Blood pressure management in hemorrhagic stroke

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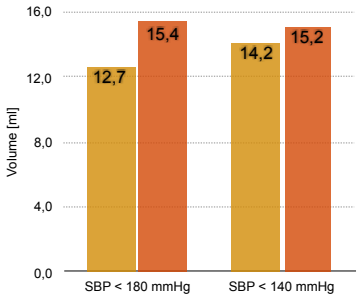
Blood pressure in acute ICH
Do we need additional trials after INTERACT2 and ATTACH-II?

Content

1. **What is known from clinical studies?**
2. What else should be taken into consideration?
3. Do we need additional trials?

Intensive blood pressure reduction (≤140 mmHg) decreases the risk of hematoma expansion

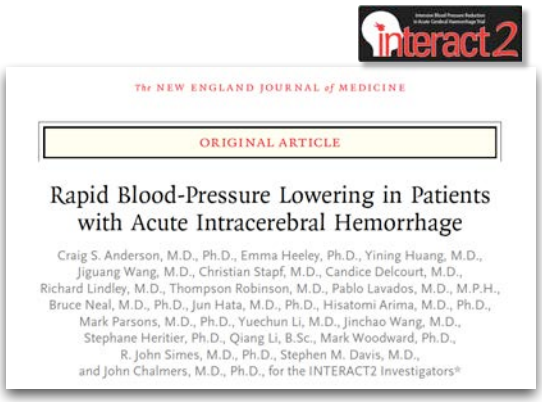
INTEACT-1: Hematoma volumes



Primary endpoint:
Mean proportional hematoma growth:
- **36.3%** (<140-group)
- **13.7%** (<180-group)
- Difference 22.6%, (95% CI 0.6-44.5%; p=0.04)

Mean absolute increase: 1.7 ml, p=0.12

Anderson CS, et al. *Lancet Neurol.* 2008;7:391-399


The NEW ENGLAND JOURNAL of MEDICINE

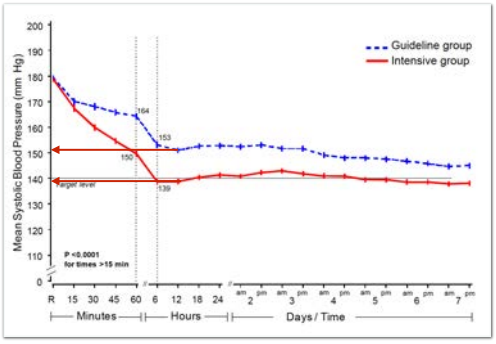
ORIGINAL ARTICLE

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*

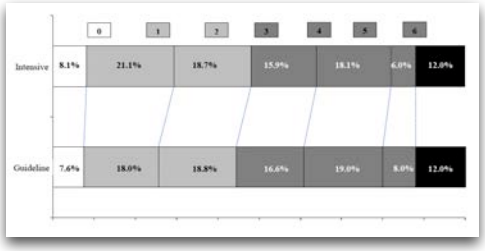
Anderson CS et al. *N Engl J Med.* 2013;368:2355-2365

INTERACT-2: Systolic blood pressure levels at and after randomization



Anderson CS et al. *N Engl J Med.* Supplement 2013;368:2355-2365

INTERACT-2: mRS



Primary outcome, mRS 0-2 vs 3-6:
- Odds ratio (with < 140 mmHG): 0.87; 95% confidence interval [CI], 0.75 to 1.01; p=0.06

Ordinal analysis, mRS categorial shift:
- Odds ratio for greater disability (with <180mmHg): 0.87; 95% CI, 0.77 to 1.00; p=0.04

Anderson CS et al. *N Engl J Med.* 2013;368:2355-2365, supplement

ESO EUROPEAN STROKE ORGANISATION

For adults with acute ICH, does altering blood pressure to a particular target or with a specific agent compared to an alternative target or agent

Recommendation
In acute ICH within 6 hours of onset, intensive blood pressure reduction (systolic target <140 mmHg in <1 hour) is safe and may be superior to a systolic target <180 mmHg. No specific agent can be recommended.

