ATACH II Trial Update: Neurological Emergency Treatment Trials Network Investigators Meeting

Chicago, October 21st, 2013

Adnan I. Qureshi MD for ATACH II investigators

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

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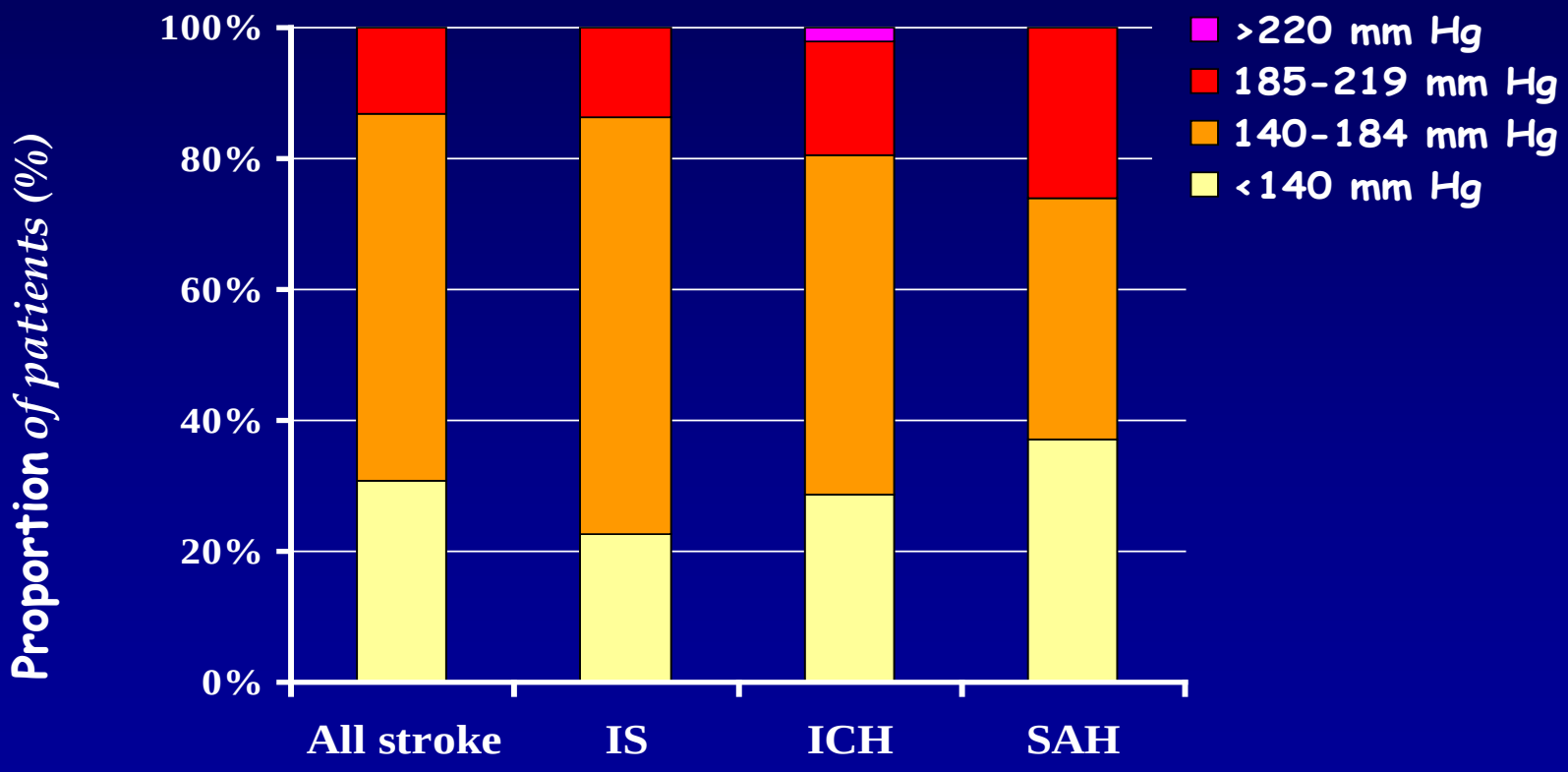
BACKGROUND

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Initial Systolic Blood Pressure in Patients Presenting to the Emergency Room with Stroke in United States (National Hospital Ambulatory Medical Care Survey 2003)



Adapted from: Qureshi AI, et al. Am J Emerg Med 2007;25(1):32-8.

Stroke specific disruption of autonomic activity

Disruption: structural and/or functional

Adaptation: functional

Parasympathetic activity

Sympathetic activity

BP

(Qureshi AI: Circulation 2008 Jul 8;118(2):176-87)

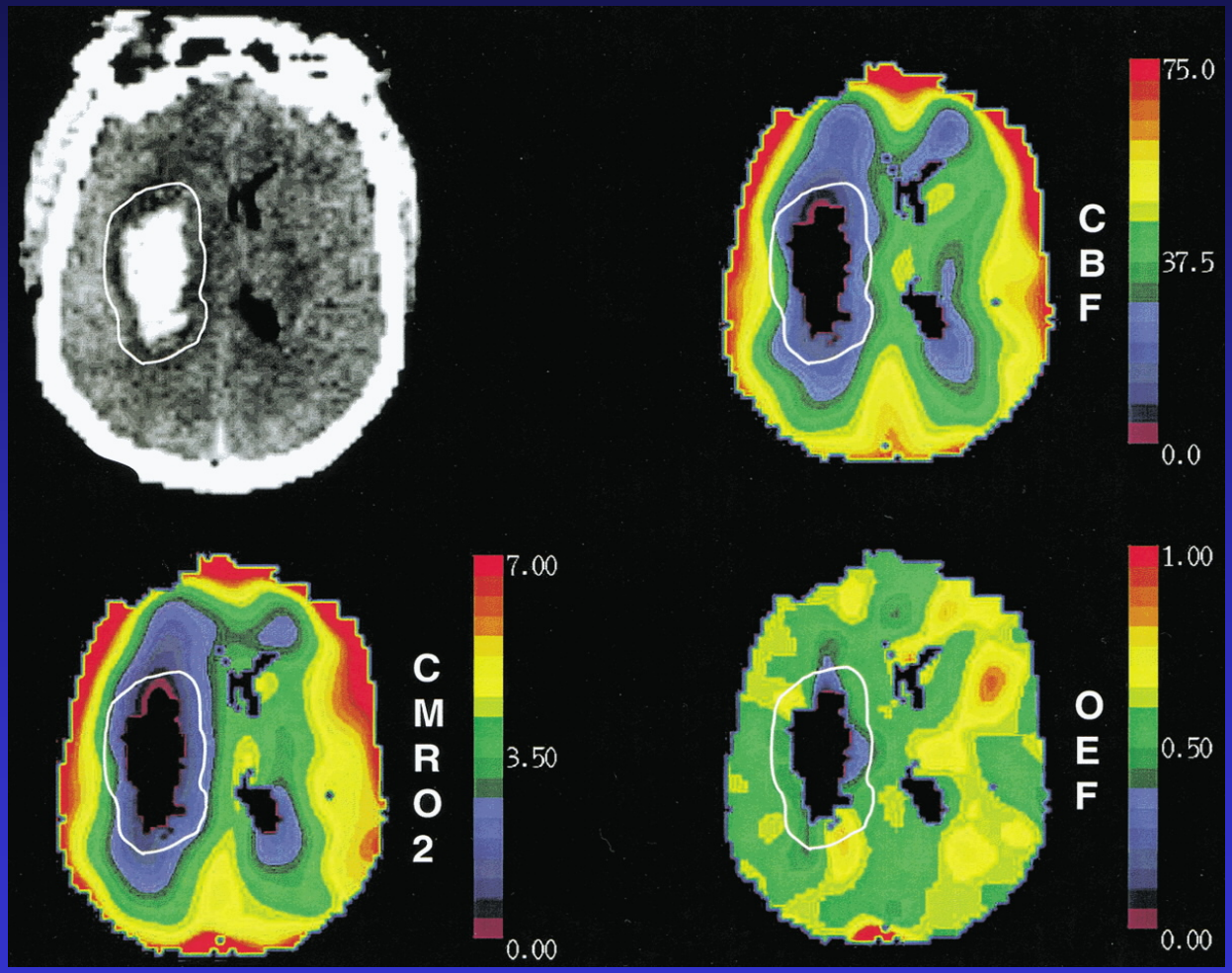
Evolution of our understanding of acute hypertensive response and ICH

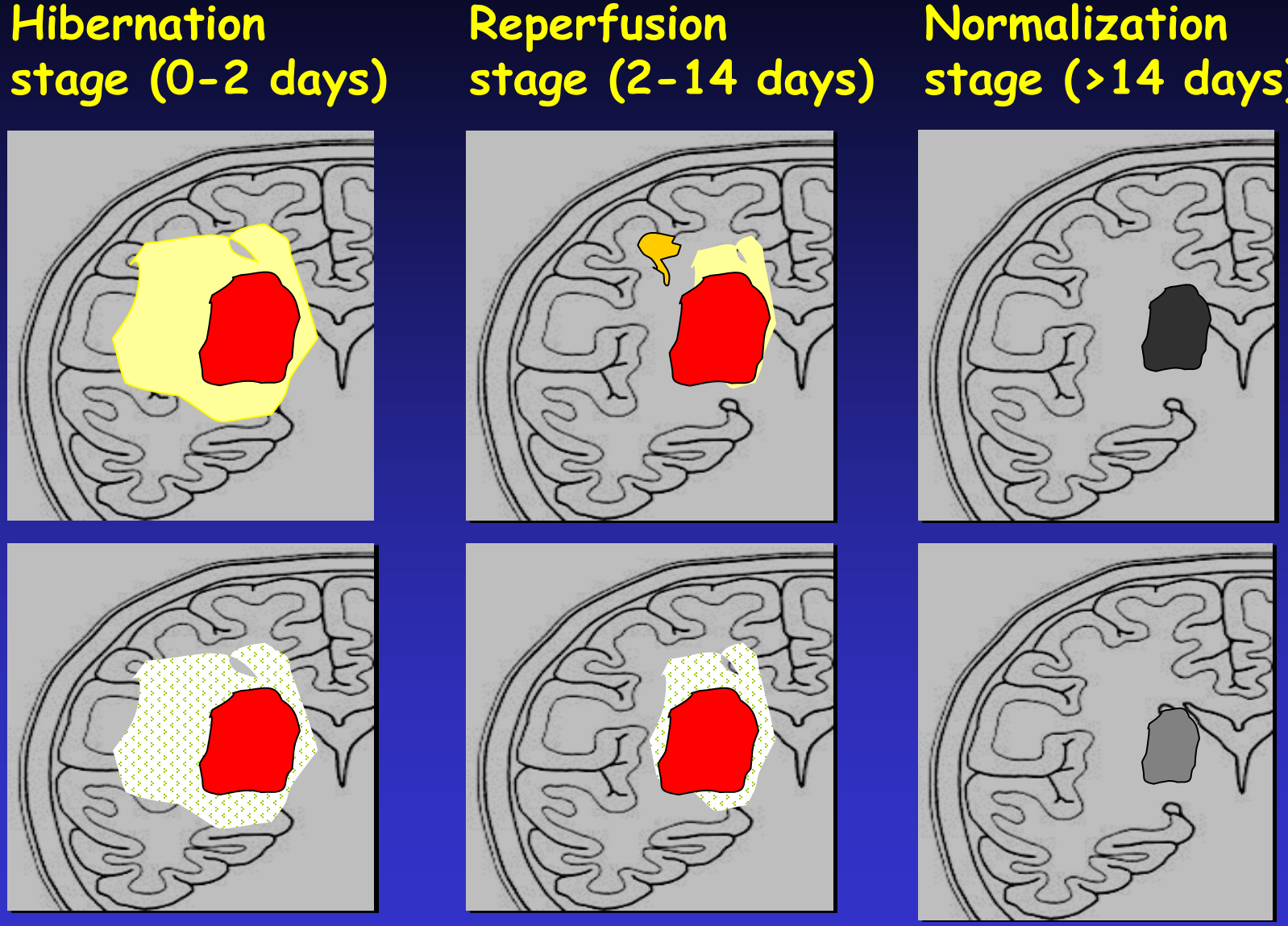
Qureshi AI. Stroke. 2013 Jun;44(6 Suppl 1):S67-9.

Period I (1985-1997)	Period II (1998-2003)	Period III (2004-2009)	Period IV (2010---)
DONOT TREAT BP IN ACUTE ICH- *EXPERIMENTAL/CLINICAL RESEARCH*	REDUCE BP - MODESTLY- *CASE SERIES*	AGGRESSIVE BP REDUCTION EXPLORED- *PILOT STUDIES*	AGGRESSIVE BP REDUCTION CONFIRMED- *PHASE III STUDIES*
PERI-HEMATOMA ISCHEMIA	HIGH BP ~ HEMATOMA EXPANSION	BP REDUCTION~ HEMATOMA EXPANSION	BP REDUCTION ~ PATIENT OUTCOMES

