Treatment of High Blood Pressure in ICH

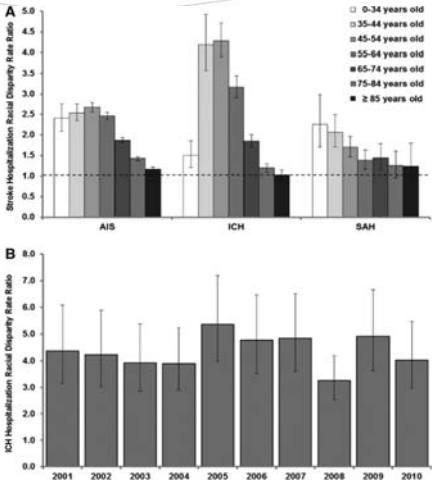
Mark J. Alberts, MD

ICH in the Stroke Belt Buckle

- Data from South Carolina, 2001-2010
- 84,179 stroke hospitalizations
- 31,137 (37%) were < 65 years of age
- 29,846 (35.5%) were African-Americans

Boan et al., Stroke, 2014

A, Age- and stroke subtype–specific racial difference in stroke hospitalization rate per 100 000 (10-year combined).



Andrea D. Boan et al. Stroke. 2014;45:1932-1938

American Heart Association.

ICH and Hypertension

- Major risk factor for ICH is hypertension
  - 70-80% of patients with ICH have HTN as a risk factor
- The vast majority of patients with ICH present with HTN
  - Sometime extreme (> 200 systolic)

ATACH: Antihypertensive Treatment of Acute Cerebral Hemorrhage Trial

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- An open-label, dose-escalation, multicenter, prospective study of patients with ICH with elevated SBP ≥170 mm Hg presenting to the ED within 6 hours of symptom onset
- Patients were enrolled in 3 respective tiers of SBP treatment goals
  - Tier 1 SBP goal: 170 to 200 mm Hg (n=18)
  - Tier 2 SBP goal: 140 to 170 mm Hg (n=20)
  - Tier 3 SBP goal: 110 to 140 mm Hg (n=22)
- CARDENE® I.V. (nicardipine hydrochloride) was initiated at 5 mg/hr, and then increased by 2.5 mg/hr every 15 minutes as needed, up to a maximum of 15 mg/hr

Abbreviations: ED, emergency department; ICH, intracerebral hemorrhage; SBP, systolic blood pressure.

Reference: Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) Investigators. *Crit Care Med*. 2010;38(2):637-648.

ATACH I Study Results

Outcome	SBP Reduction >=60 mm	SBP Reduction < 60 mm Hg
N	11	9
Hematoma Expansion	18%	37.5%
Edema Expansion	30%	37.5%
Death/Disability	12.5%	43%

Qureshi et al., J Vasc Int Neur, 2012

Original Article

Blood-Pressure Lowering in Patients with Acute Intracerebral Hemorrhage

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., John Chalmers, M.D., Ph.D., for the INTERACT2 Investigators

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INTERACT 2 Study Design

- 2839 patients with ICH
- Treatment within 6 hours
- Two treatment goals: Intense = BP < 140
  Guideline = BP < 180
- Endpoint was death or significant disability

Study Overview

- In this trial involving patients with intracerebral hemorrhage, intensive BP lowering (target systolic BP <140 mm Hg) did not significantly reduce the rate of the primary outcome of death or major disability but did significantly improve overall functional outcomes.
- Death/Disability 52% vs 55% NS
- 13% decrease in modified Rankin (p = 0.04)

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Baseline Characteristics of the Participants.