Strength of recommendation: weak
Quality of evidence: moderate

AHA/ASA Guideline

Blood pressure

Recommendation
For ICH patients presenting with SBP between 150 and 220 mm Hg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mm Hg is safe (Class I; Level of Evidence A)
and can be effective for improving functional outcome (Class IIa; Level of Evidence B).
(Revised from the previous guideline)

Hemphill JC, 3rd et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2015;46:2032-2060

ATACH-II
What does it add to this?

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

The NEW ENGLAND JOURNAL of MEDICINE

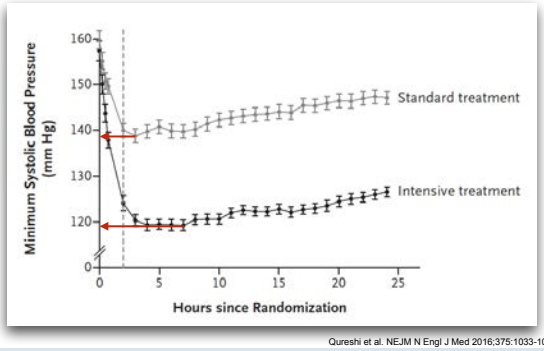
ORIGINAL ARTICLE

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*

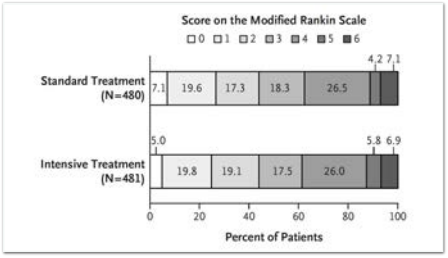
Qureshi et al. N Engl J Med 2016;375:1033-1043

ATACH-2: Blood pressure courses



Qureshi et al. NEJM N Engl J Med 2016;375:1033-1043

ATACH-2: clinical outcome



Primary endpoint: mRS 0-3 vs. 4-6
110-139 mmHg-group): **38.7%** vs.
140-180 mmHg group: **37.7%**
Relative risk, 1.04; 95% CI, 0.85 to 1.27

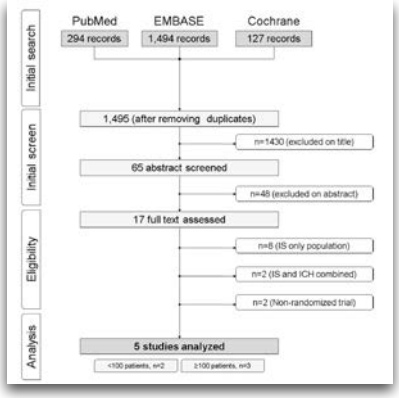
Qureshi et al. NEJM N Engl J Med 2016;375:1033-1043, supplement

Meta-Analysis

RESEARCH PAPER

Intensive blood pressure lowering in patients with acute intracerebral haemorrhage: clinical outcomes and haemorrhage expansion systematic review and meta-analysis of randomised trials

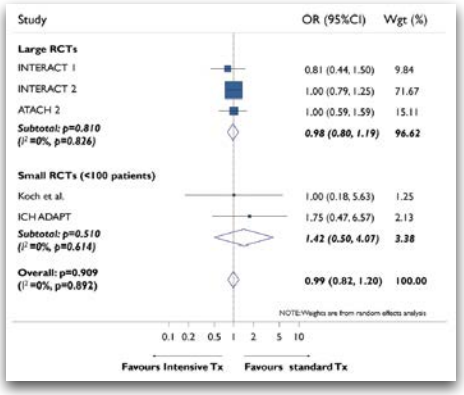
Boulouis G et al. J Neurol Neurosurg Psychiatry 2017;88:339-345