Hypoperfusion without ischemia

From: Zazulia: J Cereb Blood Flow Metab, 21(7). 2001.804-810

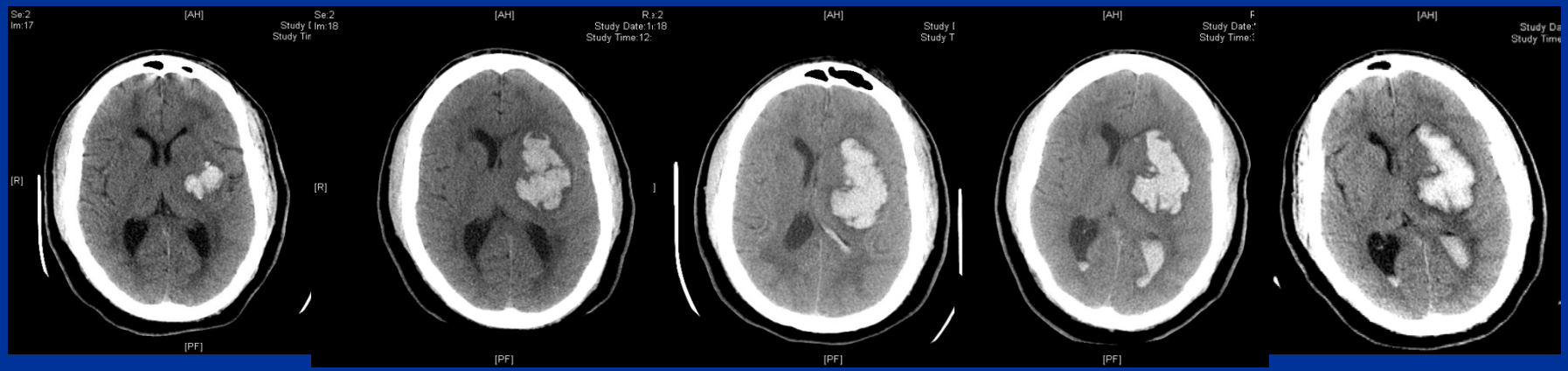


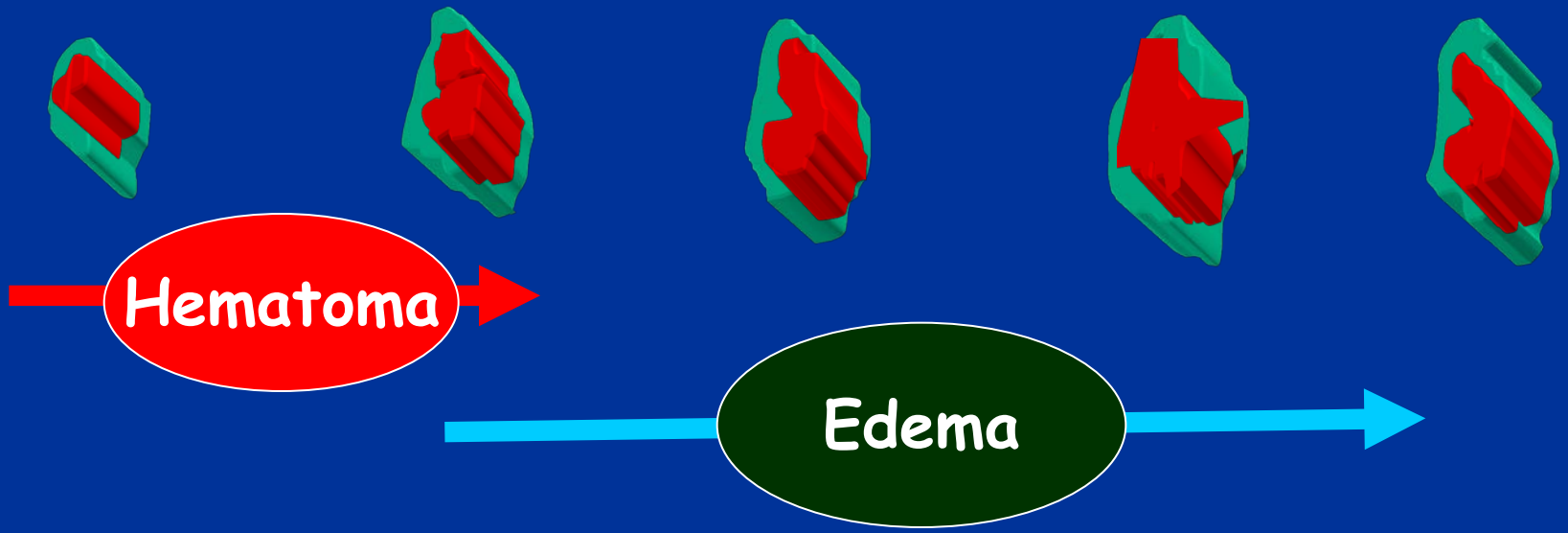


Qureshi AI, et al. Neurosurg Clin N Am 2002;13:355-370.

Pathophysiology of intracerebral hemorrhage

Baseline | 14 hours | 24 hours | 72 hours | 1 week

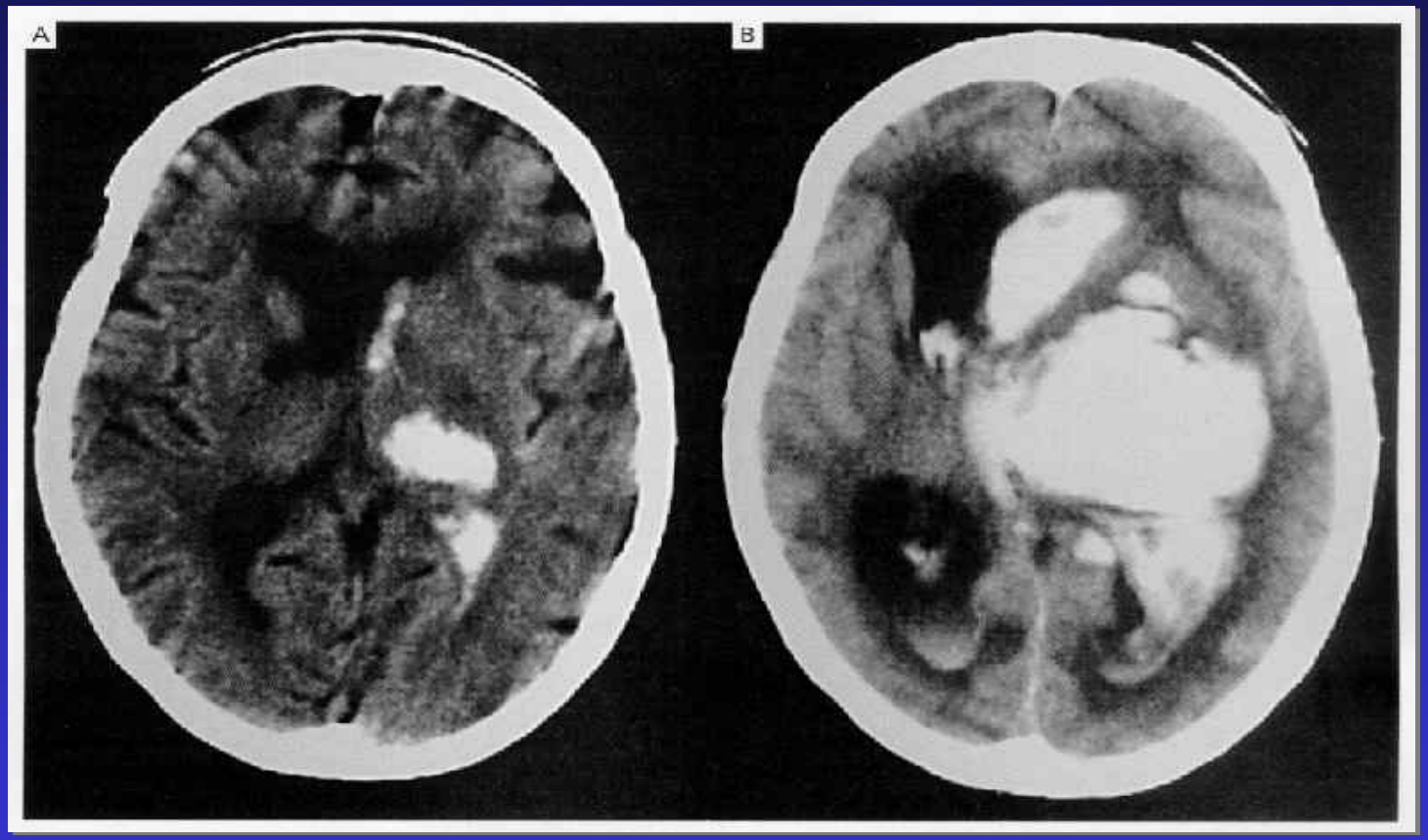




Qureshi AI, Mendelow AD, Hanley DF. **Lancet**. 2009 9;373:1632-44.

Hematoma Enlargement

(From: Qureshi: N Engl J Med; 344.: 2001.1450-1460)

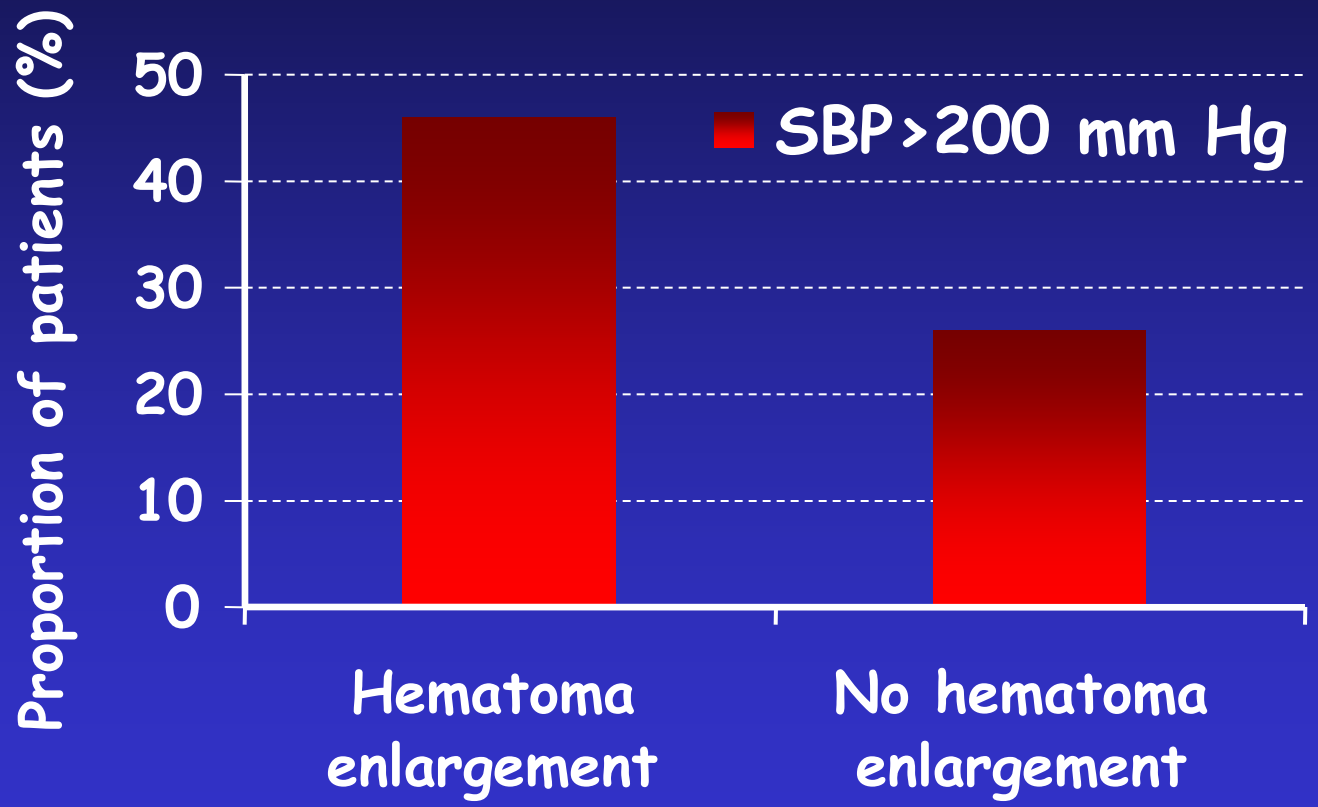


Baseline

6 hours

Elevated systolic blood pressure may predispose to hematoma enlargement

Kazui: Stroke, Volume 28(12).December 1997.2370-2375



Intracerebral Hemorrhage Specific Intensity of Care Quality Metrics-BP management

An algorithm that evaluates principles of care using the "best available" evidence in a semi-quantitative manner

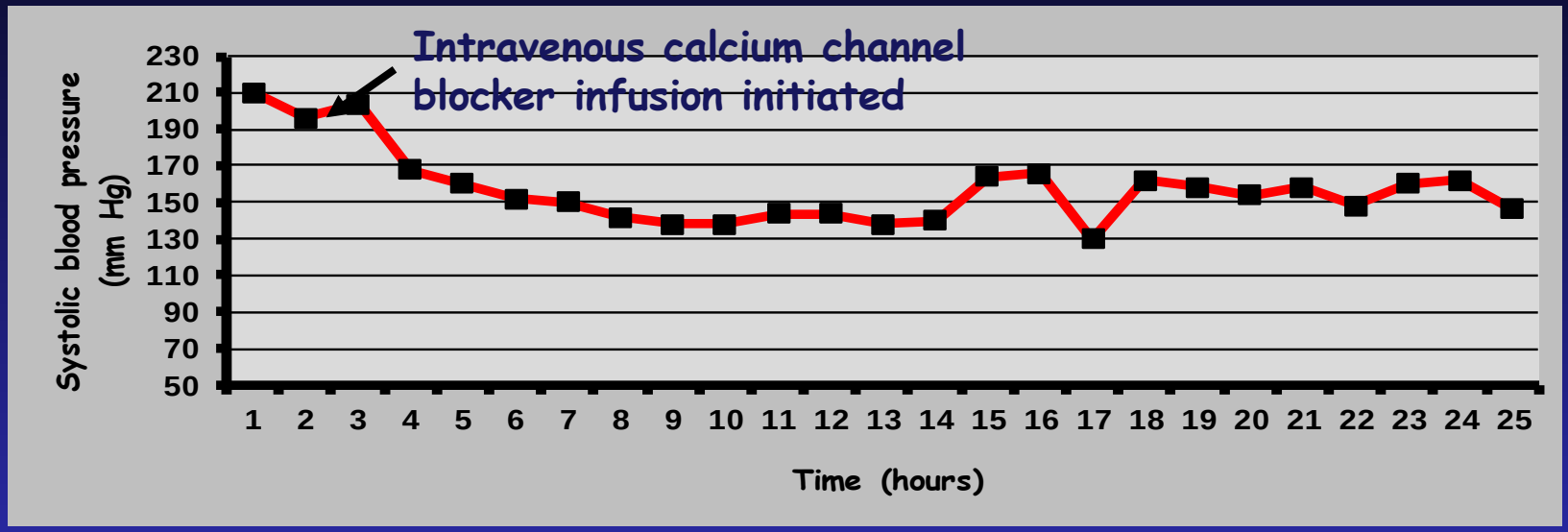
Variable	Quality parameter	1 points if YES or not applicable
Treatment of acute hypertensive response (SBP ≥180 mm Hg)	Time interval between two consecutive SBP≥180 mm Hg AND first SBP<180 mm Hg recording	Achieved target range with 2. 5 hours of second of the two consecutive measurements OR not applicable

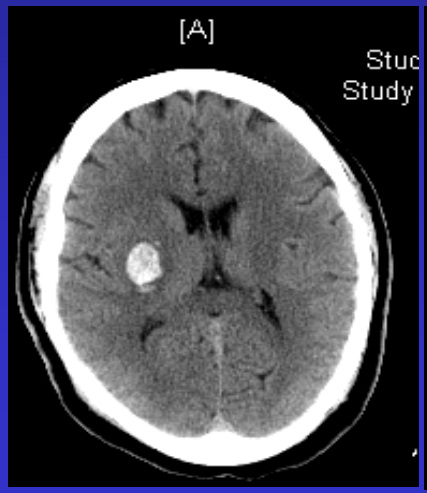
26 quality indicators related to 18 facets of care

