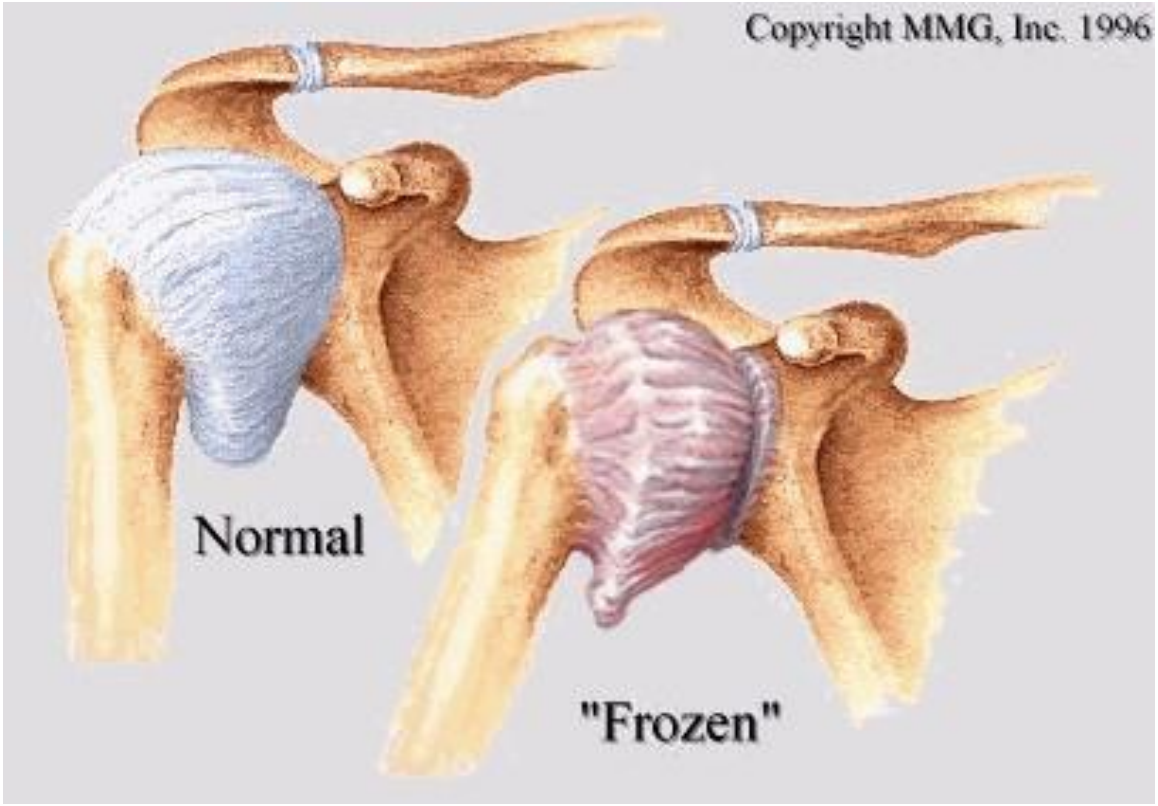
•Patient should shift position q 15 minutes

•Avoiding malnutrition

•Cleanliness, particularly if incontinent

•Vigilance for early areas of redness or induration





Frozen shoulder (Adhesive capsulitis, periarthritis humeroscapularis). In stroke, shoulder pain reported by 17% at 7days; 23% by 6 months.

Take Home Points

- Intracerebral hemorrhage remains a severe disease
- Blood pressure lowering is safe and may have a mild benefit on disability
- Prevention is critical
- Stroke unit care is an important intervention
- Future research is critical

Canada's First Stroke Ambulance

Thank-you