Flowchart for studies selection

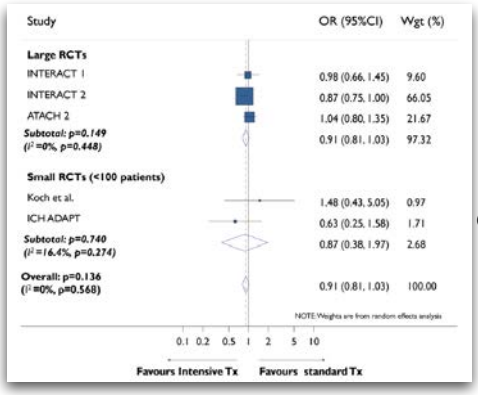
ICH, intracerebral haemorrhage; IS, ischaemic stroke

Boulouis G et al. J Neurol Neurosurg Psychiatry 2017;88:339-345



3-month mortality risk

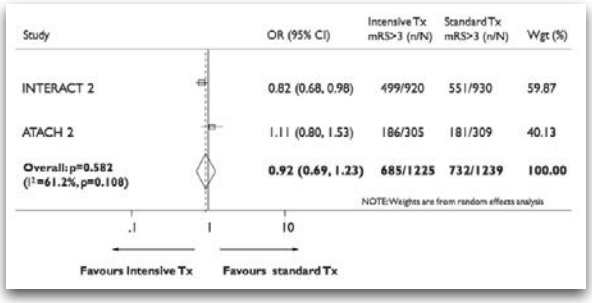
Boulouis G et al. J Neurol Neurosurg Psychiatry 2017;88:339-345



3-month death or dependency

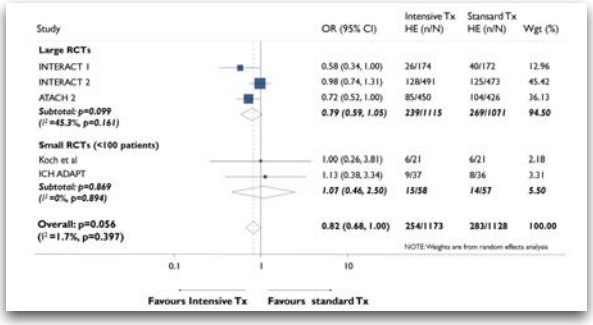
Boulouis G et al. J Neurol Neurosurg Psychiatry 2017;88:339-345

3-month mRS>3



Boulouis G et al. J Neurol Neurosurg Psychiatry 2017;88:339-345

Significant haemorrhage expansion at 24 hours



Boulouis G et al. J Neurol Neurosurg Psychiatry 2017;88:339-345

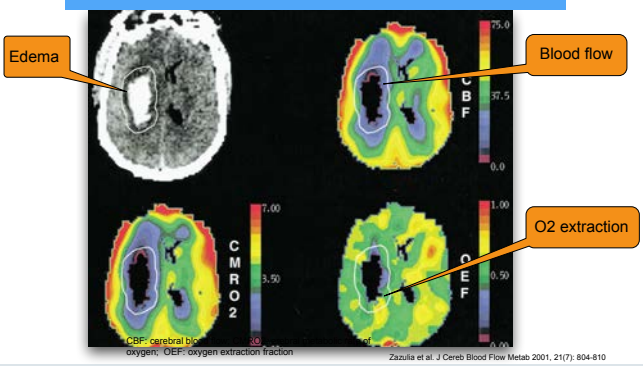
Blood pressure in acute ICH
Do we need additional trials after INTERACT-2 and ATTACH-II?

1. What is known from clinical studies
2. **What else should be taken into consideration?**
3. Do we need additional trials?

What else should be taken into consideration?

Ischemia?