Re: Qureshi AI. Neurocrit Care 2011;14:291-317

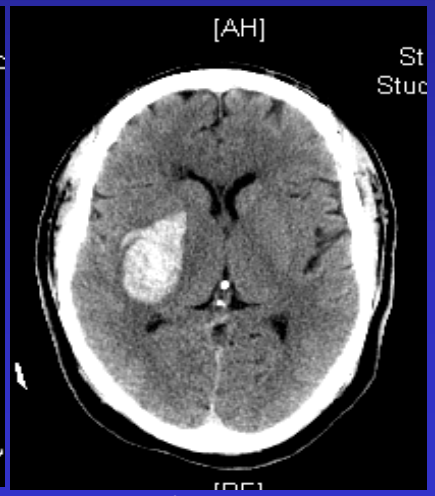
Figure 3

Treatment of acute hypertensive response (SBP ≥180 mm Hg)= 1

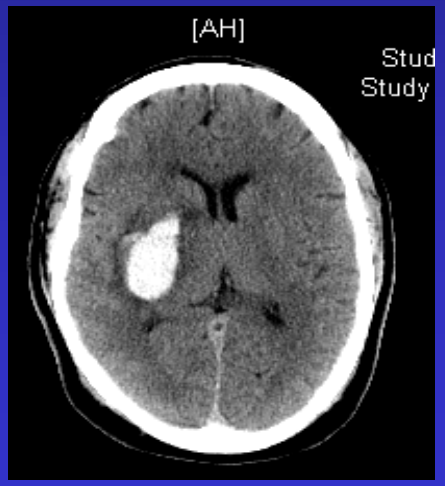




Baseline



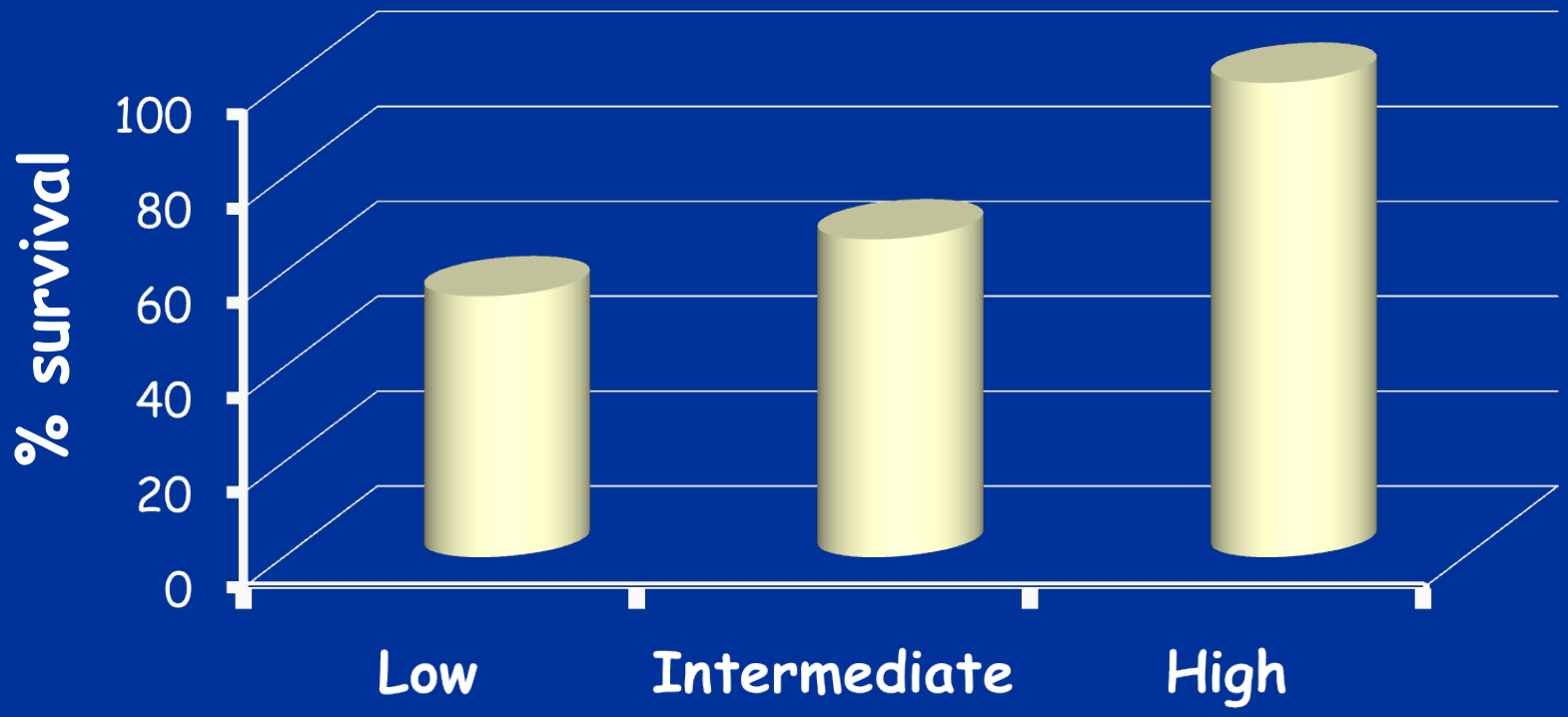
2 hours



24 hours

Intracerebral Hemorrhage Specific Intensity of Care Quality Metrics-BP management+25 quality indicators

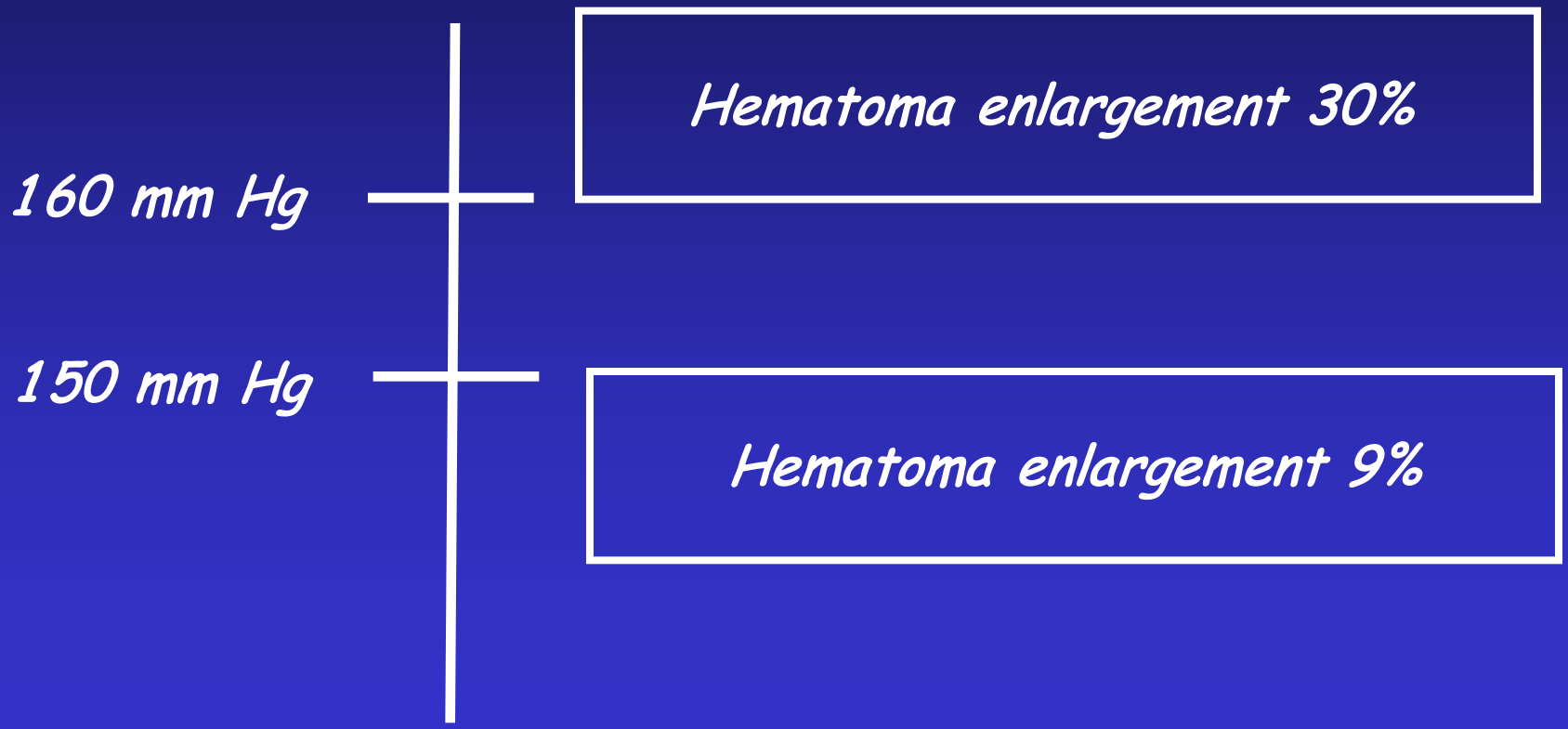
Score on performance metrics and survival



Re: Qureshi AI. J Stroke Cerebrovasc Dis 2013 Jul;22(5):661-7.

More aggressive BP reduction maybe beneficial?

Ohwaki K, Stroke. Jun 2004;35(6):1364-1367.



Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT) Lancet Neurology 2008;7:391-399

Variables	Intensive SBP<140mmHg (n=203)	AHA-guideline SBP<180mmHg (n=201)	p-value
Hematoma expansion (>33% or 12.5 ml)	15%	23%	0.05

Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) Study. Arch Neurol 2010: 67(5):570-6.

Variables	SBP reduction ≥60 mmHg (n=32)	SBP reduction <60 mmHg (n=28)	RR (95% CI)
Hematoma expansion(>33%)	19%	33%	0.6 (0.2, 1.4)

Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT) Lancet Neurology 2008;7:391-399

Treated <3 hrs after onset

Variables	Intensive SBP<140mmHg (n=52)	AHA-guideline SBP<180mmHg (n=52)	p-value
ematoma pansion (>33% 12.5 ml)	12%	27%	0.08

Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) Study. Arch Neurol 2010: 67(5):570-6.

riables	SBP reduction ≥60 mmHg (n=11)	SBP reduction <60 mmHg (n=9)	RR (95% CI)
matoma pansion(>33%)	18%	38%	0.5 (0.1, 2.3)

Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT) Lancet Neurology 2008;7:391-399

Treated <3 hrs after onset

Variables	Intensive SBP<140mmHg (n=52)	AHA-guideline SBP<180mmHg (n=52)	p-value
ematoma	12%	27%	0.08
	(n=11)	(n=9)	
matoma pansion(>33%)	18%	38%	0.5 (0.1, 2.3)

Attenuation of hematoma expansion with intensive SBP reduction. Attenuation most prominent in patients recruited within 3 h

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TRIAL DESIGN

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Primary hypothesis: ATACH II

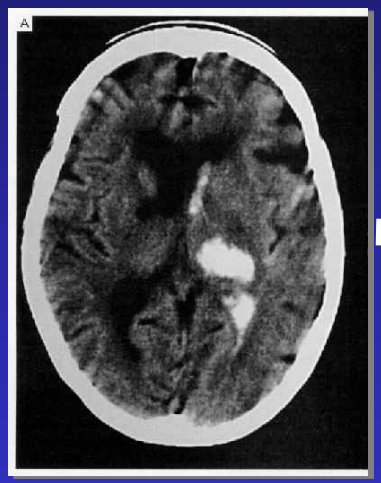
Intensive SBP reduction[1] reduces the likelihood of death or disability at 3m after ICH by 10% or greater when compared with standard SBP reduction.

1. SBP<140 mmHg using IV nicardipine with treatment initiated within 4.5 h of onset of ICH and continued for the next 24h
2. Defined by mRS score of 4-6
3. SBP<180 mmHg

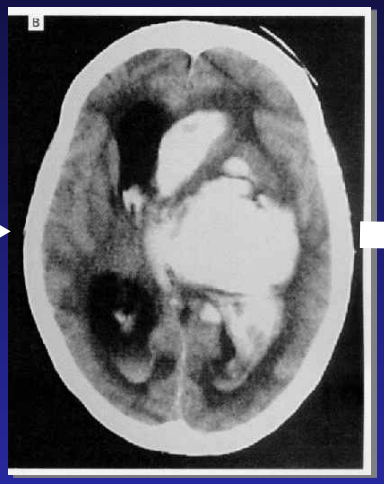
ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Trial design: ATACH II

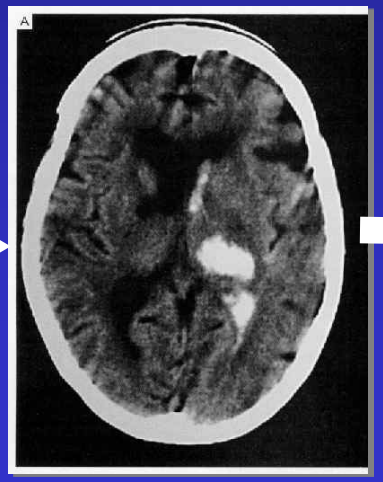
re. Qureshi AI, Palesch YY. Neurocrit Care. 2011;15(3):559-76.



SBP<180 mm Hg



SBP<140 mm Hg



Baseline

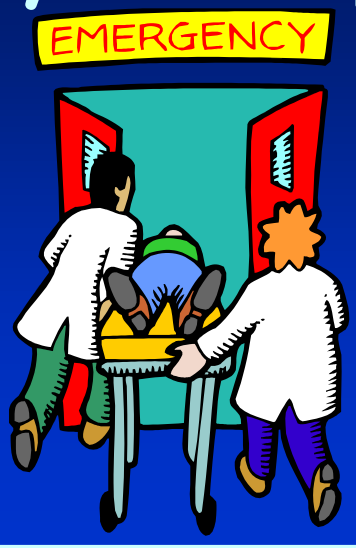
24 hrs

3 m

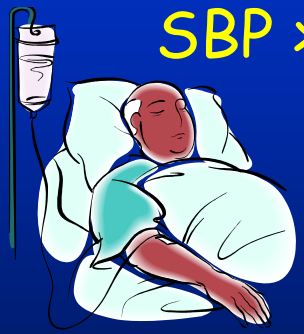
Key Inclusion Criteria

- Age ≥18 years
- Randomized treatment can be started within 4.5 hrs of symptom onset
- The total GCS score of ≥5
- CT scan-manual hematoma volume < 60 cc
- Pre-treatment SBP > 180 mmHg