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Intensive Blood-Pressure Lowering (N = 1399)	Guideline-Recommended Blood-Pressure Lowering (N = 1430)
Time from onset of ICH to randomization — hr		
Median	3.7	3.7
Interquartile range	2.8–4.8	2.9–4.7
Age — yr	63.0±13.1	64.1±12.6
Male sex — no. (%)	898 (64.2)	882 (61.7)
Recruited from China — no. (%)	947 (67.7)	973 (68.0)
Blood pressure — mm Hg		
Systolic	179±17	179±17
Diastolic	101±15	101±15
NIHSS score†		
Median	10	11
Interquartile range	6–15	6–16
GCS score‡		
Median	14	14
Interquartile range	12–15	12–15
History of hypertension — no./total no. (%)	1012/1398 (72.4)	1036/1428 (72.5)
Current use of antihypertensive drugs — no./total no. (%)	627/1398 (44.8)	647/1428 (45.3)
Prior intracerebral hemorrhage — no./total no. (%)	115/1398 (8.2)	114/1428 (8.0)
Prior ischemic or undifferentiated stroke — no./total no. (%)	157/1398 (11.2)	166/1428 (11.6)
Prior acute coronary event — no./total no. (%)	39/1398 (2.8)	42/1428 (2.9)
Diabetes mellitus — no./total no. (%)	155/1398 (11.1)	150/1428 (10.5)
Use of warfarin anticoagulation — no./total no. (%)	50/1398 (3.6)	31/1428 (2.2)
Use of aspirin or other antiplatelet agent — no./total no. (%)	123/1398 (8.8)	142/1428 (9.9)
Baseline hematoma volume — ml		
Median	11	11
Interquartile range	6–19	6–20
Deep location of hematoma — no./total no. (%)§	1084/1294 (83.8)	1098/1319 (83.2)
Left hemisphere site of hematoma — no./total no. (%)	644/1294 (49.8)	669/1319 (50.7)
Intraventricular extension of hemorrhage — no./total no. (%)	371/1294 (28.7)	369/1319 (28.0)

* There were no significant differences between the groups in any of the characteristics listed here. ICH denotes intracerebral hemorrhage.
† Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 (normal neurologic status) to 42 (coma with quadriplegia).
‡ Scores on the Glasgow Coma Scale (GCS) range from 15 (fully conscious) to 3 (deep coma).
§ Deep location refers to location in the basal ganglia or thalamus.

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Treatment of Patients with Intracerebral Hemorrhage.

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)	
Medical and surgical treatment during the first 7 days — no./total no. (%)			
Intubation	96/1379 (7.0)	93/1400 (6.6)	0.74
Admission to an intensive care unit	532/1379 (38.6)	529/1400 (37.8)	0.67
Prophylactic treatment for deep-vein thrombosis	306/1379 (22.2)	304/1400 (21.7)	0.76
Compression stockings	147/1379 (10.7)	146/1400 (10.4)	0.84
Subcutaneous heparin	248/1379 (18.0)	245/1400 (17.5)	0.74
Use of intravenous mannitol	855/1379 (62.0)	864/1400 (61.7)	0.88
Hemostatic therapy*	57/1379 (4.1)	40/1400 (2.9)	0.07
Any surgical intervention	77/1379 (5.6)	77/1400 (5.5)	0.92
Evacuation or decompression of the hematoma	43/1379 (3.1)	38/1400 (2.7)	0.53
Insertion of a ventricular drain	41/1379 (3.0)	44/1400 (3.1)	0.80
Decision to withdraw active treatment and care	75/1379 (5.4)	46/1400 (3.3)	0.005

* Hemostatic therapy included the use of fresh-frozen plasma, vitamin K, and recombinant tissue factor VIIa.

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Primary, Secondary, and Safety Outcomes at 90 Days.

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		
Safety outcomes — no./total no. (%)				
Neurologic deterioration in first 24 hr¶	198/1369 (14.5)	211/1395 (15.1)	0.95 (0.77–1.17)	0.62
Nonfatal serious adverse events‖	326/1399 (23.3)	338/1430 (23.6)		0.92
Any neurologic deterioration from intracerebral hemorrhage**	47/1399 (3.4)	55/1430 (3.8)		0.49
Recurrent intracerebral hemorrhage	4/1399 (0.3)	4/1430 (0.3)		
Ischemic or undifferentiated stroke	8/1399 (0.6)	8/1430 (0.6)		
Acute coronary event	5/1399 (0.4)	5/1430 (0.3)		
Other cardiovascular disease	22/1399 (1.6)	26/1430 (1.8)		
Noncardiovascular disease	160/1399 (11.4)	152/1430 (10.6)		0.49
Severe hypotension††	7/1399 (0.5)	8/1430 (0.6)		