PET study: hypo-perfusion in ICH without peri-lesional ischemia



CBF: cerebral blo
oxygen; OEF: oxygen extraction fraction

Zazulia et al. J Cereb Blood Flow Metab 2001, 21(7): 804-810

Moderate BP reduction does not impair CBF (n=14)

Parameter	Baseline	Treated	p value
Mean arterial pressure, mm Hg, mean +/- SD (range)	**143** +/- 10 (129-158)	**119** +/- 11 (90-133)	
MCANS, mean +/- SD	46 +/- 23	46 +/- 26	0,846
Arterial PCO2, mm Hg, mean +/- SD	36,6 +/- 6,1	35,4 +/- 5,1	0,909
Arterial O2 saturation, %, mean +/- SD	96,1 +/- 2,3	96,7 +/- 1,5	0,473
Global CBF, mL 100 g/min, mean +/- SD 95% CI difference	32,1 +/- 7,1 +1,4 to 2,7	31,5 +/- 8,4	0,49
Periclot CBF, mL 100 g/min, mean +/- SD 95% CI difference	**18,9** +/- 9,7 +1,1 to - 2,7	**18,1** +/- 8,8	0,402

MCANS = Middle Cerebral Artery Neurological Scale; CBF = cerebral blood flow

Powers WJ et al. Neurology. 2001;57:18-24

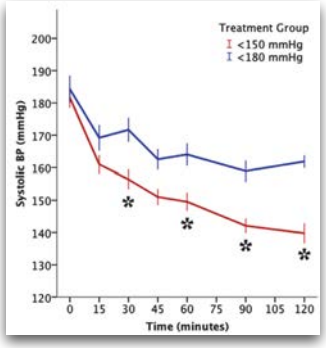
ICH-ADAPT

The Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial

Kenneth S. Butcher, MD, PhD; Thomas Jeerakathil, MSc, MD; Michael Hill, MD, MSc; Andrew M. Demchuk, MD; Dariush Dowlatshahi MD, PhD; Shelagh B. Coutts, MD; Bronwen Gould, BSc; Rebecca McCourt; Negar Asdaghi, MD, MSc; J. Max Findlay, MD, PhD; Derek Emery, MD, MSc; Ashfaq Shuaib, MD; for the ICH ADAPT Investigators

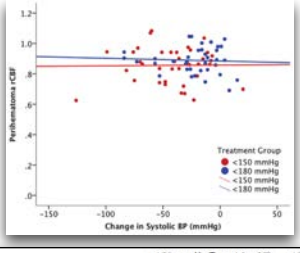
Butcher KS, et al. Stroke. 2013;44:620-626

Systolic blood pressure (BP) in ICH-ADAPT



Butcher KS, et al. Stroke. 2013;44:620-626

No relationship between the absolute change in systolic blood pressure (BP) and perihematoma relative cerebral blood flow (rCBF)

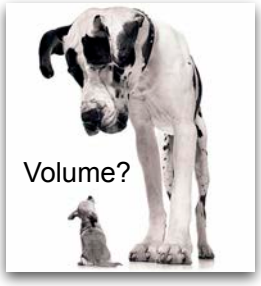


	<150 mm Hg Target (n=37)	<180 mm Hg Target (n=36)	P Value
Relative perfusion measures (mean±SD)			
Perihematoma rCBF	0.86±0.12	0.89±0.09	0.18

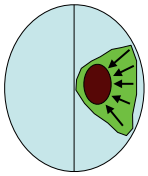
Butcher KS, et al. Stroke. 2013;44:620-626

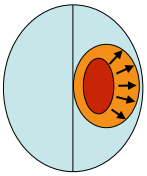
What else should be taken into consideration?

What else should be taken into consideration?



Basic difference in trial design:
Cerebral ischemia vs intracerebral hemorrhage

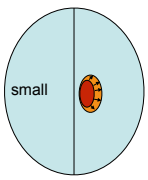


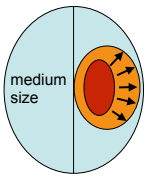


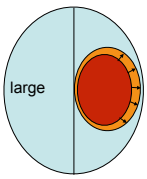
Cerebral ischemia
Improvement of disability