Eligibility blood pressure



EMS	ED	ED
measure	arrival	monitor
SBP >180 mm Hg	SBP >180 mm Hg	SBP >180 mm Hg

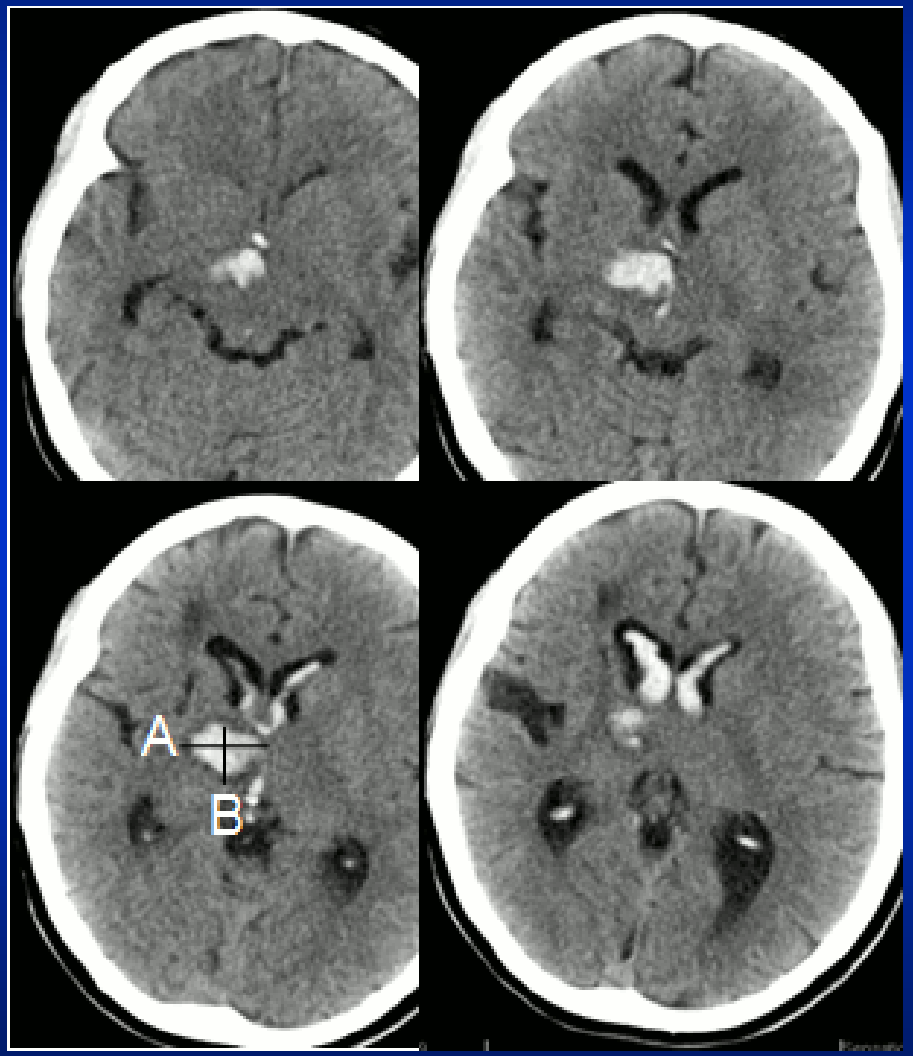


IV antihypertensive meds

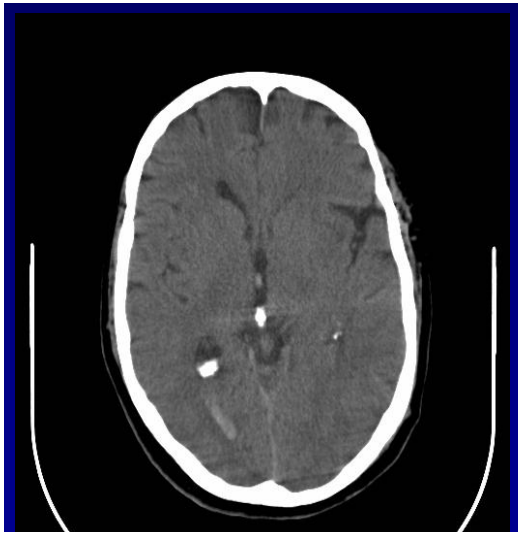
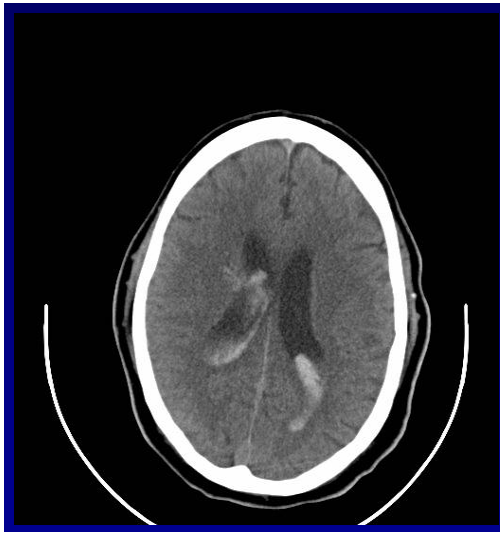
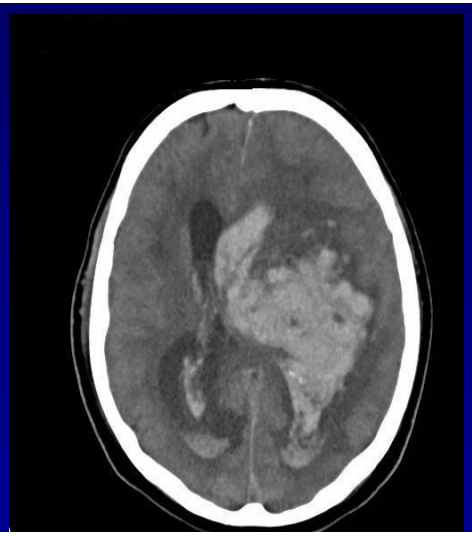
SBP >140 mm Hg SBP >140 mm Hg SBP >140 mm Hg

Measurement of hematoma volume (exclude >60 cc)

A = 2cm
B = 1cm
C = slice thickness X number of slices
= 0.5 x 4 = 2cm
Hematoma volume = 2 X 1 X 2 ÷ 2 = $2cm^3$



Exclude if blood completely fills one lateral ventricle or more than half of both ventricles

Grade 1	*Grade 2*	*Grade 3*
		

INCLUDE

EXCLUDE

Overview of the study design

Patient screened		ED personnel
Patient meets eligibility criteria		Site investigator
Randomize subjects 1:1		WebDCU™ system at MUSC
Intensive treatment SBP<140mmHg using IV nicardipine ±labetalol	Standard treatment SBP<180mmHg using IV nicardipine ±labetalol	Site investigator
Best management according to AHA guidelines and "best available evidence"		Site investigator/ treating physicians

FDA-IND-exempt # 107804

Overview of the study design

Intensive treatment SBP<140mmHg using IV nicardipine	Standard treatment SBP<180mmHg using IV nicardipine	Site investigator
Neurological evaluation		Site investigator/ treating physicians
CT scan for hematoma expansion		Blinded central image analysis
AEs (up to discharge), SAEs, care parameters		Site investigator (adjudication by IOC)
mRS and Euro-QOL		Blinded neurological evaluation by site investigator

Summary of required evaluations

	Baseline	24h	48h	Discharge	Day 30 (tel)	Day 90
Screening	X					
Eligibility	X					
Demo/ED examination	X					
Medical History	X					
Cardiology/EKG	X					
Vital signs	X	X				
Prior medications	X					
GCS score	X	X				
NIHSS score	X	X				X
Lab Tests	X	X	X			
CT scan	X	X				

Summary of required evaluation according to time points of ascertainment

	Baseline	24h	48h	Discharge	Day 30 (tel)	Day 90
Nicardipine administration		X				
Hospital discharge summary				X		
Concomitant medications		X	X	X		
Concomitant procedures		X	X	X		
Concomitant acute therapies		X				

Qureshi AI, Palesch YY. Neurocrit Care. 2011 Dec;15(3):559-76.

Summary of required evaluation according to time points of ascertainment

	Baseline	24h	48h	Discharge	Day 30 (tel)	Day 90
AEs		X	X	X		
SAEs		X	X	X	X	X
Follow-up					X	X
mRS					X	X
EuroQOL						X
End of Study						X

Qureshi AI, Palesch YY. Neurocrit Care. 2011 Dec;15(3):559-76.

Primary outcome (dichotomized mRS)

Scale	Criteria
0	No symptoms
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability requiring some help, but able to walk without assistance
4	Moderate severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Death

Secondary outcomes

- EuroQOL
- Hematoma expansion as determined by serial CT scans
- Treatment-related SAEs within 72 h

Qureshi AI, Palesch YY. Neurocrit Care. 2011 Dec;15(3):559-76.

Statistical considerations

Proportion of mRS 4-6 in intensive SBP reduction group

Proportion of mRS 4-6 in standard SBP reduction group

Sample size

Expected difference between two groups

Statistical considerations

Proportion of mRS 4-6 in intensive SBP reduction group (50%)

Proportion of mRS 4-6 in standard SBP reduction group (60%)

Sample size (n=1,280)

Expected difference between two groups (10%)

Statistical considerations

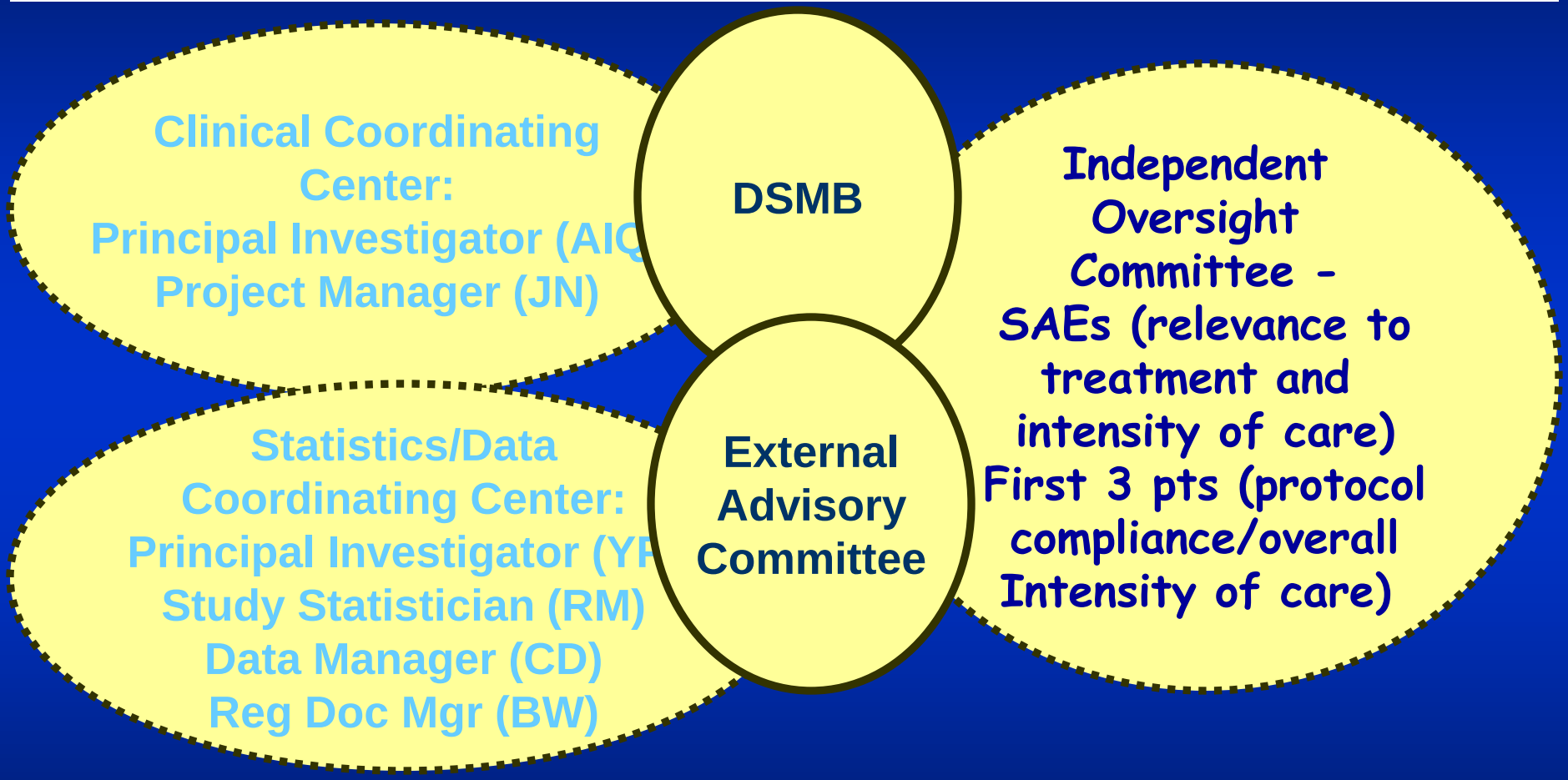
Standard therapy group	Sample size estimation*
45%	1244
50%	1282
55%	1296
60%	1282
65%	1244

Effect size	Sample size estimation*
10%	1282
9%	1582
8%	2002
7%	2610
6%	3550
5%	5100

National Institute of Neurological Disorders and Stroke

National Institutes of Health

Reducing the burden of neurological disease...



Clinical Trial Sites
(Site PI/Research Coordinators)

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CURRENT STATUS

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Current participating countries

- The trial continues in USA, Japan, China, and Taiwan, South Korea and anticipated to start in Germany and Canada.

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Current Status-Active Sites

Overall	USA	Japan	China	Taiwan	S. Korea
First DSMB meeting (October 22nd, 2012)					
50	43	5	1	1	
Second DSMB meeting (April 22nd, 2013)					
76	52	15	4	4	1
Third DSMB meeting (October 7th, 2013)					
82	51	15	6	6	4

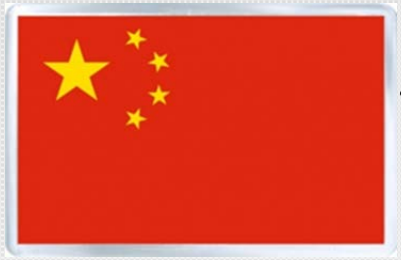
ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Current Status-Recruitment

Overall	USA	Japan	China	Taiwan	S. Korea
First DSMB meeting (October 22nd, 2012)					
89	79	10	0	0	0
Second DSMB meeting (April 22nd, 2013)					
207	125	53	17	11	1
Third DSMB meeting (October 7th, 2013)					
359	187	97	43	25	7

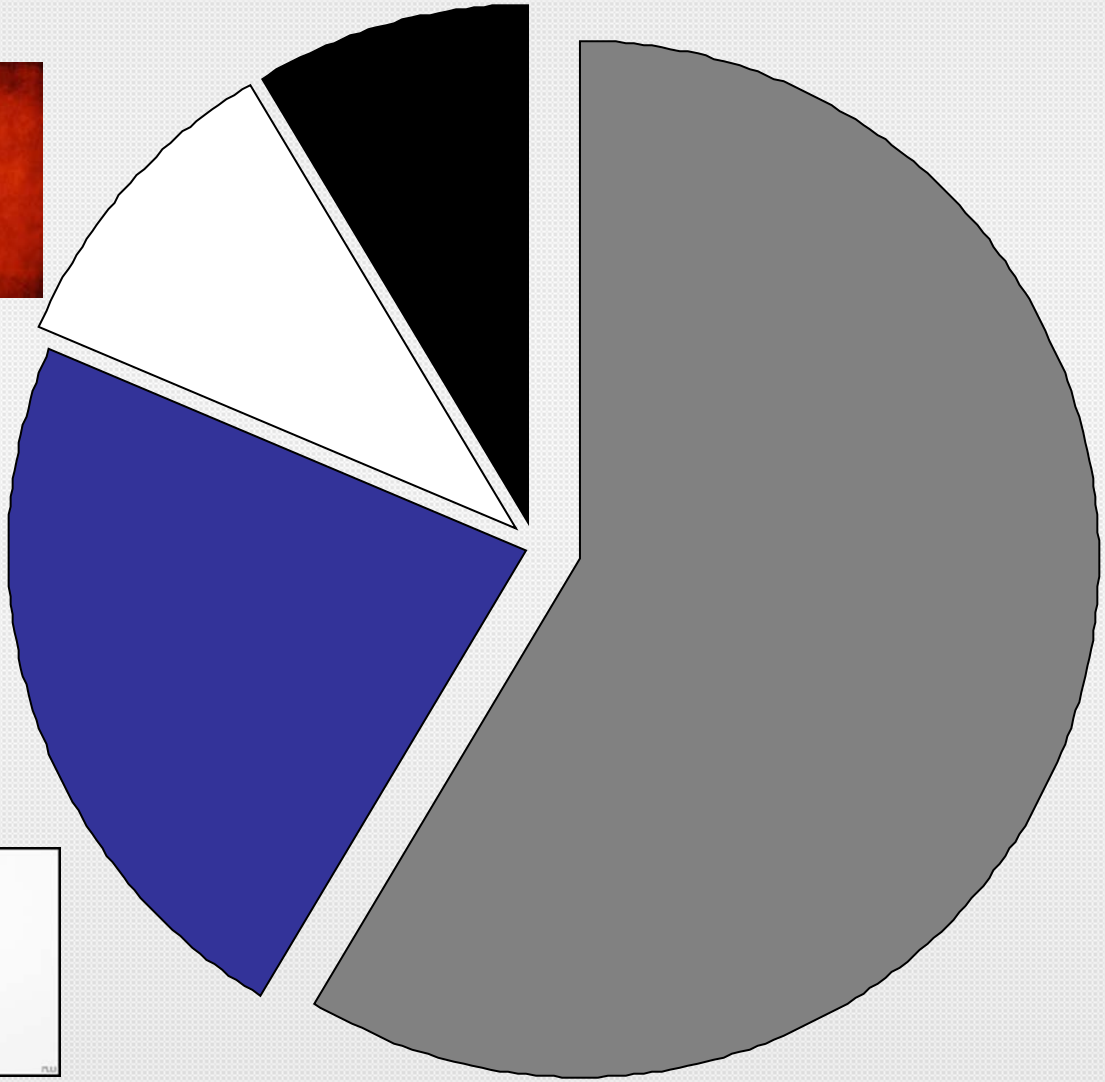
ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Enrollment By Country