* Plus–minus values are means ±SD. All odds ratios are unadjusted.
† The modified Rankin scale evaluates global disability and functioning; scores range from 0 (no symptoms) to 6 (death); the primary outcome of death or major disability was assessed as a score on the modified Rankin scale of 3 to 6 at 90 days.
‡ The difference between the groups in scores across all seven levels of the modified Rankin scale was determined with the use of a logistic-regression analysis of the ordinal data.
§ Possible responses in each domain were "no problems," "moderate problems," or "extreme problems"; for these analyses, the latter two levels were combined as "any problems." The overall health utility score was calculated with the use of population norms from the United Kingdom.
¶ Neurologic deterioration was defined as an increase from baseline to 24 hours of 4 or more points on the National Institutes of Health Stroke Scale or a decline of 2 or more points on the Glasgow Coma Scale.
‖ Nonfatal serious adverse events included those that were life-threatening, required inpatient hospitalization or prolongation of an existing hospitalization, or resulted in disability or a medical or surgical intervention; a patient could have more than one event.
** This category includes clinician-reported neurologic deterioration in a patient with cerebral mass effect or extension of the hematoma.
†† Severe hypotension was defined as hypotension with clinical consequences (including acute renal failure) that required corrective therapy with intravenous fluids, vasopressors, or hemodialysis.

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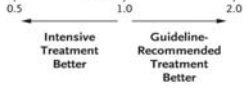
Effect of Early Intensive Blood-Pressure–Lowering Treatment on the Primary Outcome, According to Prespecified Subgroups.

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)	



Conclusions

- In patients with intracerebral hemorrhage, intensive lowering of blood pressure did not result in a significant reduction in the rate of the primary outcome of death or severe disability.
- An ordinal analysis of modified Rankin scores indicated improved functional outcomes with intensive lowering of blood pressure.

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2015 ICH Guidelines AHA

- **For ICH…..Treat BP with goal of systolic BP < 140 mm HG (Class I, Level A)**
- **Appears to be a safe approach**
- **No evidence of harm with lowering of BP**

Hemphill et al., Stroke, 2015

2015 AHA Guidelines

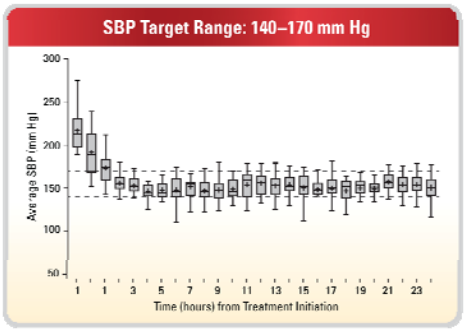
- Recommend that BP be treated with a continuous IV infusion
- IV Nicardipine is preferred agent (my opinion)
  - Easy to use
  - Very titratable
  - Few side effects
  - Does not increase ICP or cerebral bloodk volume

Ready-to-use CARDENE® I.V. (nicardipine hydrochloride) Delivers Smooth, Predictable BP Control

17

Rapid BP reduction in patients with ICH, with control maintained over 24 hours (Tier 2 results shown)

- 20 patients treated
- 212 mm Hg (median) initial SBP
- 90% of patients achieved SBP goals within 2 hours (all tiers)
- Gradual titration of CARDENE® I.V. (nicardipine hydrochloride) was used



CARDENE I.V. is not indicated for treatment or prevention of AIS, ICH, or aSAH.

Safety Information

CARDENE® I.V. (nicardipine hydrochloride) is contraindicated in patients with advanced aortic stenosis.

Abbreviations: AIS, acute ischemic stroke; aSAH, aneurysmal subarachnoid hemorrhage; BP, blood pressure; ICH, intracerebral hemorrhage; SBP, systolic blood pressure.

Reference: Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) investigators. *Crit Care Med*. 2010;38(2):637-648.

Advantages of IV Nicardipine (pre-mixed bag)

- Gentle agent—can be used in a Stroke Unit or NICU
- Pre-mixed bag can be stored on Stroke Unit for up to 24 months
- Cardene does not impact cerebral autoregulation
- Improves cardiac output
- Reduces cardiac afterload

Opportunities to Improve Care and Outcomes

- Mandate BP parameters for therapy in patients with ICH
- Ensure proper therapies are used
- Define treatment times
- Change to oral medications when possible
- **CLINICAL SECRET: When all else fails, try Minoxidil to control BP, especially in African-American patients**

Conclusions

- ICH is a common and serious, but somewhat neglected stroke type in the Stroke Belt
- Acute therapy aimed at reducing elevated blood pressures appears to be safe and may improve outcomes
- The use of IV medications to treat acutely elevated BP is preferred in many cases
- PROPOSAL: Monitor acute BP treatment and success in Stroke Centers to ensure optimal care