Intracerebral hemorrhage
Prevention of deterioration

Intracerebral hemorrhage
Concept: prevention of deterioration







Small hematomas grow small - too small to make a clinical difference

Large hematomas may grow - but that will not make a big clinical difference

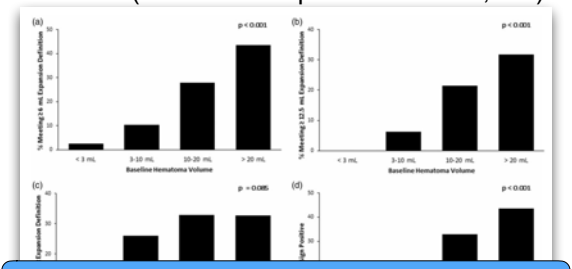
Determinants of intracerebral hemorrhage growth

Specific Model	% Change in ICH	% Change in ICH+IVH	Absolute Change in ICH	Absolute Change in ICH+IVH	Categoric Change in ICH
Treatment, rFVIIa vs placebo	0.0245	0.0123	0.0113	0.0184	0.0780
Time from onset to baseline CT, per 30 minutes	0.0623	0.0292	0.0252	0.0144	0.0064
ICH volume on baseline CT, per 10 mL	<0.0001	0.0092	...	0.0347	0.0146
IVH volume on baseline CT, per 10 mL	...	0.0429	...	...	...
Baseline weight, per 5 kg	0.0478	0.0462	...	...	...
Glucose, per 3 mmol/L	...	0.0767	0.02	0.0306	...
Antiplatelet use	...	...	...	...	0.0734
Total serum cholesterol, per 1 mmol/L	0.0680	...	...	...	...
Serum creatinine, per 30 μmol/L	...	0.0483	...	0.0102	...

Larger hematomas on the baseline CT were associated with increased absolute ICH growth.

Broderick JP at al. Stroke 2007;38:1072-1075

Hematoma expansion stratified by baseline ICH volume (in different expansion models, a-d)



Small intracerebral hemorrhages have a low spot sign prevalence and are less likely to expand

Dowlatshahi D et al. Int J Stroke 2016;11:191-197

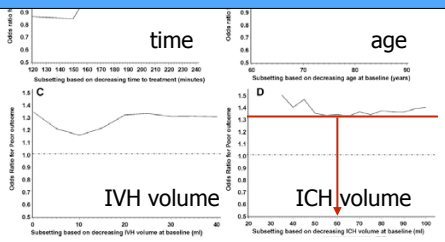
Baseline volumes and timing in RCT on RR management ICH?

	INTERACT-I		INTERACT-II		ATACH-II		ADAPT		RBPR-ICH		Mean
	<180	<140	<180	<140	<180	<140	<180	<150	MAP <110	MAP 110-130	
Baseline volume (median, cm³)	16,2 (17,1)	16,2 (16,1)	11 (6-19)	11 (6-20)	10,3 (2.3–85.2)	10,2 (0.98 – 79.1)	22,61 ±21.35	23,90 ±28.30	8,5 ± 9.8	12, 5 ± 17.2	**14**
Onset to randomisation [hours]	3.4 (2.5–4.5)		3.7 (2.8–4.8)		3,6 ±0,95	3,07 ±0,94	7.8 (3.3–16.8)	8.54 (3.8–15.9)	3.1 ±2.2		4,3
Onset to start of treatment [hours]	?	?	4 2,9-5, 1	4,5 (3,0 - 7,0)	2,4 ±1	4,6 ±0,95			3,1 ± 2,2	3,2± 2,2	2,4 (<180) to 5,1 (<140)
Onset to reach of target pressure [hours]	>3.4 (2.5–4.5) +6 hours	> 3.4 (2.5–4.5)	4 (= as above, because occurred immediately)	10,7 hours	3,4 ±1	2,75 ±1,7			≈ 6,1	≈ 6,2	**5,7**

Anderson CS et al. INTERACT-II N Engl J Med. 2013;368:2355-2365, Anderson CS et al. INTERACT-I, Lancet Neurol. 2008;7:391-399, Qureshi et al. NEJM N Engl J Med 2016;375:1033-1043, Butcher KS et al. ADAPT. Stroke 2013;44:620-626, Koch S et al.Neurocrit Care 2008;8:316-321

Influence of time, age, IVH-, ICH-volume on ODs for severe disability or death in FAST

Baseline volume >60ml predict mRS 5 or 6



Mayer SA et al. Stroke 2009;3:833-840

What else should be taken into consideration?

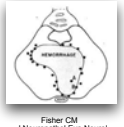
Course of haematoma expansion

The primary study target

- Hyper-acute (minutes to hours) - is a matter of coagulation and blood pressure

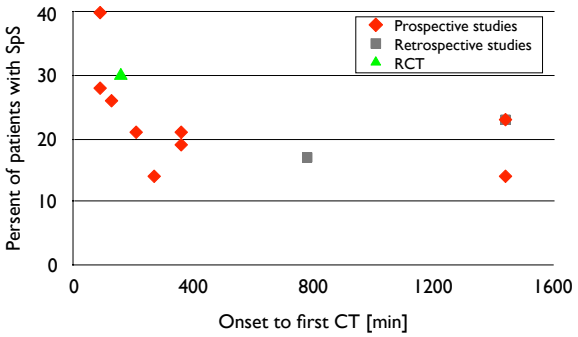
Reason why to continuously control BP

- Sub-acute (hours) - is a matter of inflammation (cell damage) and blood pressure

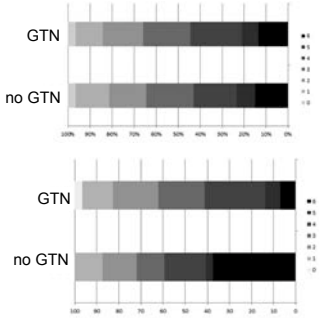


Fisher CM
J Neuropathol Exp Neurol
1971;30:536-550

Presence of spot sign depends on onset to CCT time



Modified Rankin Scale scores from ENOS for ICH at day 90



Randomized < 24 hours
(GTN 310 vs. no GTN 319)
Adjusted common odds ratio, 1.04 (95% confidence interval, 0.78–1.38; P=0.81

However
Mean baseline volumes GTN vs No-GTN
13 ml vs 20 ml

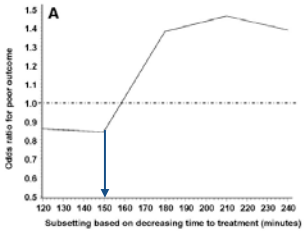
Shorter time to treatment - better outcome

Randomized < 6 hours
(GTN 29 vs. no GTN 32)
Adjusted common odds ratio, 0.19 (95% confidence interval, 0.06–0.59; **P=0.004**

GTN: transdermal glyceryl trinitrate (5 mg/d for 7 days)

Krishnan K et al. Stroke 2016;47:44-52

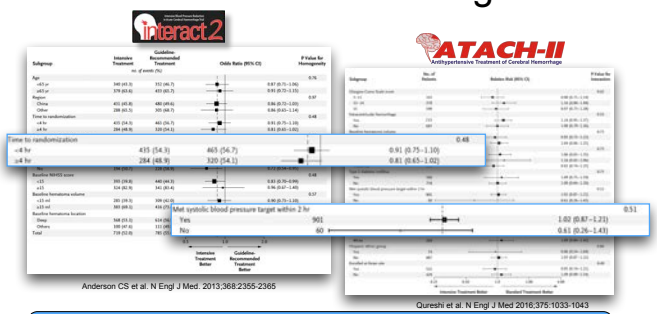
Influence of time on ODs for severe disability or death in FAST



Time to treatment > 2,5 hours: predicts mRS 5 or 6

Mayer SA et al. Stroke 2009;3:833-840

Influence of timing



Anderson CS et al. N Engl J Med. 2013;368:2355-2365

Qureshi et al. N Engl J Med 2016;375:1033-1043

Results go in different directions

Baseline volumes and timing in RCT on RR management ICH?

	INTERACT-I		INTERACT-II		ATACH-II		ADAPT		RBPR-ICH		Mean
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Onset to randomisation	3.4		3.7		3,6	3,07	7.8	8.54	3.1		4.3
Onset to reach of target pressure [hours]	>3.4 (2.5–4.5) +6 hours	> 3.4 (2.5–4.5)	4 (= as above, because occurred immediately)	10,7 hours	3,4 ±1	2,75 ±1,7			≈ 6,1	≈ 6,2	**5,7**

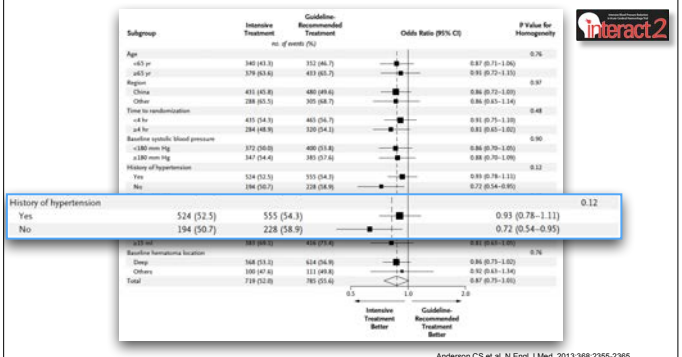
Mean time to traget pressure too long to expect an effect on outcome

Anderson CS et al. INTERACT J N Engl J Med. 2013;368:2355-2365

What about chronic hypertension

Do we need to differentiate between patients with and without a history of chronic hypertension?

Chronic hypertension

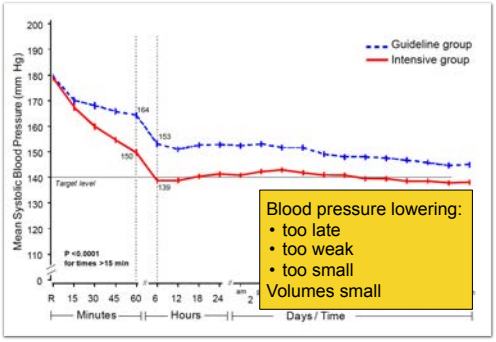


Anderson CS et al. N Engl J Med. 2013;368:2355-2365

Preliminary conclusion

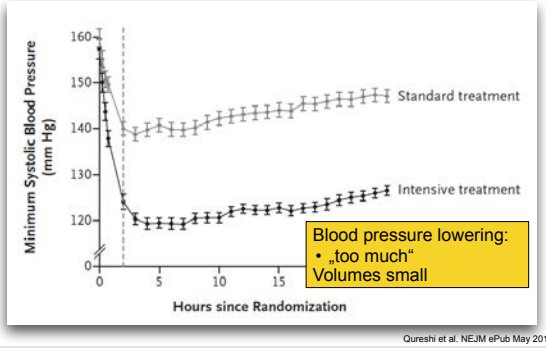
with respect to INTERACT-2 and ATACH-2

INTERACT-2: Systolic blood pressure levels at and after randomization



Anderson CS et al. *N Engl J Med*. Supplement 2013;368:2355-2365

ATACH-2: Blood pressure courses



Qureshi et al. NEJM ePub May 2016

Blood pressure in acute ICH
Do we need additional trials after INTERACT-2 and ATTACH-II?

Content

1. What is known from clinical studies
2. What else should be taken into consideration?
3. **Do we need additional trials?**

Blood pressure in
Do we need additional trials
ATTACH

Suggestions

- RCT
- Adult patients (<70-75 years) with spontaneous ICH (CCT proven and a systolic press > 140 mmHg,
- Pre-mRS <1
- Volume 10-60 ml, IVH < 5ml
- **Onset to treatment: < 3 hours (better 2,5 hours)**
- with a fast-acting iv-antihypertensive: Clevidipine
- to a systolic blood pressure >120 and <140 mmHg
- compared to systolic blood pressure 140-160 mmHg
- Outcome: shift in mRS categories