TAIWAN, N=25

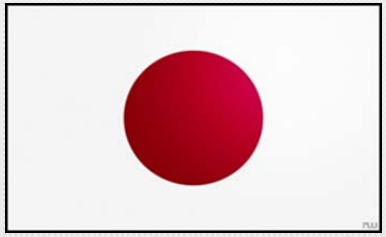
CHINA, N= 43



SOUTH KOREA, N=7

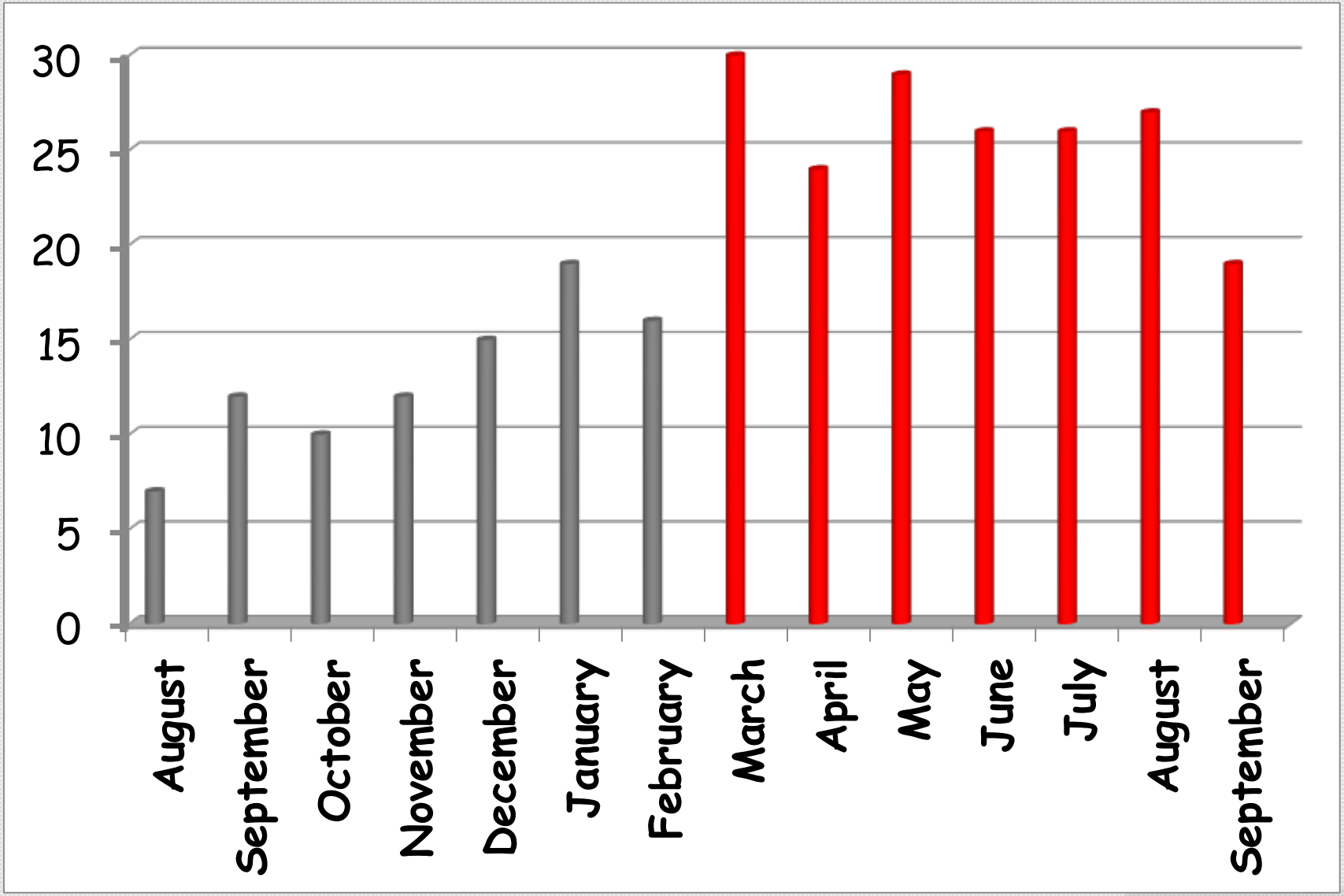
USA, N=187

JAPAN, N=97



ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

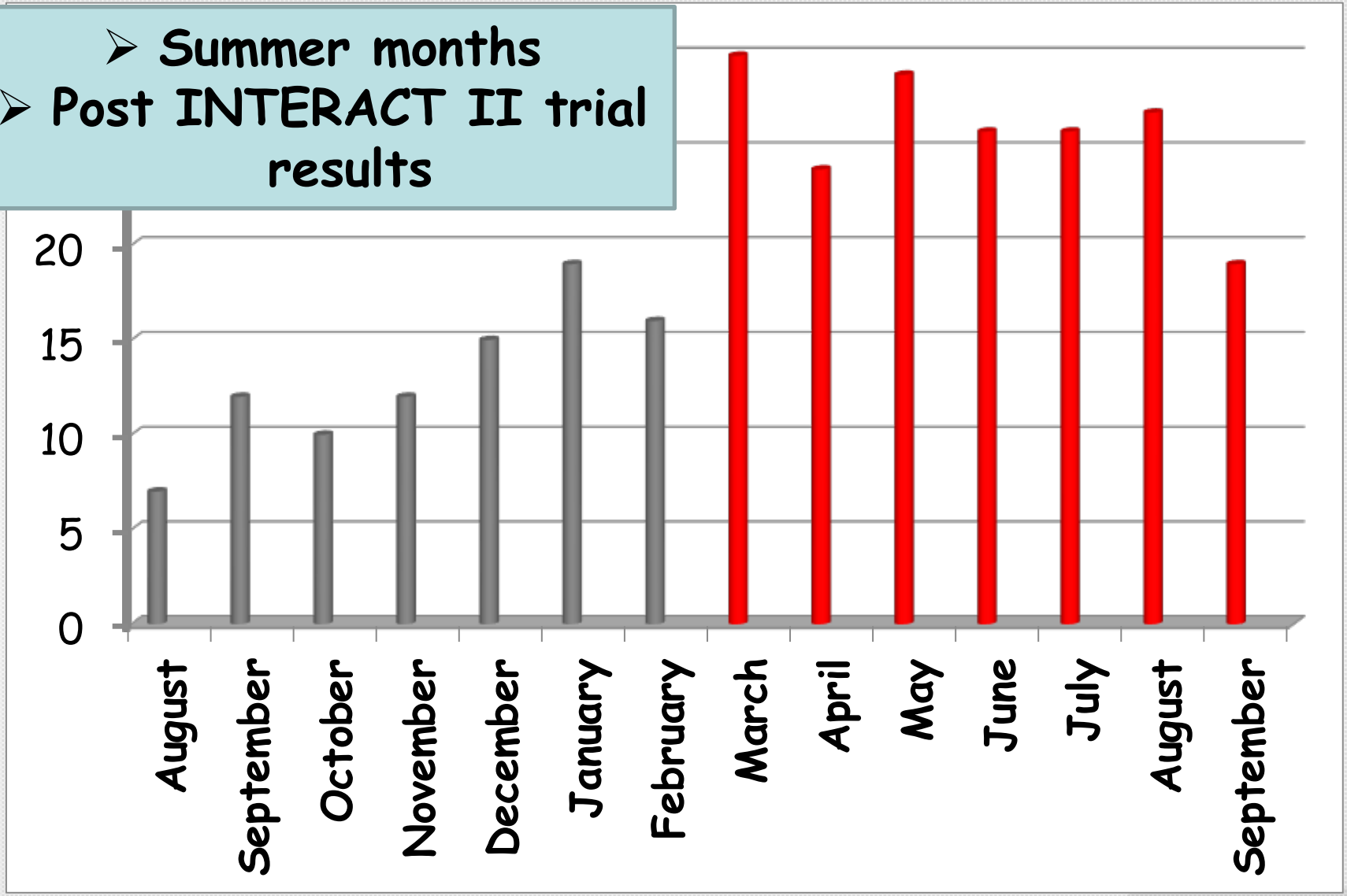
Last 6 months



ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Last 6 months

- Summer months
- Post INTERACT II trial results



ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

ATACH II—July 26th, 2013
Clarification regarding INR in patients on warfarin

- A subject may be eligible for enrollment based on a re-draw of the INR showing a value of < 1.5 (i.e., 1.4 or less) if reversal is achieved before the close of the 4.5-hour window from symptom onset and all other inclusion/exclusion criteria are met.
- INR reversal using PCC is generally a two-step process, using appropriately diluted IV vitamin K_1 in addition to the administration of the intravenous PCC product. A change to INR with PCC administration becomes evident starting after approximately 10 minutes, with peak effect at 30 min.

Andrews CM, Jauch EC, Hemphill JC, 3rd, Smith WS, Weingart SD. Emergency neurological life support: Intracerebral hemorrhage. *Neurocrit Care*. 2012;17 Suppl 1:S37-46

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Real Time Feedback to Sites

WebDCU™ Email Notification

Site Enrollment Summary

This is a monthly site enrollment summary for ATACH II trial.

Site Name: Hennepin County Medical Center

Date Released to Enroll: Mar 22 2011 12:00AM

Total Enrolled: 9

Date of Last Enrollment: May 14 2013 7:08PM

Days since Last Enrollment: 143

This email was generated by WebDCU System.
For more information, log on to the WebDCU study website. Powered by **DCU.musc.edu**

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Achievements

- The ATACH II investigators in collaboration with MentorMate released the ATACH-II Patient Recruitment Guidelines mobile application available on iPhone, Android, and Blackberry in 2011. The application allows screening and randomization through iPhone, Android, and Blackberry and has been widely adopted among investigators and even in other time sensitive clinical trials.

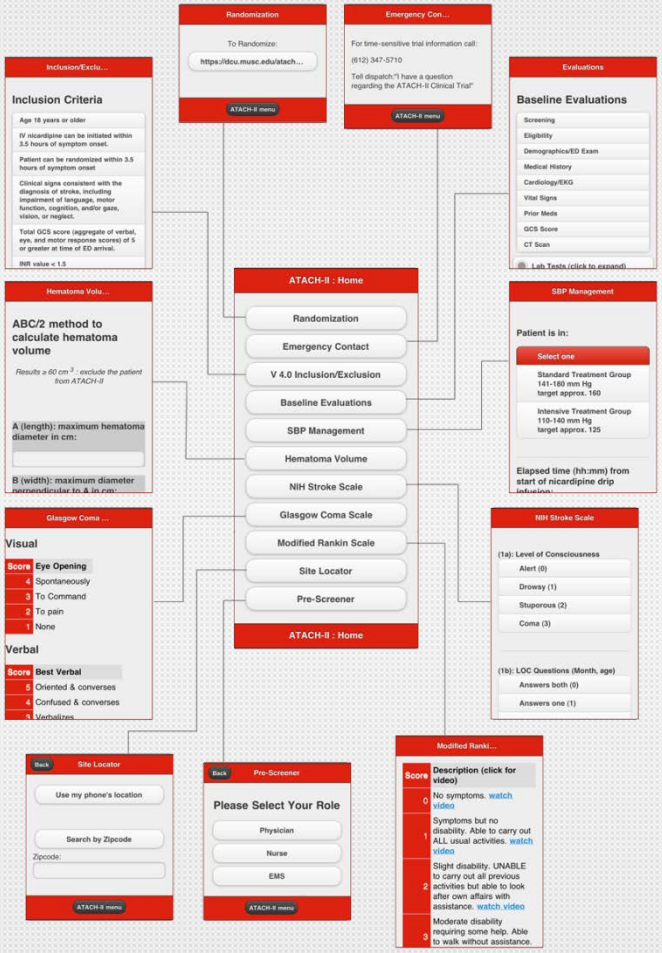
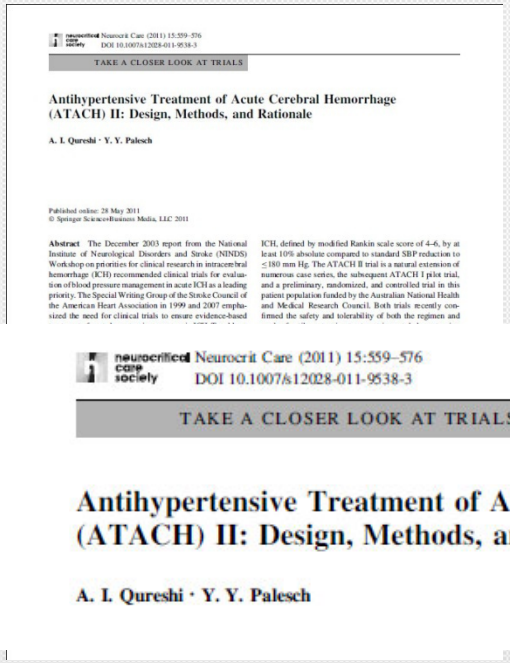


Figure 1

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Achievements

- The educational impact of the ATACH II trial has been very high. This is seen with several publications in peer-reviewed journals, numerous presentations in various national and international forums, and recently a supplement of Journal of Vascular and Interventional Neurology dedicated to the ATACH II trial.



ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Japan-South Korea Investigators meeting, Oct 6th, 2013, Osaka, Japan

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Eastern US investigators meeting- ICIN 2013, Oct 11th, Philadelphia, PA

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INTERACT II RESULTS

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Rapid Blood Pressure Lowering for Intracerebral Hemorrhage: INTERACT 2 Results Leave More Questions Than Answers

BY GINA SHAW

ARTICLE IN BRIEF

A large randomized trial found mixed results: Rapid, intensive lowering of intracerebral blood pressure (BP) did not appear to reduce death or severe disability in patients with intracerebral hemorrhage, but an analysis of modified Rankin scores indicated that patients who underwent intensive blood pressure BP-lowering had improved functional outcomes.

Rapid, intensive lowering of intracerebral blood pressure (BP) does not appear to reduce death or severe disability in patients with intracerebral hemorrhage, according to findings from the second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT 2), published online before the June 20 print edition of the *New England Journal of Medicine*.

The international multicenter trial, which accrued 2,839 patients at 144 hospitals in 21 countries, randomized participants to either intensive treatment to lower their blood pressure (with a target systolic level of <140 mm Hg within 1 hour) or guideline-recommended treatment (with a target systolic level of <180 mm Hg) with the use of agents of the physician's choosing.

Among the participants for whom outcome could be determined, 719 of 1382 participants (52 percent) receiving intensive treatment had a primary outcome event (death or major disability), as compared with 785 of 1412 (55.6 percent) receiving guideline-recommended treatment (odds ratio with intensive treatment, 0.87; 95% confidence interval [CI], 0.75 to 1.01; $p = 0.06$).

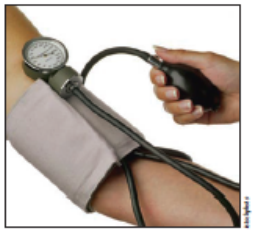
Strictly based on primary endpoints, then, INTERACT 2 is a negative trial. But the take-home message from the study remains in question. A preplanned ordinal analysis of modified Rankin scores did indicate that patients who underwent intensive blood pressure lowering had improved functional outcomes. And the study found no major safety issues linked to aggressive lowering of intracerebral blood pressure.

"It's an interesting set of results," observed Adnan Qureshi, MD, professor and executive director of the Zeenat Qureshi Stroke Research Center in Minneapolis, MN. "While the primary outcome came close to statistical significance, it did not achieve it. I think that one would have expected a greater benefit from the intensive BP reduction if the primary hypothesis was true. The investigators had anticipated a 7 percent absolute risk reduction for the primary endpoints, and in the end it was just 3.6 percent."

One possible explanation is that, while the mean systolic blood pressure in the intensive BP-lowering group was indeed lower than the standard treatment group, it never reached the range that the investigators initially set out to achieve. Only 462 patients, or 33.5 percent, in the intensive group actually attained the target BP of <140 mm Hg after one hour of treatment.

"One wonders if blood pressure control had been more effectively reduced, perhaps they would have seen the magnitude of benefit that they were expecting," said Dr. Qureshi, who was not involved with the INTERACT 2, but is one of the lead investigators of the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH II) trial. He noted that, given the number of countries involved in the trial, standardization of protocols for achieving BP reduction goals may have been particularly challenging.

DR. ADNAN QURESHI: "We do need to be cautious before we start advocating a relatively untested threshold [for blood-pressure lowering]. This trial may not have ascertained the full magnitude of risk or benefit profile if you achieve the predefined threshold."



DR. JOSEPH BRODERICK: "I do think this [study] will nudge people toward being more aggressive with blood pressure."

The trial's underlying hypothesis rested on the theory that intense systolic blood pressure reduction reduces the rate of hematoma expansion. But that was also not borne out in the results. The difference in hematoma growth between the groups in the 24 hours after baseline was not significant either in relative (4.5 percent [95% CI, –3.1 to 12.7; $p = 0.27$], or absolute terms (1.4 ml [95% CI, –0.6 to 3.4; $p = 0.18$]).

"This question may need to be revisited," Dr. Qureshi noted. "Perhaps a greater level of BP reduction is necessary to reduce the rate of hematoma enlargement, although the possibility of diminishing returns cannot be excluded. Based on prior studies, one would think that more is better, and it's also possible that given that there were fewer sites involved in those pilot studies, that blood pressure reduction was achieved in a more effective manner."

Will the study change practice? That's hard to predict. Dr. Qureshi believes that the recommendation to reduce and maintain systolic BP <140 mm Hg may be premature because the INTERACT 2 reported on the risk-benefit profile of systolic BP slightly above 140 mm Hg — but not on the risk-benefit profile of systolic BP around 125 mm Hg, which is what would be expected if the majority of patients had a reduction in systolic BP <140 mm Hg. A greater benefit may be expected with larger magnitude of systolic BP reduction but the risk of cerebral, coronary, and renal ischemia may also be higher, he said.

"We do need to be cautious before we start advocating a relatively untested threshold," he said. "This trial may not have ascertained the full magnitude of risk or benefit profile if you achieve the predefined threshold."

But another leading stroke expert sees the INTERACT 2 results differently. "The trial nearly reached significance for its primary endpoint, and did achieve secondary endpoints in favor of the more aggressive treatment, with no observed safety differences," said Joseph Broderick, MD, chair of the department of neurology at the University of Cincinnati and the director of Greater Cincinnati-Northern Kentucky Stroke. "That's a good thing."

However, Dr. Broderick pointed out that the relatively small hematoma-volume reduction is confounding. "We were involved in trials with NovoSeven where the decrease in volume of hemorrhage was between 3-4 ccs, whereas the absolute difference after adjustment in this trial was 1.4 ccs. That's very small. It goes in the right direction, but you would like to understand the biology of an outcome and that finding makes it a little harder."

Unlike Dr. Qureshi, however, Dr. Broderick believes that the trend toward a positive primary outcome,

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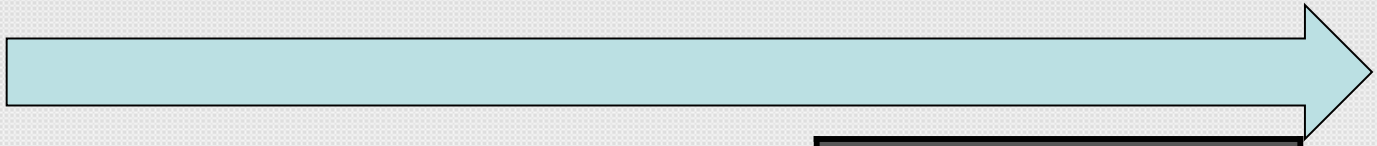


INTERACT II

- Onset <6 hours
- SBP 150-220 mm Hg

ATACH II

- Onset <4.5 hours
- SBP >180 mm Hg
- Hematoma vol.<60 cc

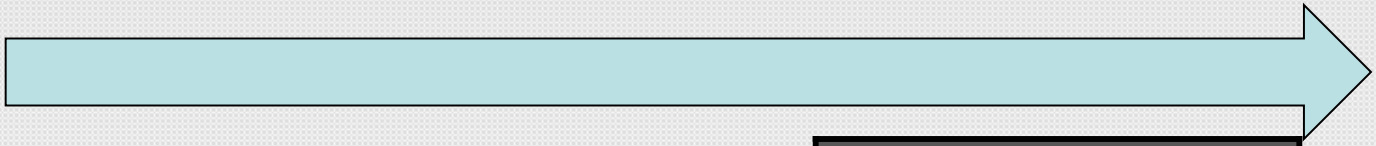
SCORE IT
CT spot sign

SBP-66% in 6h

SBP-90% in 2h

Inten-sity of care

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage



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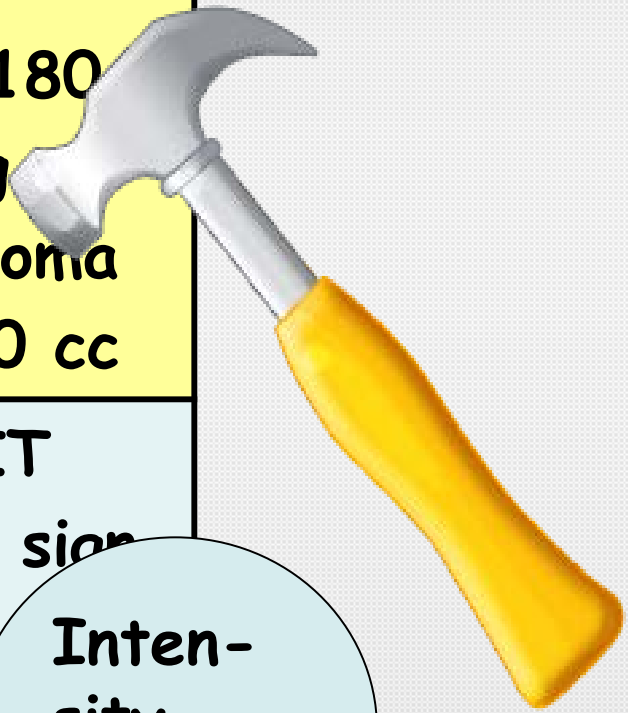

Inten-sity of care

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

INTERACT-Baseline characteristics

	INTERACT II (N=2794)
Baseline SBP <180 mm Hg	1488 (53%)
Time interval from symptom onset to randomization ≥4 hr	1173 (42%)
No IV antihypertensive treatment required	921 (33%)
IV antihypertensive meds used not available in US	645 (23%)
IV antihypertensive meds used not preferred in US	733 (26%)

Anderson CS; the INTERACT2 Investigators.
N Engl J Med. 2013 May 29. [Epub ahead of print]

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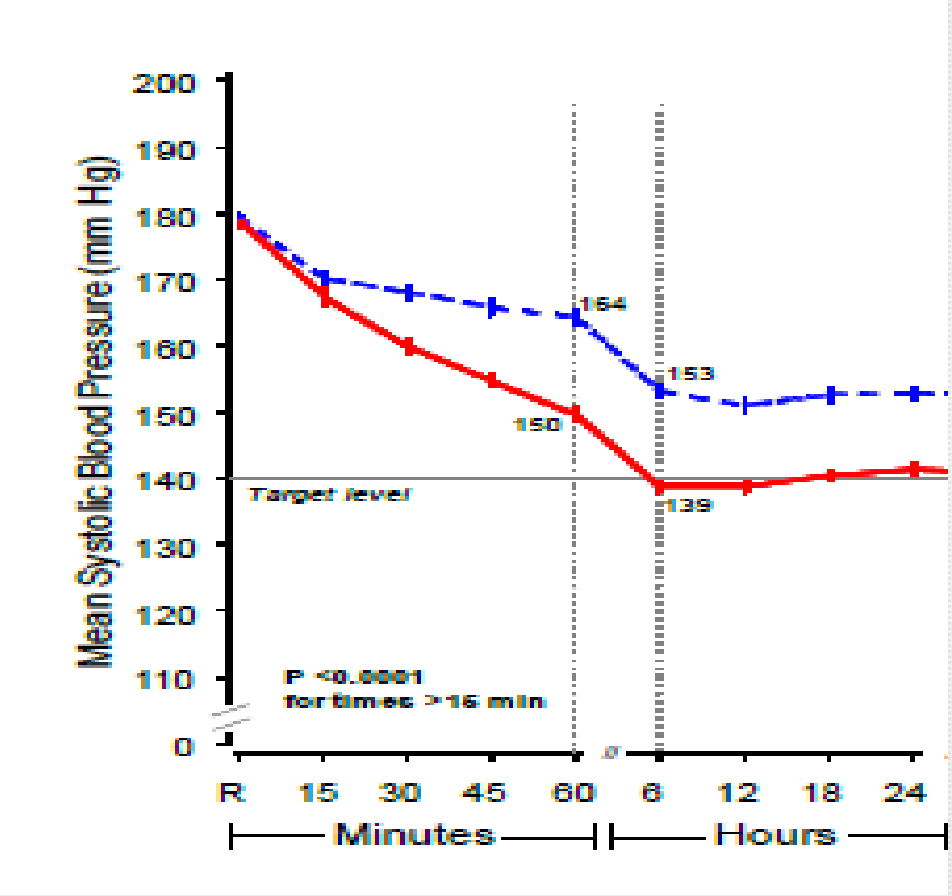
INTERACT II: Lack of early therapeutic effect



	Intensive BP lowering (N =491)	Guideline-based BP lowering (N =473)
Hematoma growth	26.1%	26.4%
Neuro deteriorate	14.5%	15.1%

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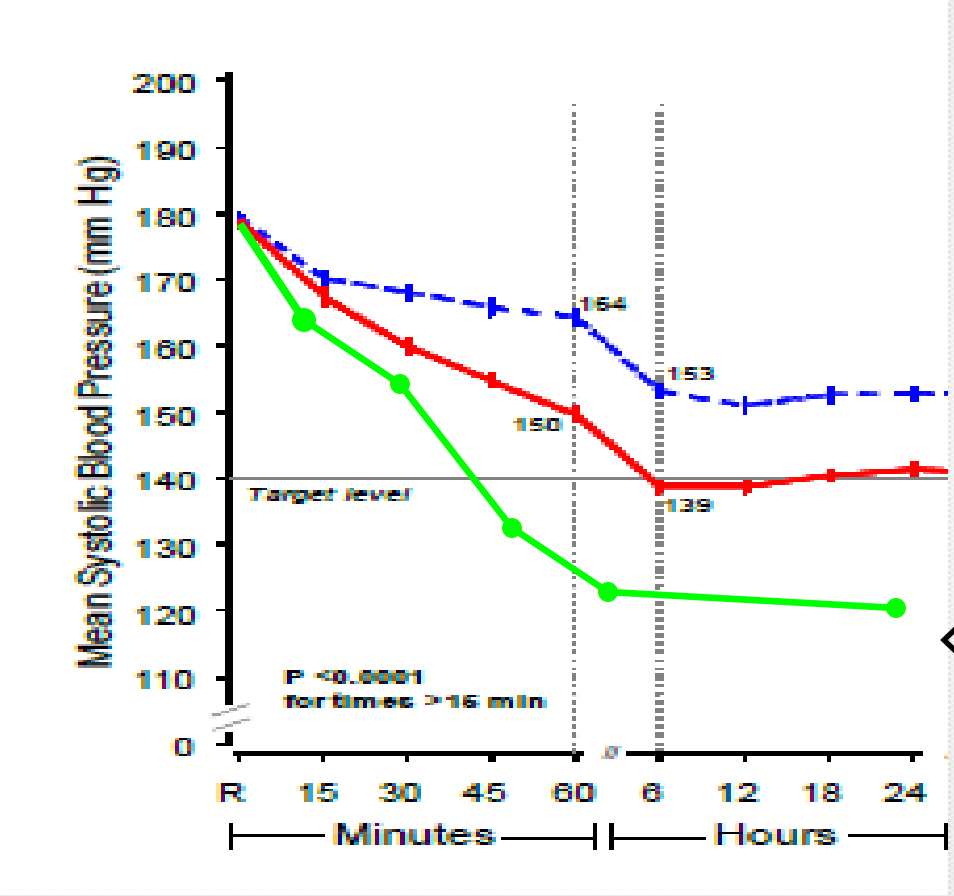
INTERACT II:
Lack of early therapeutic effect



	Intensive BP lowering (N =491)	Guideline-based BP lowering (N =473)
Hematoma growth	26.1%	26.4%
Neuro deteriorate	14.5%	15.1%

Greater SBP reduction required?

Safety profile?

Anderson CS; the INTERACT2 Investigators.
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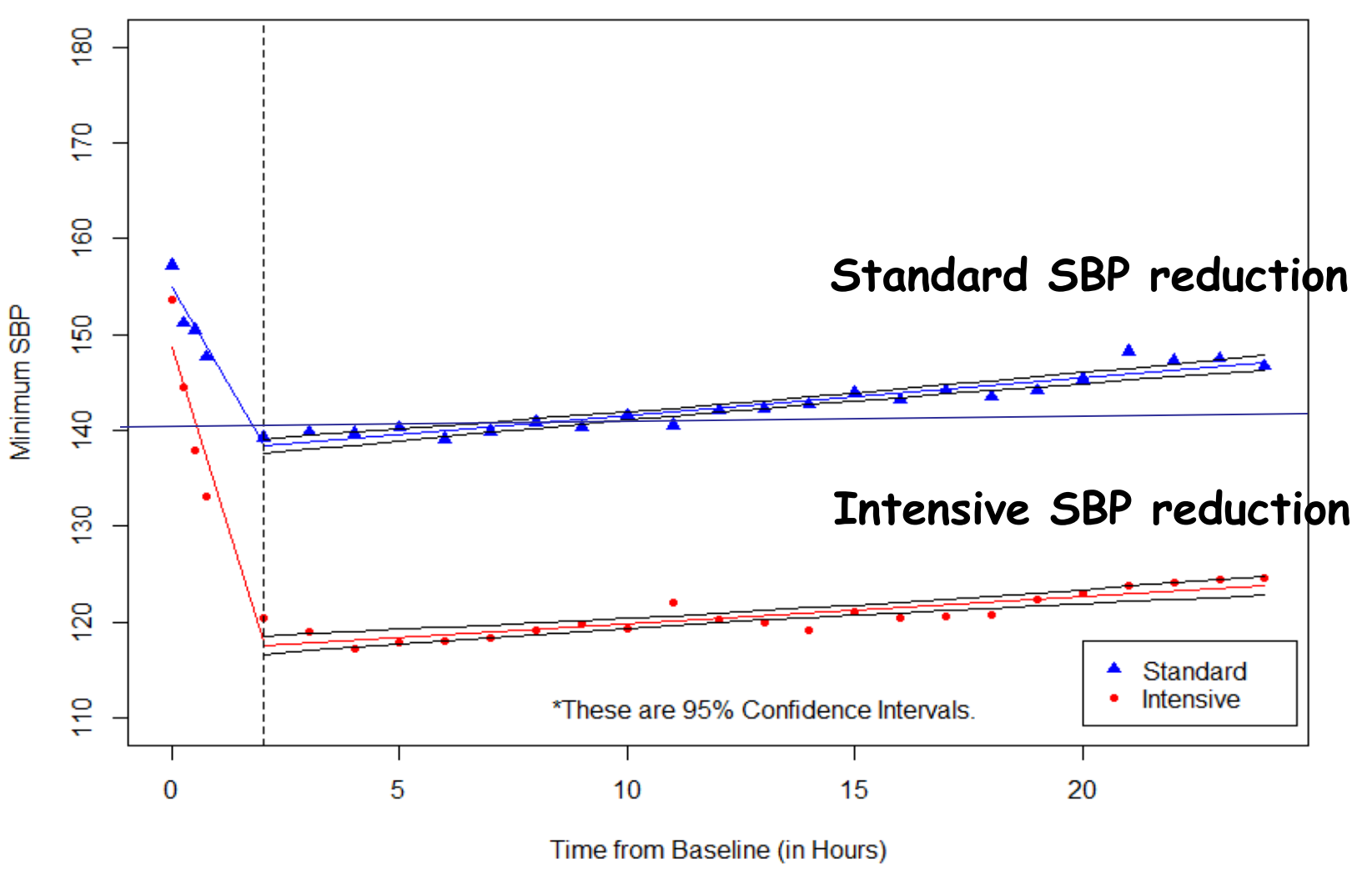
SBP profiles by treatment group in ATACH II (data censored Sept 5th, 2013)



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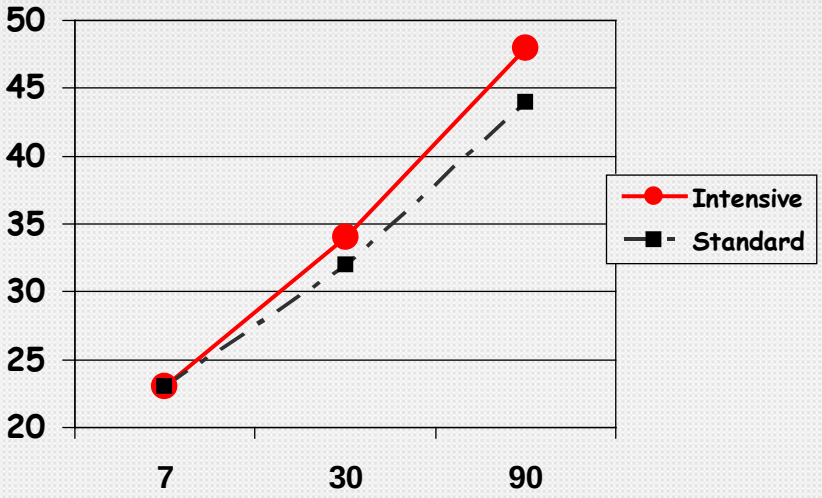
Late emergence of benefit in rate of mRS 0-2



	Intensive BP lowering (N =491)	Guideline-based BP lowering (N =473)
Withdrawal of care	5.4%	3.3%

Disproportionate use of withdrawal of care obscured early benefit of intensive SBP reduction?
OR
Post 24 hour intensity of care differed between the two groups?

Anderson CS; the INTERACT2 Investigators.
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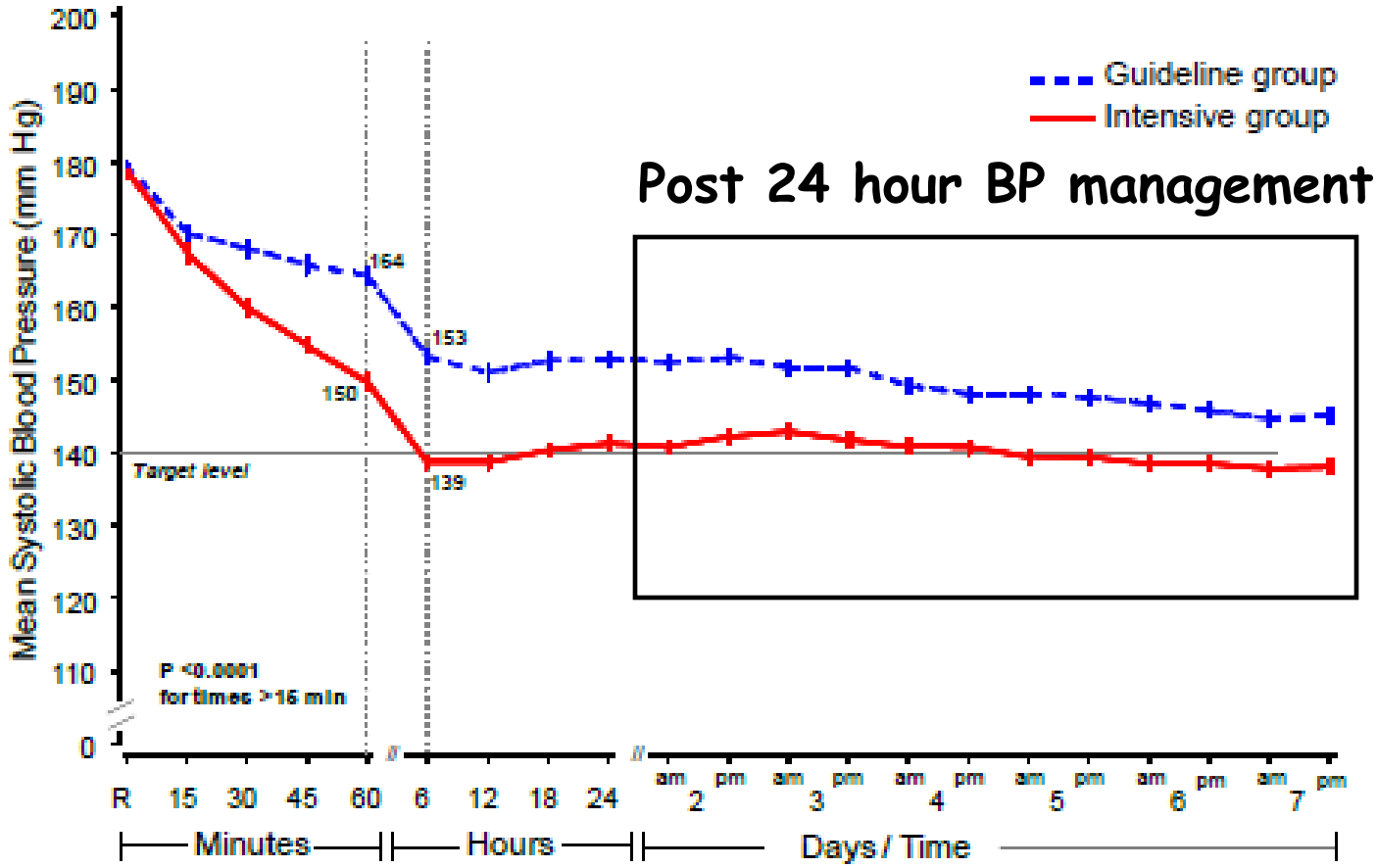
Post 24 hr intensity of care between the two groups



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Is INTERACT study definitive?

- Statistical significance not achieved in primary analysis and further reduced after adjustment for confounders such as NIHSS score, hematoma volume, and IVH.
- Statistical significance achieved in secondary analysis in unadjusted analysis but not after adjustment for confounders such as NIHSS score, hematoma volume, and IVH.
- Intensive SBP reduction as applied in INTERACT II was of small magnitude with no effect on hematoma expansion and small benefit (absolute benefit of 3.6%) on rate of severe disability and death.
- Results are hypothesis generating but not compelling to change standard of care.

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Antihypertensive Treatment of Cerebral Hemorrhage

Lessons for ATACH II?

- Ensure that intensive SBP reduction meets the SBP goals (<140 mm Hg) effectively and consistently. A mere difference from standard SBP reduction may not adequately test the primary hypothesis.
- Monitor time to initiate treatment and post 24 hr BP management to avoid differences secondary to unblinded nature of trial.
- No modification in inclusion/exclusion criteria as no heterogeneity of the treatment effect on the primary outcome in eight prespecified in INTERACT II.
- Safety profile maybe different with greater magnitude of SBP reduction.
- Maintain a low proportion of untreated patients to adequately test "pharmacological reduction" as an intervention.

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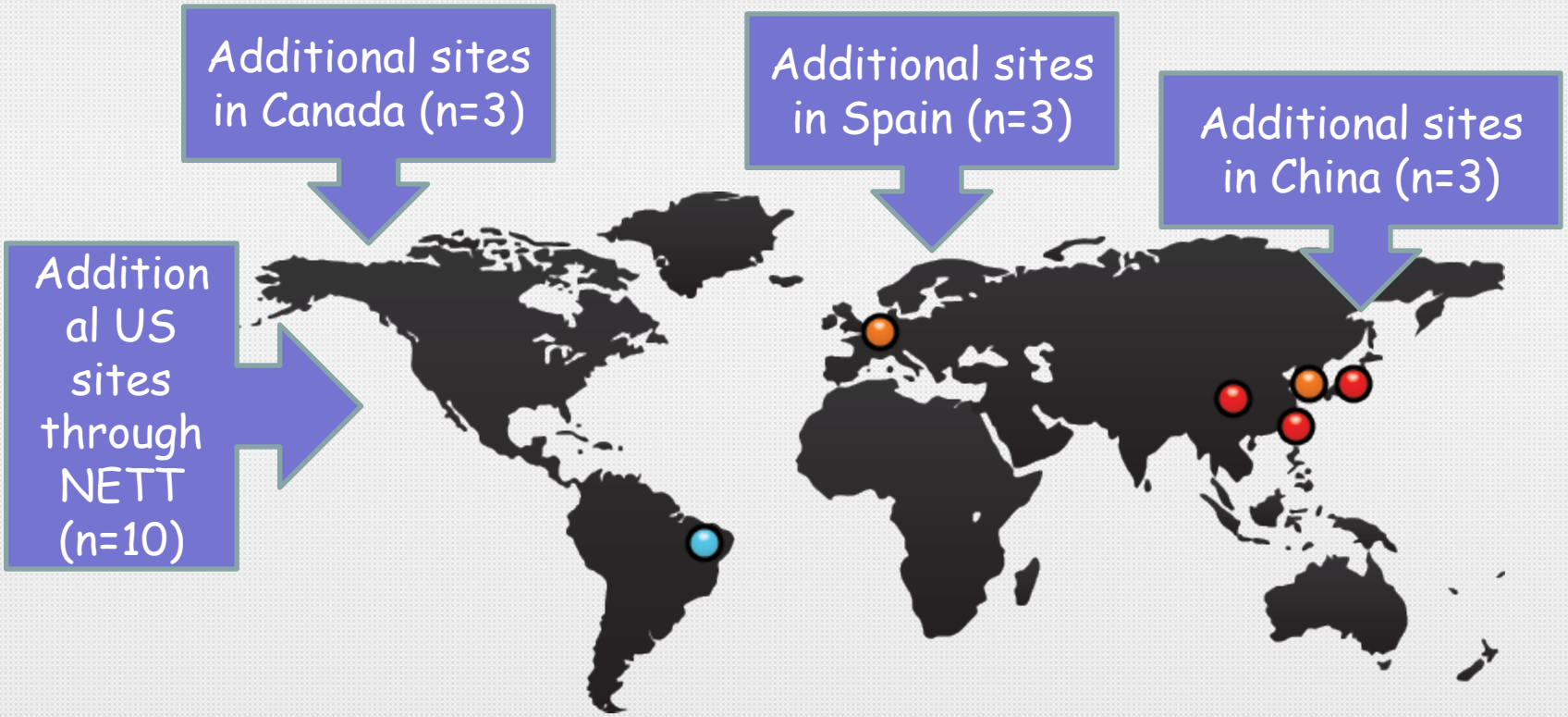
Anticipated New Initiatives



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Partnership with the NETT CCC

- The NETT Clinical Coordinating Center at the University of Michigan will manage domestic clinical sites in the fourth year of the trial.
- Transition of responsibilities expected on 11/1/13.
- 33 Additional sites in YR 4:
  - 10 additional NETT sites.
  - 10 additional domestic sites.
  - 13 additional foreign sites.
  - Cumulative active sites by close of YR 4: 115.

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Antihypertensive Treatment of Cerebral Hemorrhage

Sites in Germany

- University Hospital Dresden
- Clinic Frankfurt Hoechst
- University Hospital Halle
- University Hospital Heidelberg
- University Hospital Leipzig
- University Hospital Mannheim
- Hospital Barmherzige Bruder

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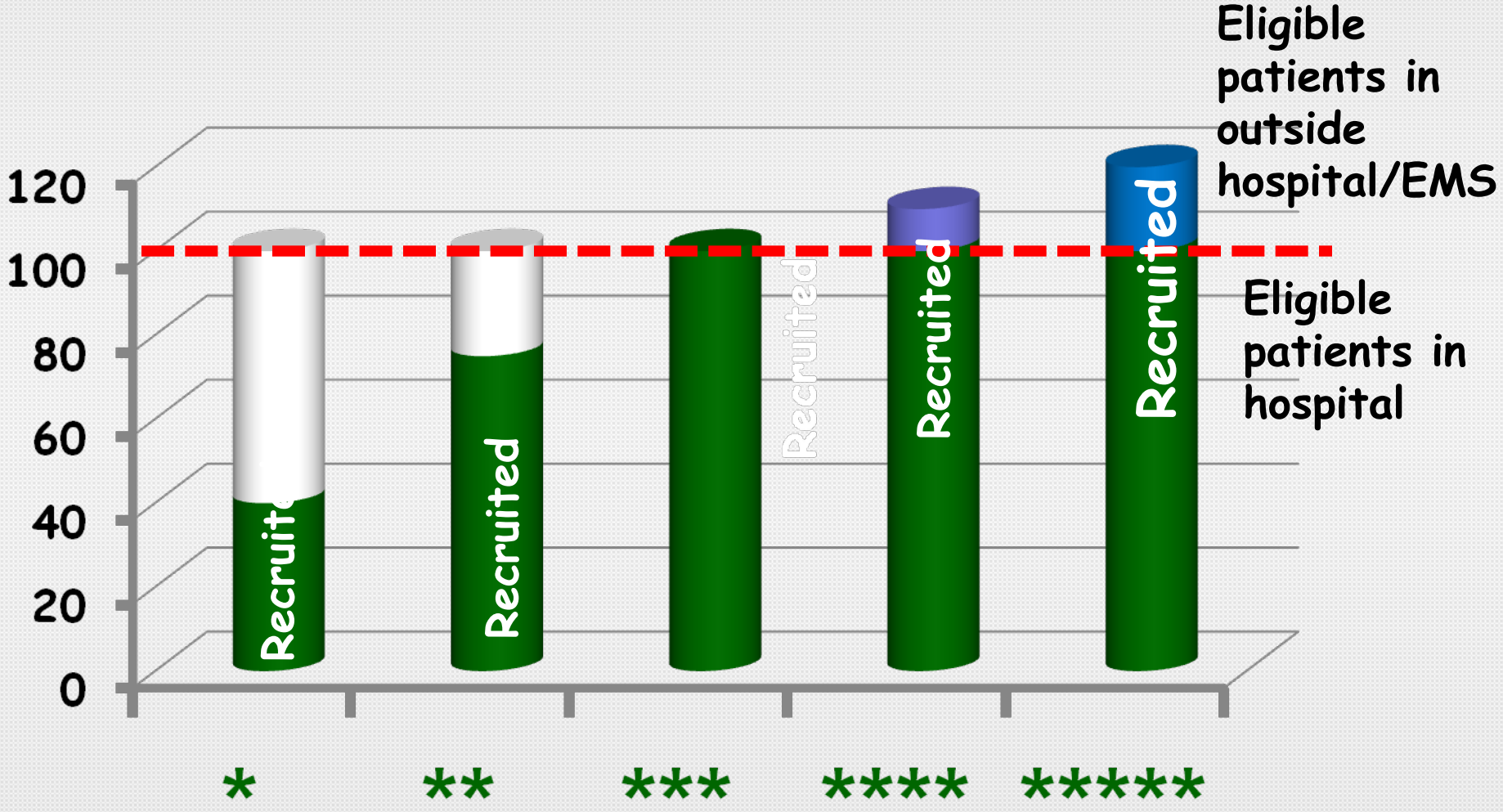
ATACH II Trial Update: Neurological Emergency Treatment Trials Network Investigators Meeting

Chicago, October 21st, 2013

CURRENT CHALLENGES

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Classification of sites by proportion recruitment of eligible patients



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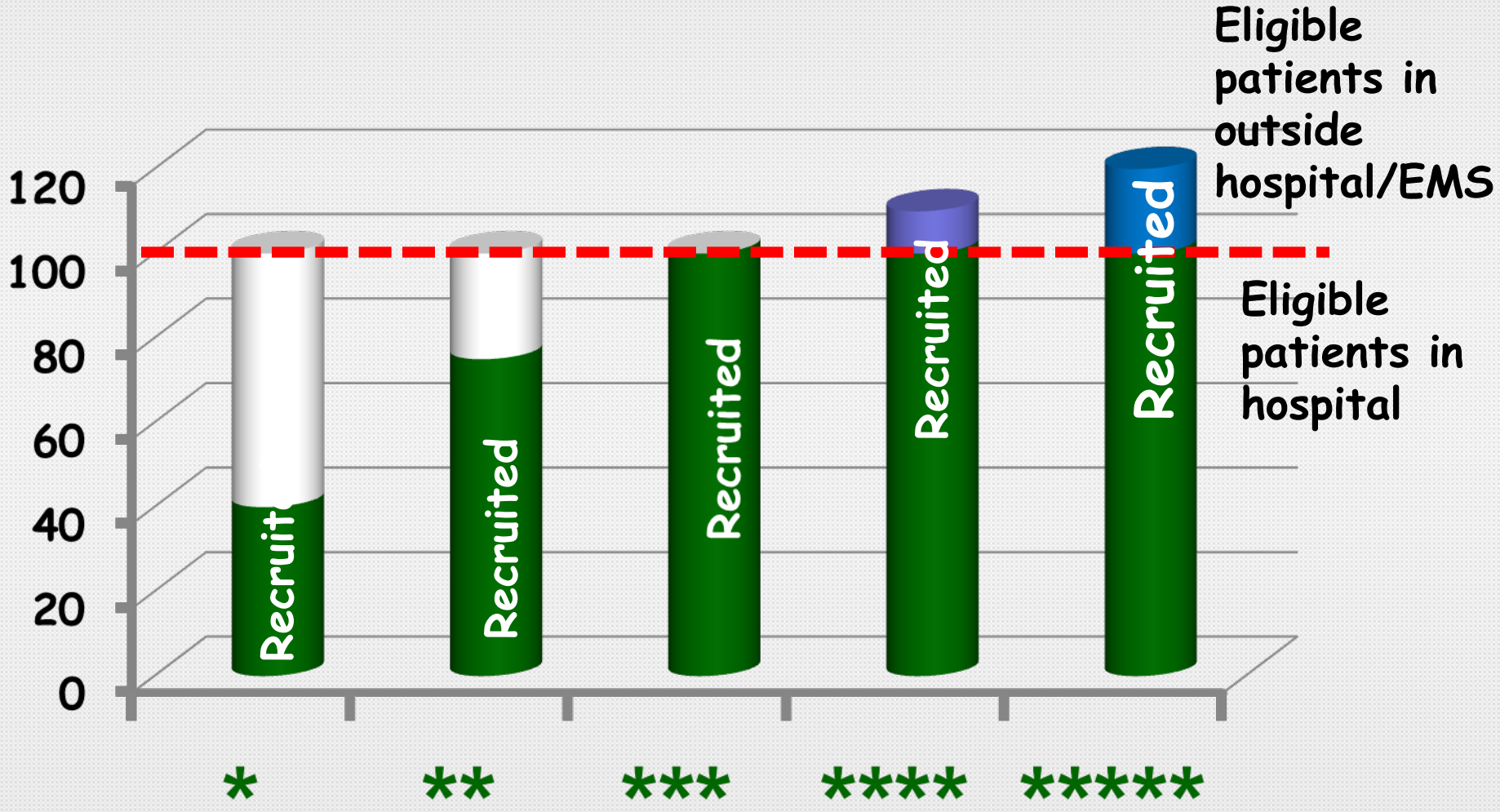

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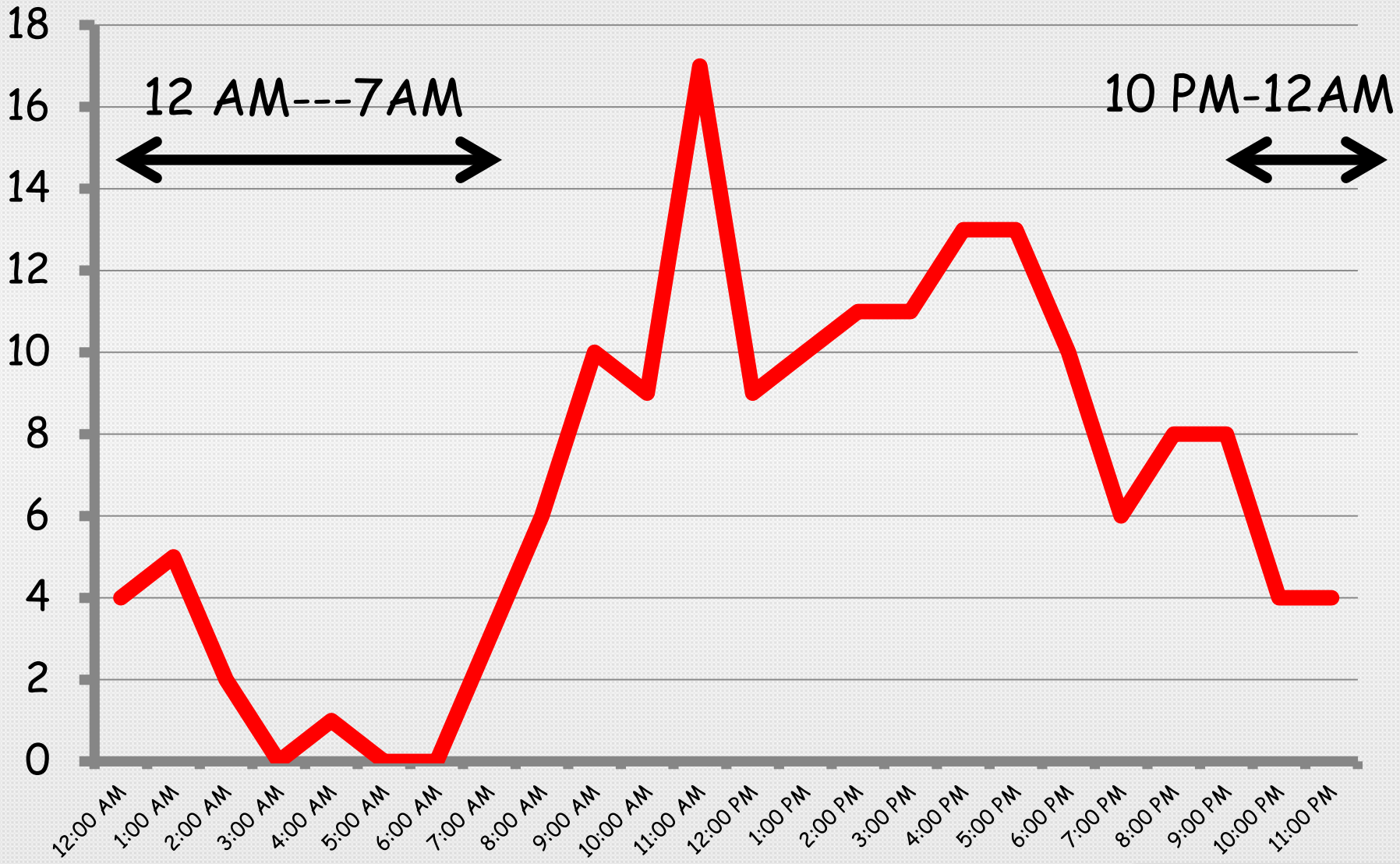
Randomization according to time of day



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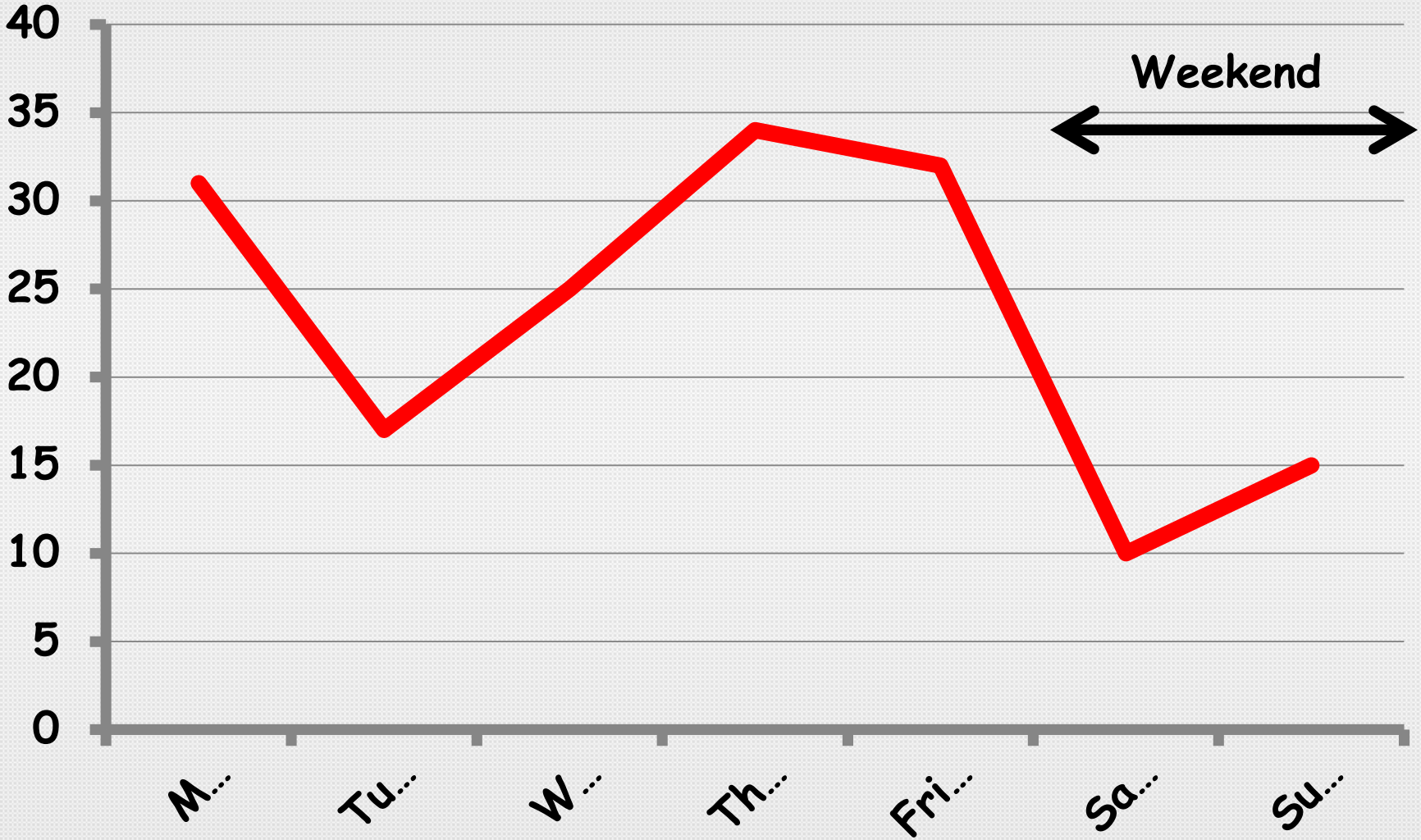
Randomization according to day of week



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Integration: additive OR synergistic?

ATACH II
INTERACT II

SBP reduction
<140 mm Hg

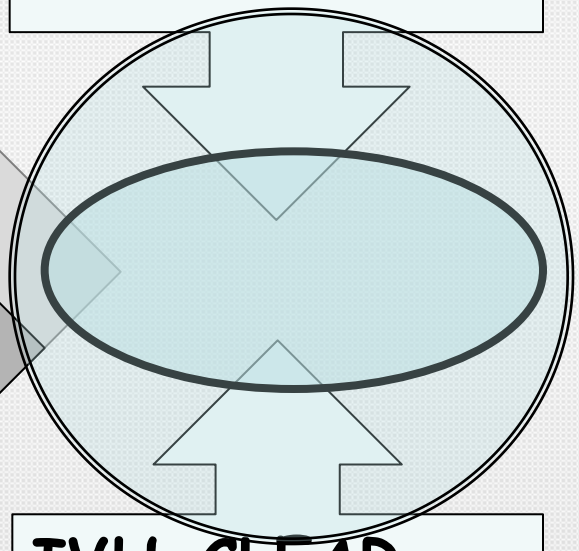
Time window

Patient subset

Time to reach
SBP goals

Intensity
of care

STICH II
Surgical
evacuation
of lobar ICH



IVH-CLEAR
Intraventricula
r hemorrhage+
thrombolytics

Thank you for all your support and guidance

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage