ATACH-II Investigator's Meeting

What was learned from ATACH-II? What is needed for our future projects?

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National Cerebral and Cardiovascular Center,
Suita, Osaka

26th Apr 2016

COI disclosure

No disclosure that exceeds the standards set by the Japan Stroke Society

脳国内循

Leading Opinion

International Journal of Stroke WSO

What are the next breakthroughs in the management of acute intracerebral hemorrhage?

International Journal of Stroke
0(0) 1–3
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Kazunori Toyoda[1], Masatoshi Koga[2] and Shoichiro Sato[1]

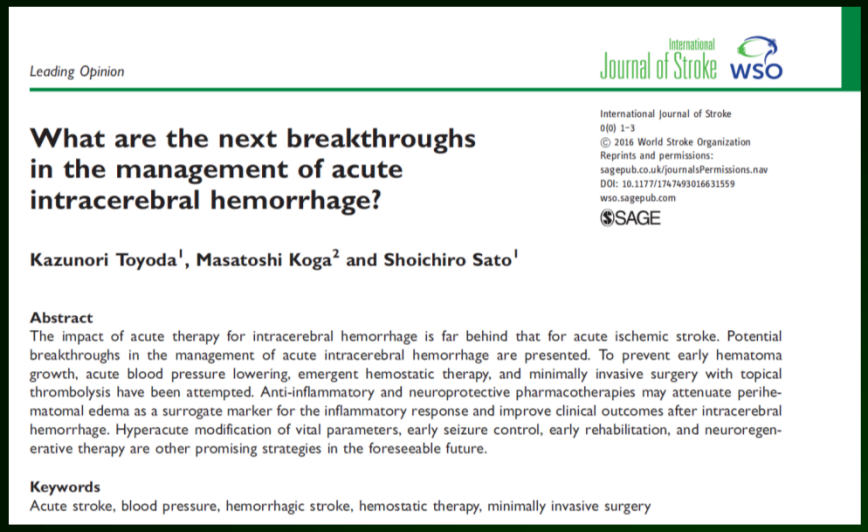
Abstract

The impact of acute therapy for intracerebral hemorrhage is far behind that for acute ischemic stroke. Potential breakthroughs in the management of acute intracerebral hemorrhage are presented. To prevent early hematoma growth, acute blood pressure lowering, emergent hemostatic therapy, and minimally invasive surgery with topical thrombolysis have been attempted. Anti-inflammatory and neuroprotective pharmacotherapies may attenuate perihematomal edema as a surrogate marker for the inflammatory response and improve clinical outcomes after intracerebral hemorrhage. Hyperacute modification of vital parameters, early seizure control, early rehabilitation, and neuroregenerative therapy are other promising strategies in the foreseeable future.

Keywords

Acute stroke, blood pressure, hemorrhagic stroke, hemostatic therapy, minimally invasive surgery

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage



Leading Opinion

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Abstract

The impact of acute therapy for intracerebral hemorrhage is far behind that for acute ischemic stroke. Potential breakthroughs in the management of acute intracerebral hemorrhage are presented. To prevent early hematoma growth, acute blood pressure lowering, emergent hemostatic therapy, and minimally invasive surgery with topical thrombolysis have been attempted. Anti-inflammatory and neuroprotective pharmacotherapies may attenuate perihematomal edema as a surrogate marker for the inflammatory response and improve clinical outcomes after intracerebral hemorrhage. Hyperacute modification of vital parameters, early seizure control, early rehabilitation, and neuroregenerative therapy are other promising strategies in the foreseeable future.

Keywords

Acute stroke, blood pressure, hemorrhagic stroke, hemostatic therapy, minimally invasive surgery

1. Acute blood pressure lowering
2. Emergent hemostatic therapy
3. Minimally invasive surgery
4. Anti-inflammation and neuroprotection
5. Other promising strategies
   - ✓ Hyperacute modification of BT, BG, electrolytes, etc
   - ✓ Control of early seizure
   - ✓ Early rehabilitation
   - ✓ Transplantation of stem cells
   - ✓ combination of the above strategies

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Acute BP Mx: EU vs. Japan

Table 2. Acute blood pressure (BP) management

European guidelines 2006 (EUSI)	Japanese guidelines 2009
Known hypertension (HPT) If SBP >180 mm Hg or DBP >105 mm Hg → BP <170/100 mm Hg or MAP <125 mm Hg (class IV, level C)	maintain SBP <180 mm Hg or MAP <130 mm Hg (grade C1)
Unknown history of HPT If SBP >160 mm Hg or DBP >95 mm Hg → BP <150/90 mm Hg or MAP <100 mm Hg (class IV, level C)	*when performing surgical treatment:* → more aggressive BP lowering (grade C1)
Decrease pressure not more than 20% of MAP on admission (class IV, level C)	
When ICP elevated (nitroprusside contraindicated) → adapt thresholds to cerebral perfusion pressure >70 (class IV, level C)	
Intravenous drugs recommended for better controllability (GCP)	no special hypotensive drug recommended, careful use of vasodilators (nitrates), because they induce brain HPT (grade C1)

SBP = Systolic blood pressure; DBP = diastolic BP; MAP = mean arterial pressure; HPT = hypertension.

ATACH-II Antihypertensive Treatment of Cerebral Hemorrhage

Toyoda K, Steiner T, et al: Cerebrovasc Dis 2013;35:419-429

Limitation of nicardipine use in Jpn

Table 2. Acute blood pressure (BP) management

European guidelines 2006 (EUSI)	Japanese guidelines 2009
Kı If →	the following contraindications described on the official label; 'nicardipine is contraindicated for (I) ICH patients with a suspicion of ongoing intracranial bleeding not to enhance bleeding and for (II) acute stroke patients with elevated intracranial pressure not to accelerate intracranial pressure elevation.' When nicardipine was originally approved for commercial use as an ameliorant of cerebral circulation, not as an antihypertensive agent, in Japan in 1981, a description of the above contraindications was listed on the label following that of another ameliorant of cerebral circulation. As far as we can determine,
Uı If →	
De lev	
W →	
Int	

Toyoda K, Stroke Vasc Interv Neurol 2009;2:417-424

Koga M, et al. Hypertens Res 2009;32:419-424

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Antihypertensive Treatment of Cerebral Hemorrhage

ORIGINAL ARTICLE

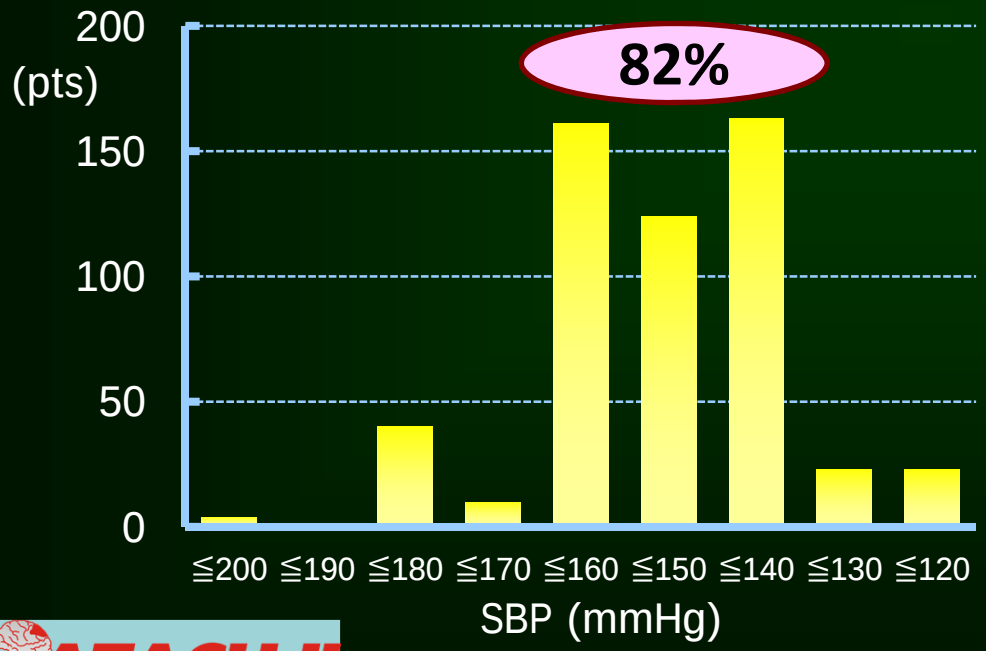
SAMURAI ICH

Koga M, et al: Hypertens Res 2009;32:759-764

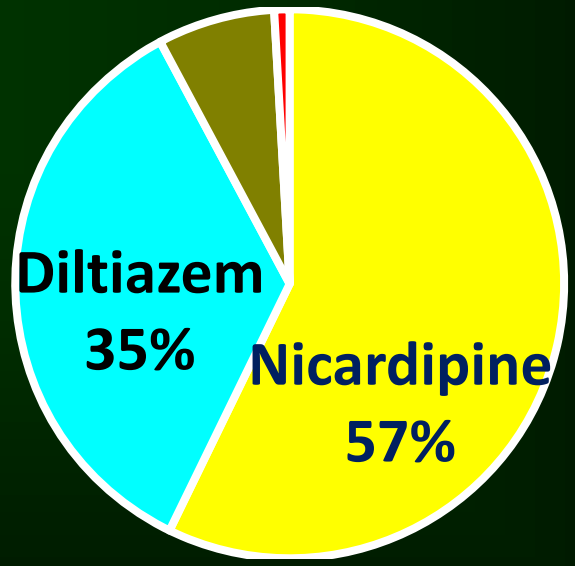
Nationwide survey of antihypertensive treatment for acute intracerebral hemorrhage in Japan

Masatoshi Koga[1], Kazunori Toyoda[1], Masaki Naganuma[1], Kazuomi Kario[2], Jyoji Nakagawara[3], Eisuke Furui[4], Yoshiaki Shiokawa[5], Yasuhiro Hasegawa[6], Satoshi Okuda[7], Hiroshi Yamagami[8], Kazumi Kimura[9], Yasushi Okada[10] and Kazuo Minematsu[1], for the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) Study Investigators

✓ Target SBP



✓ First choice of IV drug



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Antihypertensive Treatment of Cerebral Hemorrhage

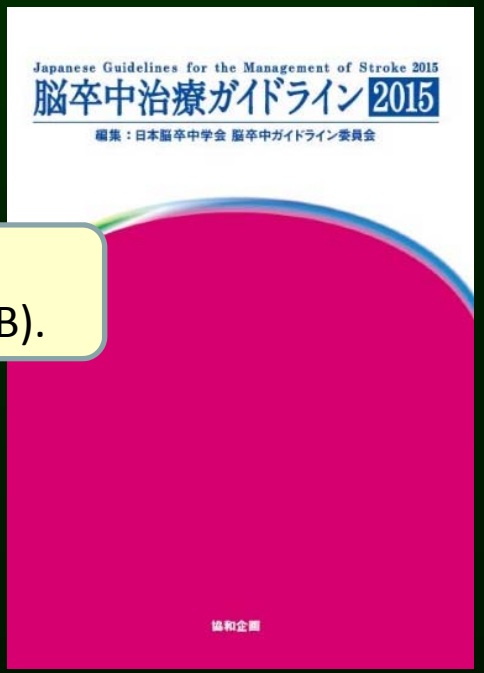
Acute BP Mx: '09 vs. '15 in Jpn

Japanese guidelines 2009
maintain SBP <180 mm Hg or MAP <130 mm Hg (grade C1)
when performing surgical treatment: → more aggressive BP lowering (grade C1)
no special hypotensive drug recommended, careful use of vasodilators (nitrates), because they induce brain HPT (grade C1)

Japanese guidelines 2015

Lower SBP <140 mmHg ASAP and maintain the level for 7 days (Grade C1).

IV CCB or IV nitrates recommended (Grade B).



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Antihypertensive Treatment of Cerebral Hemorrhage

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Stroke Acute Management with Urgent Risk-factor Assessment and Improvement

- ✓ Prospective, multicenter, observational (’09 - ’11)
- ✓ 211 pts w/supratentorial ICH / <3h after onset / <60mL / SBP >180 mmHg
- ✓ Lowering SBP to 120 – 160 mmHg using IV nicardipine

Nakamura Memorial Hospital

Jichi Medical Univ School of Med.

Natl Cerebral & Cardiovascular Ctr

Kobe City Medical Ctr

NHO Kyushu Medical Ctr

Kohnan Hospital

Kyorin Univ School of Med.

St Marianna Univ School of Med.

NHO Nagoya Medical Ctr

Kawasaki Medical School

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Antihypertensive Treatment of Cerebral Hemorrhage

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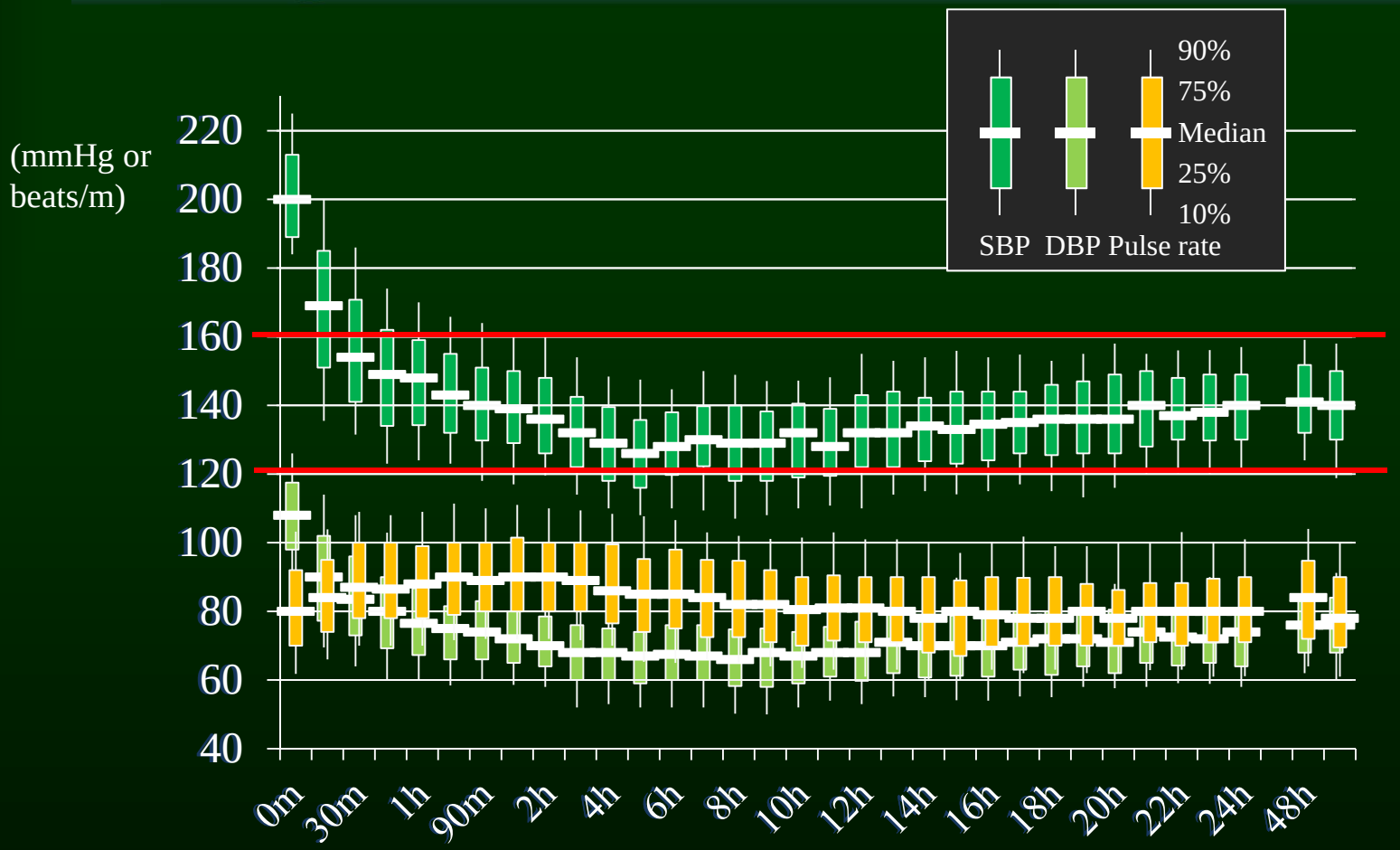

Koga M, et al: J Hypertens 2012;30:2357-2364

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Antihypertensive Treatment of Cerebral Hemorrhage

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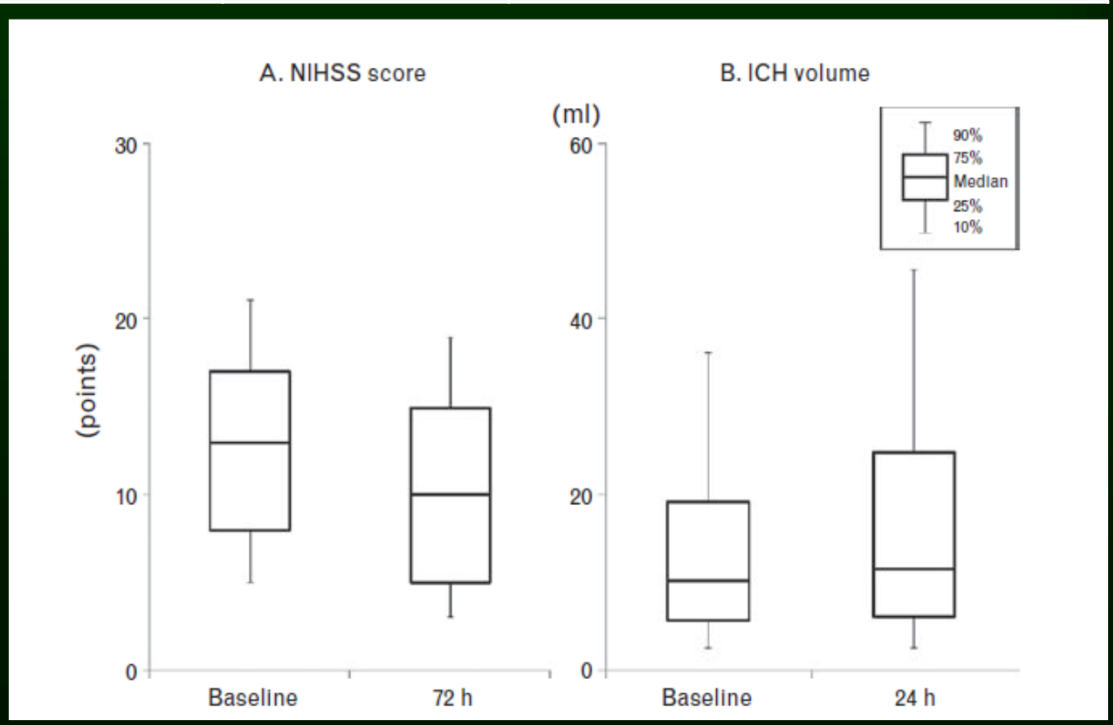
Primary endpoints	Results	90% CI of predictive proportion
⊿NIHSS ≥4 or ⊿GCS ≥2 @72h	8.1%	15.2 – 25.9%
SAE to stop nicardipine @24h	0.9%	1.8 – 8.9%



Koga M, et al: J Hypertens 2012;30:2357-2364

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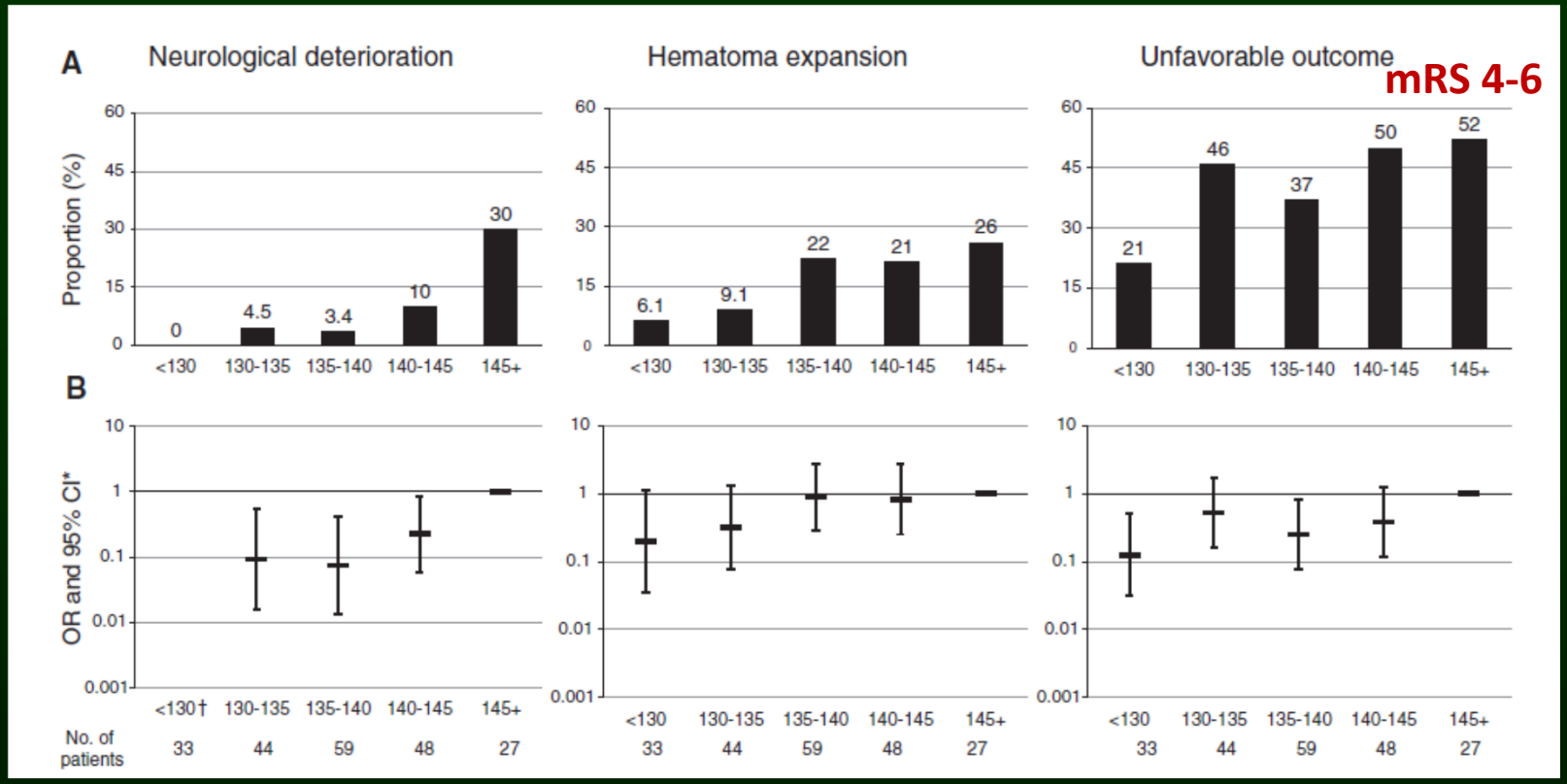
Antihypertensive Treatment of Cerebral Hemorrhage

Achieved SBP



OR 4.43 (1.98-9.90) 1.80 (1.08-2.98) 2.00 (1.23-3.26)

Per 10 mmHg .

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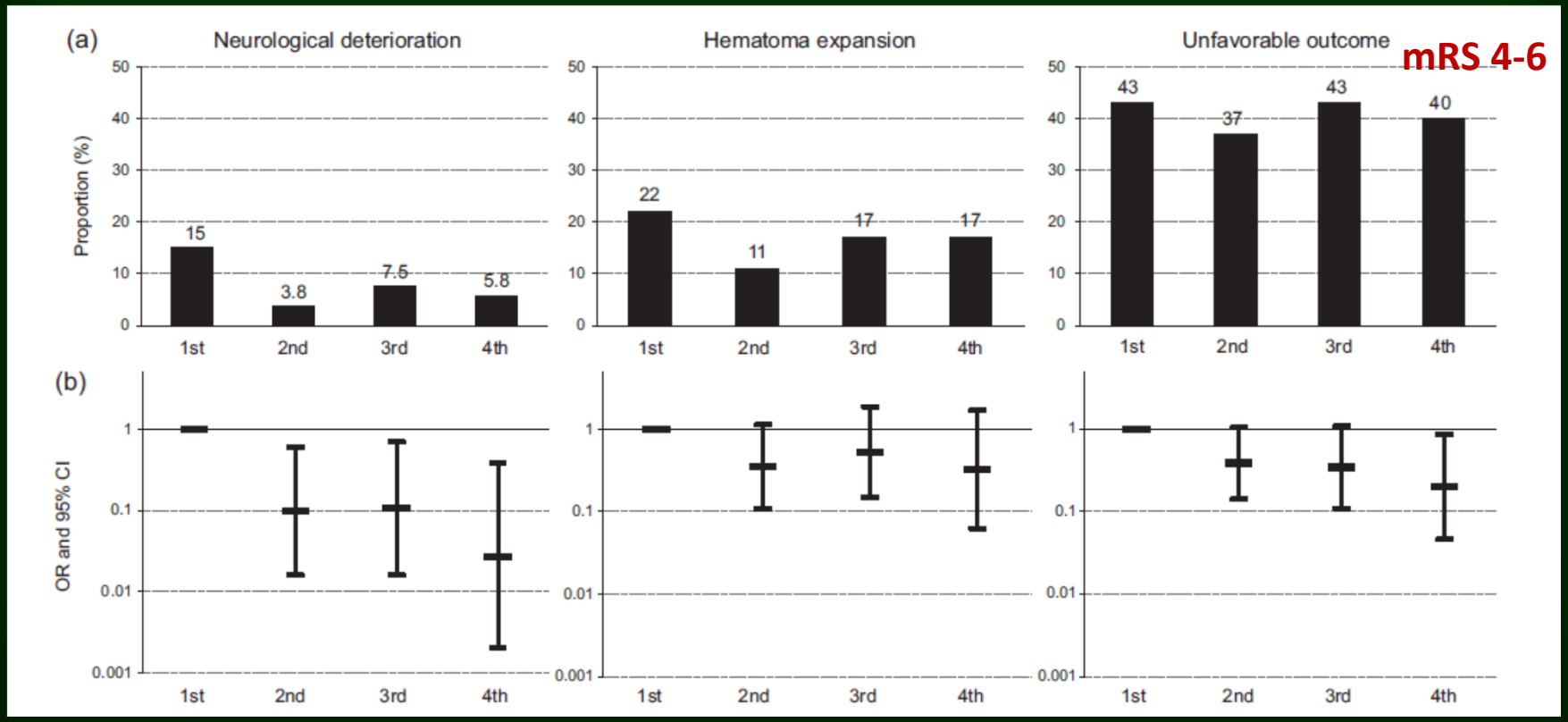
Sakamoto Y, et al: Stroke 2013;44:1846-51

SAMURAI ICH2 Achieved relative SBP



Q1 <27.4%, Q2<31.5%, Q3<36.0%

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Sakamoto Y, et al: J Hypertens 2015;33:1069-1073

8-h SBP

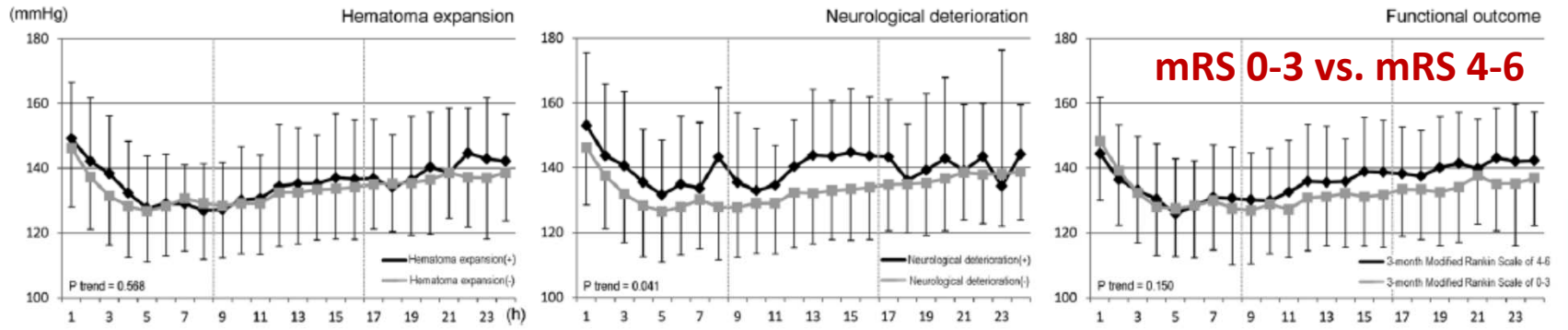

Figure. Time course of systolic blood pressure (SBP) during the initial 24 hours of antihypertensive therapy. Hourly means and 95% confidence intervals of SBP are shown.

Supplementary Table II. Results of multivariate regression to predict outcomes for a 10-mmHg increment in each mSBP.

	1st mSBP		2nd mSBP		3rd mSBP	
	Estimated OR (95% CI)					
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Hematoma expansion	1.29 (0.92-1.82)	1.20 (0.79-1.83)	1.22 (0.88-1.70)	1.17 (0.81-1.71)	1.23 (0.88-1.73)	1.29 (0.89-1.89)
Neurological deterioration	2.01 (1.26-3.31)	2.41 (1.34-4.69)	2.22 (1.34-3.87)	2.08 (1.20-3.80)	1.29 (0.79-2.09)	1.38 (0.82-2.34)
Unfavorable outcome	1.01 (0.78-1.32)	1.19 (0.83-1.71)	1.67 (1.27-2.25)	1.41 (1.02-2.00)	1.67 (1.27-2.25)	1.45 (1.05-2.05)

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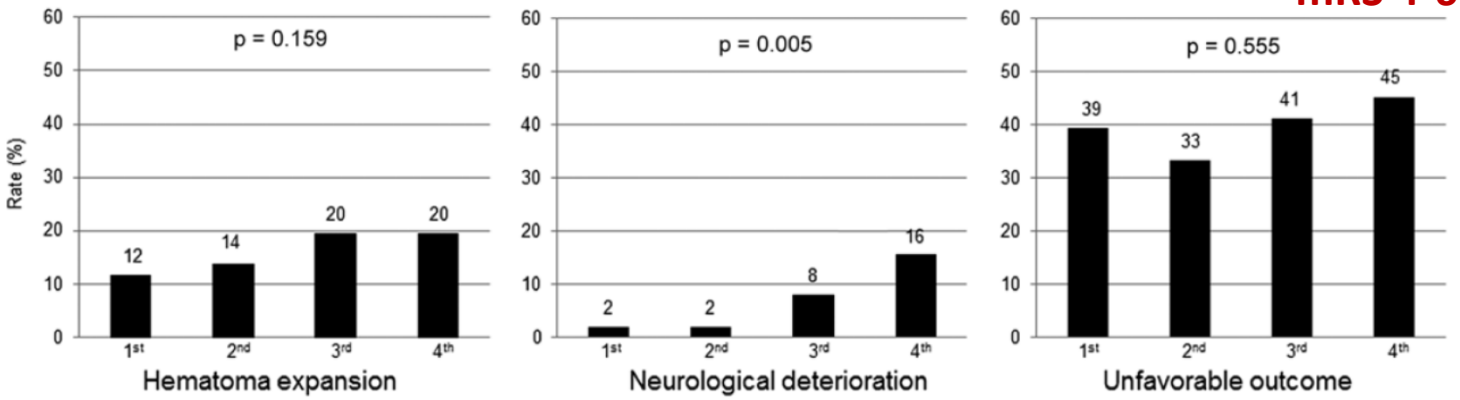
Kobayashi J, et al: Stroke 2014;45:868-870

SBP Variability

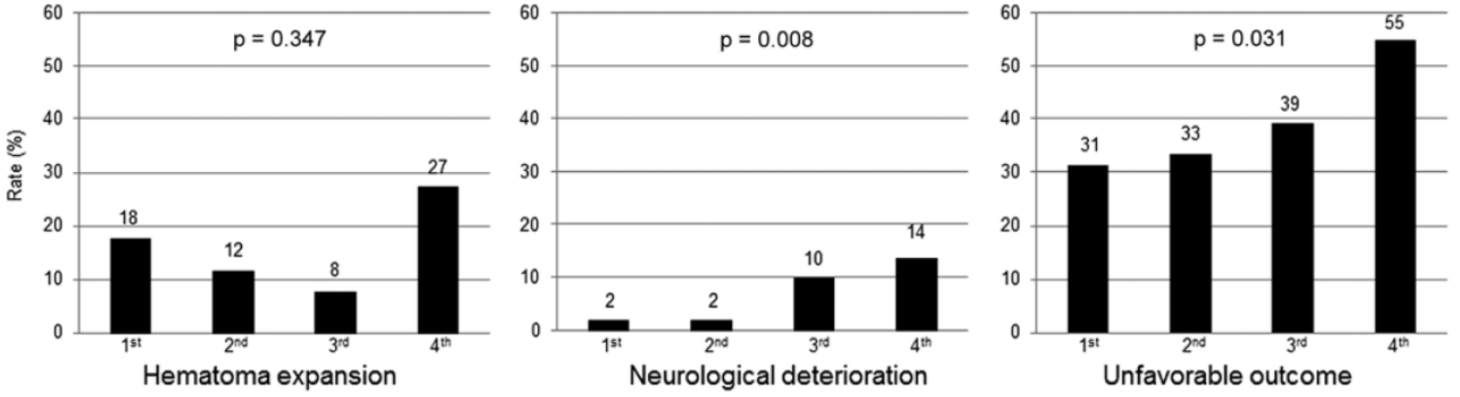
A SD：Standard Deviation

mRS 4-6



$$\sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(SBP_i - SBP_{mean})^2}$$

B SV：Successive Variation



$$\sqrt{\frac{1}{n-1}\sum_{i=1}^{n-1}(SBP_{i+1} - SBP_i)^2}$$

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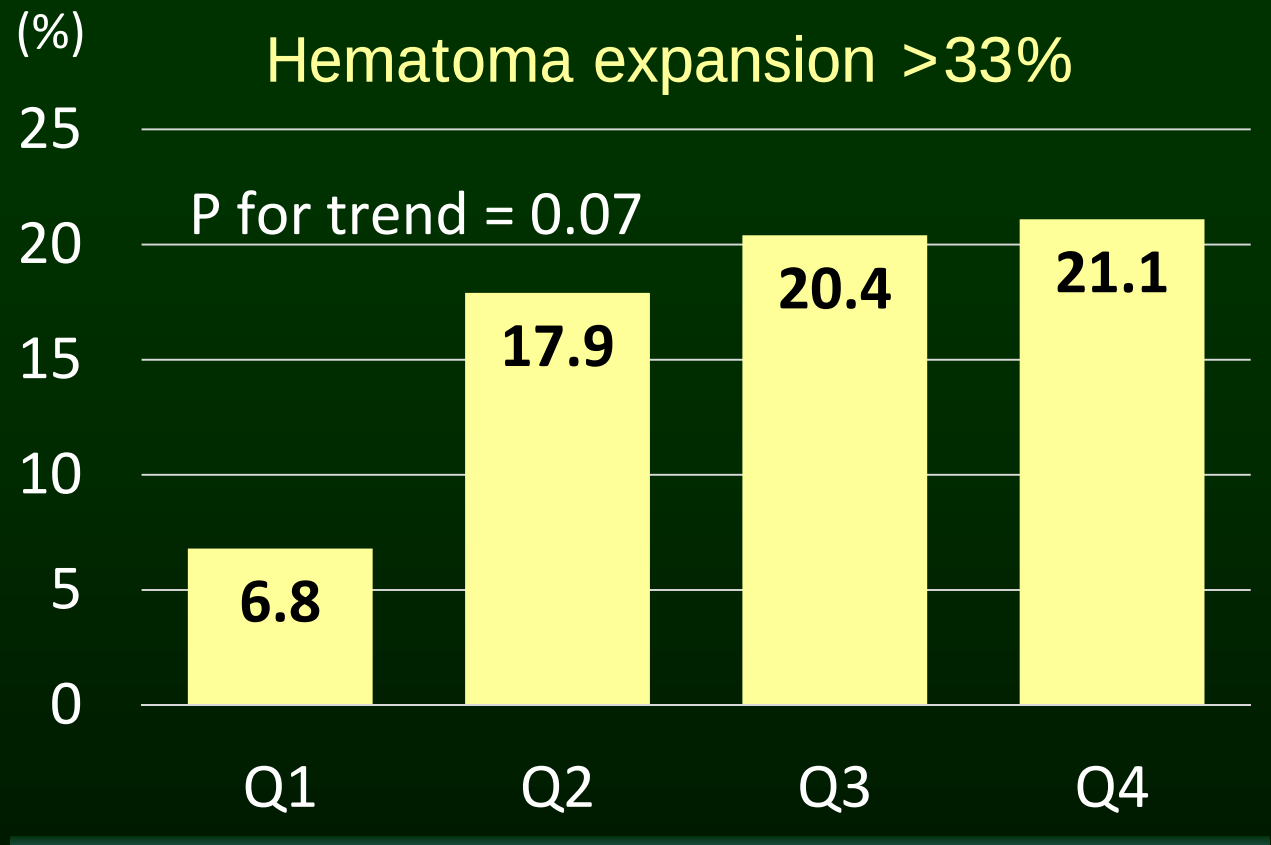
Tanaka E, et al: Stroke 2014;45:2275-2279

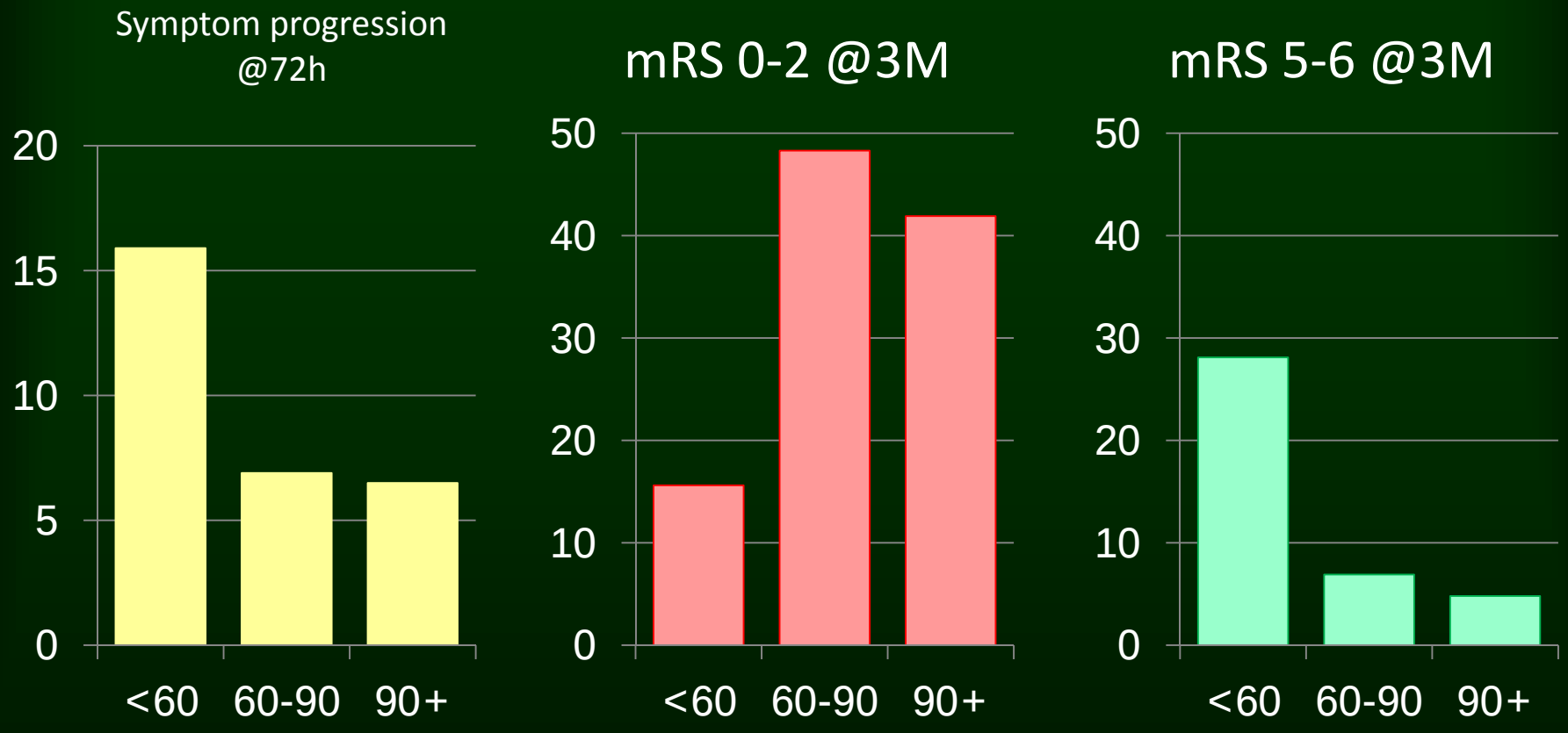
Time from onset to reaching 160mmHg



Q1 <105m, Q2<135m, Q3<165m

Yamaguchi Y, et al: in preparation

Kidney function: eGFR



OR [eGFR <60 vs. 60+]	0.17 (0.05-0.48)	5.79 (1.77-21.4)

Miyagi T, et al: J Stroke Cerebrovasc Dis. 2015;24:176-82.

Conjugate eye deviation

Any CED	OR	95% CI	P
Right-sided legion	2.36	1.18-4.93	0.015
Hematoma volume (per mL)	1.07	1.04-1.10	<0.001
GCS (per point)	0.66	0.53-0.80	<0.001

mRS 3-6 @3M	OR	95% CI	P
Any CED	1.56	0.75-3.24	0.235
Forced CED	0.94	0.30-3.14	0.921
Persistent CED (72 h)	5.77	2.27-16.9	<0.001

Sato S, et al: Stroke 2012;43:2898-2903

Questions from SAMURAI ICH

- ✓ Target SBP
- ✓ SBP Variability
- ✓ Time delay b/w onset and Tx initiation
- ✓ Time delay b/w onset and Tx goal
- ✓ eGFR
- ✓ Glucose *Koga M, et al: J Neurol Sci. 2015;350:75-78*
- ✓ Nicardipine dose

  Koga M, et al: J Stroke Cerebrovasc Dis. 2014;23:2780-2787

- ✓ ....

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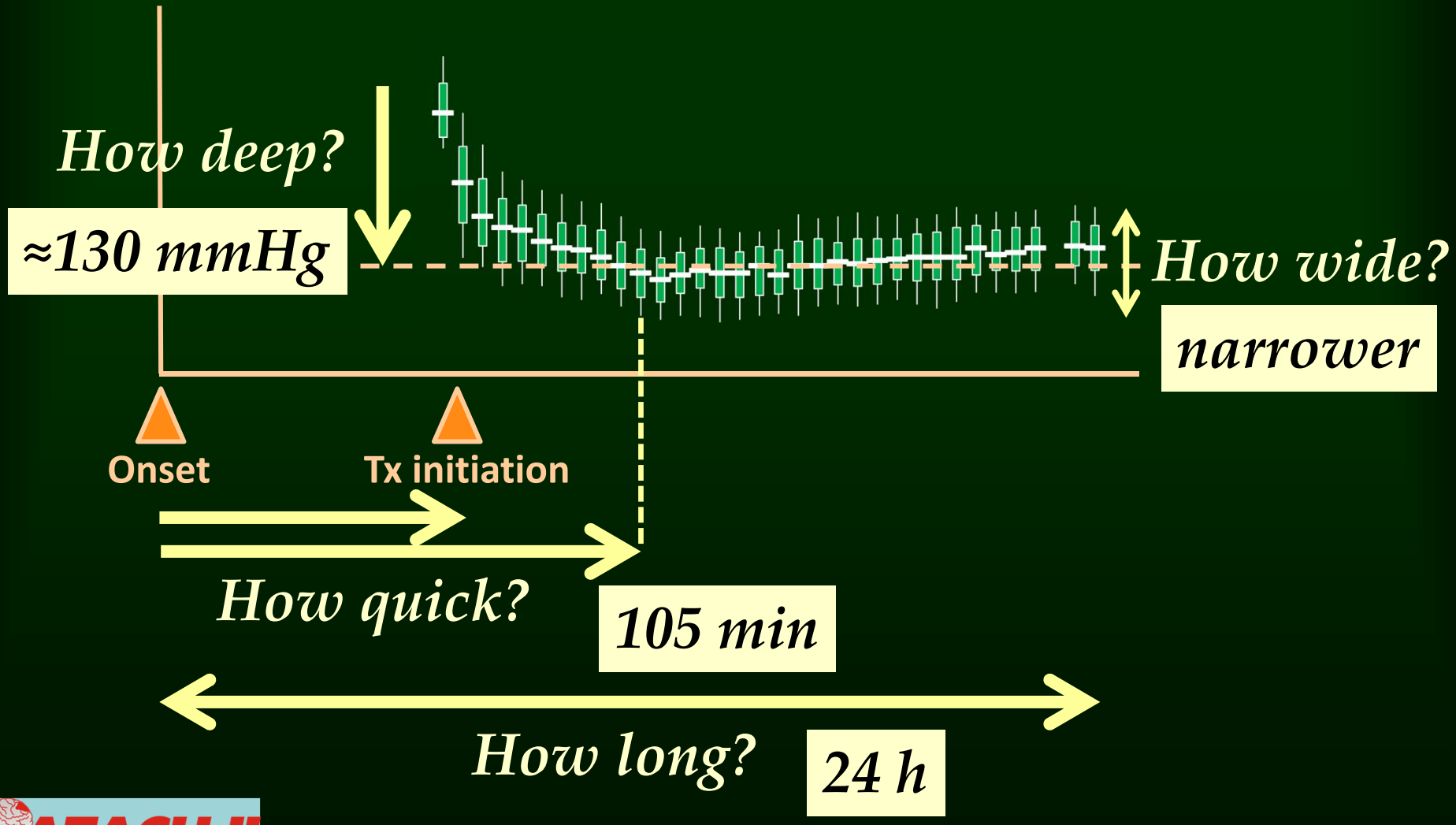
Antihypertensive Treatment of Cerebral Hemorrhage

Questions from SAMURAI ICH



ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Runup to ATACH-II

Antihypertensive Treatment of Cerebral Hemorrhage

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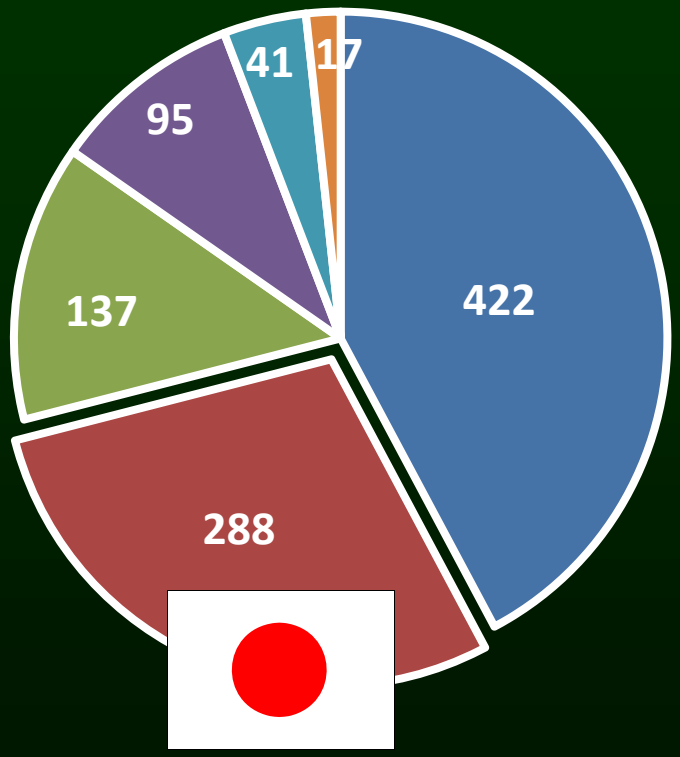
Workshop to Explore US-Japan Collaboration in an Acute Stroke Clinical Trial, June 2010, San Francisco

SAMURAI Meeting With Adnan & Yuko October 2008, Tokyo

Contribution of Japan

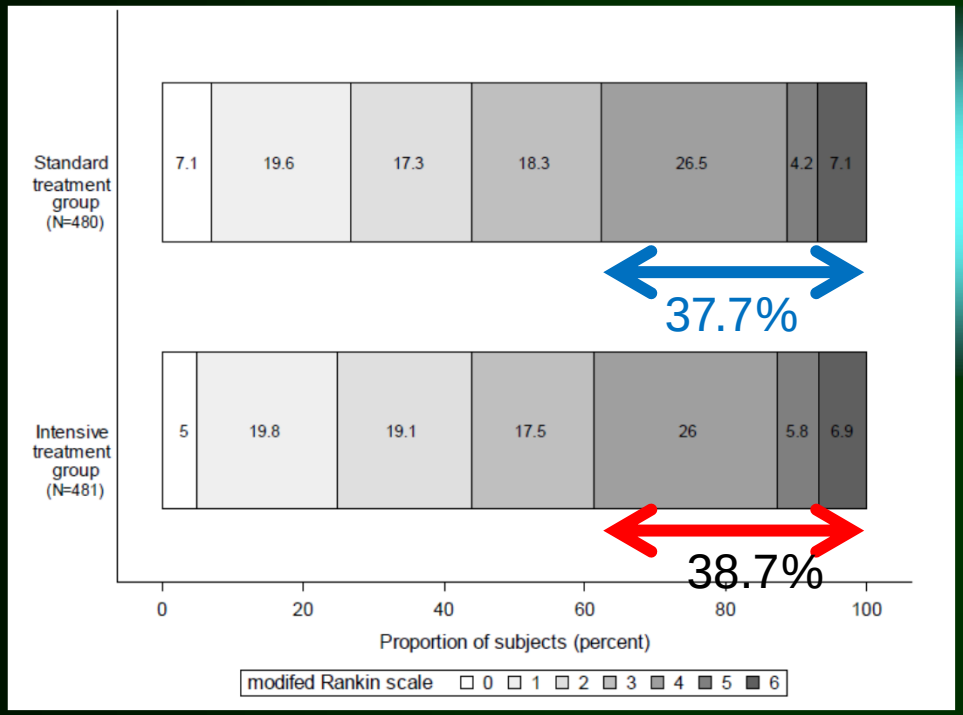
1st enrollment in Japan: March 1, 2012

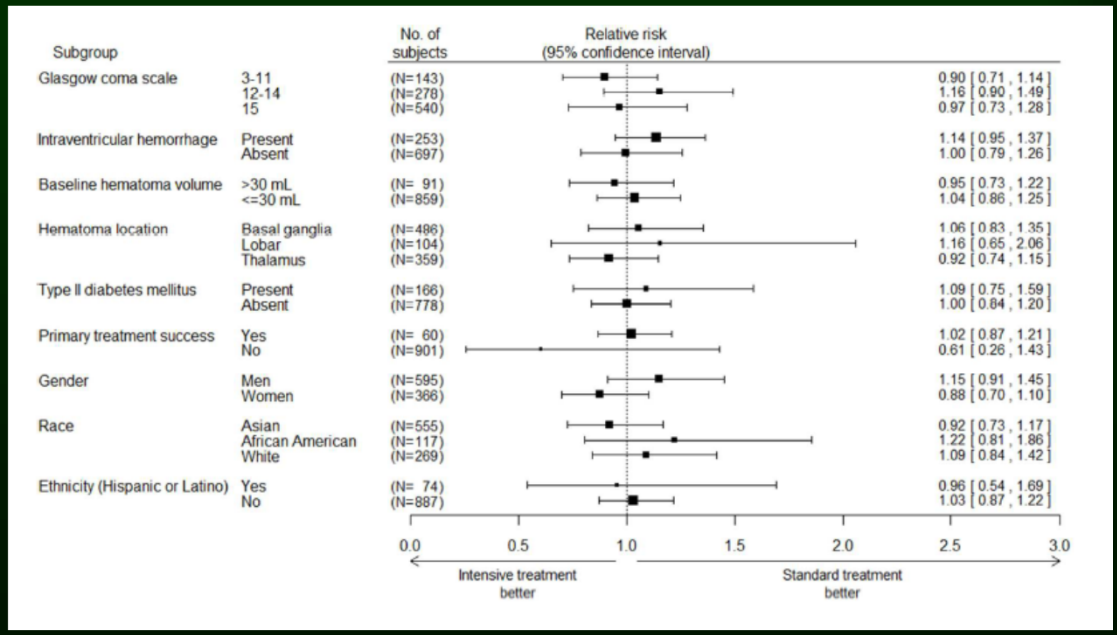
1. National Cerebral & Cardiovascular Center 79 Japan
2. Beijing Tiantan Hospital 72 China
3. Kobe City Medical Center General Hospital 53 Japan
4. Toranomon Hospital 38 Japan
5. The First People's Hospital of Taizhou 37 China



Main results of ATACH-II

Antihypertensive Treatment of Cerebral Hemorrhage





Qureshi A, et al: submitted

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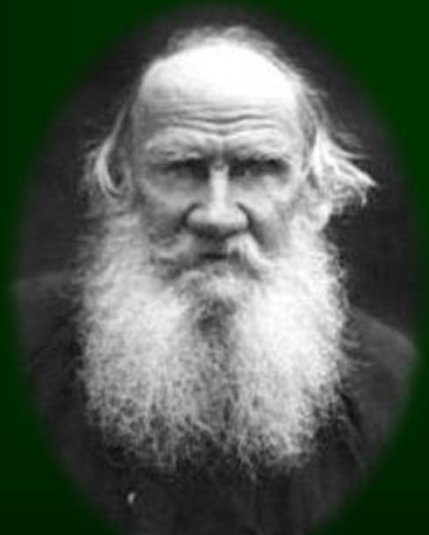
Antihypertensive Treatment of Cerebral Hemorrhage

Successful trials are all alike;

every unsatisfactory trial is unsatisfactory in its own way.



Лев Николаевич Толстой

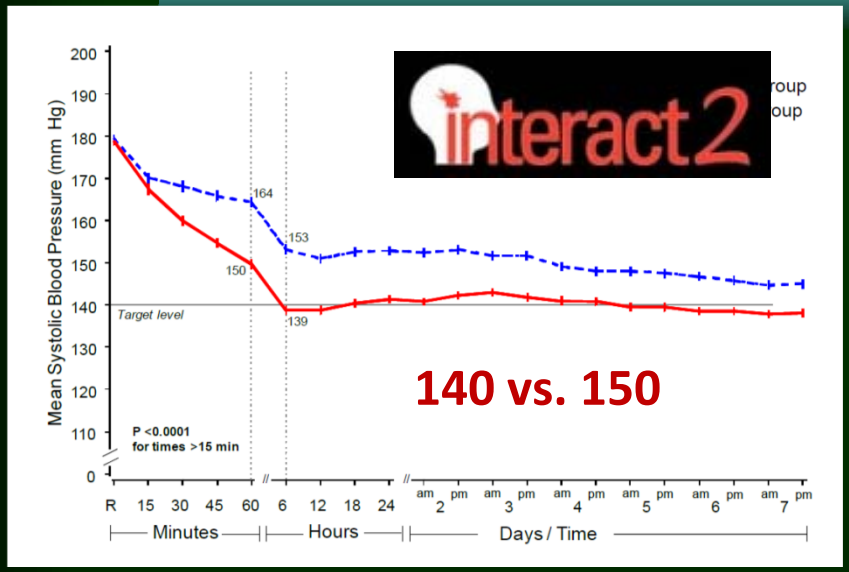
ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

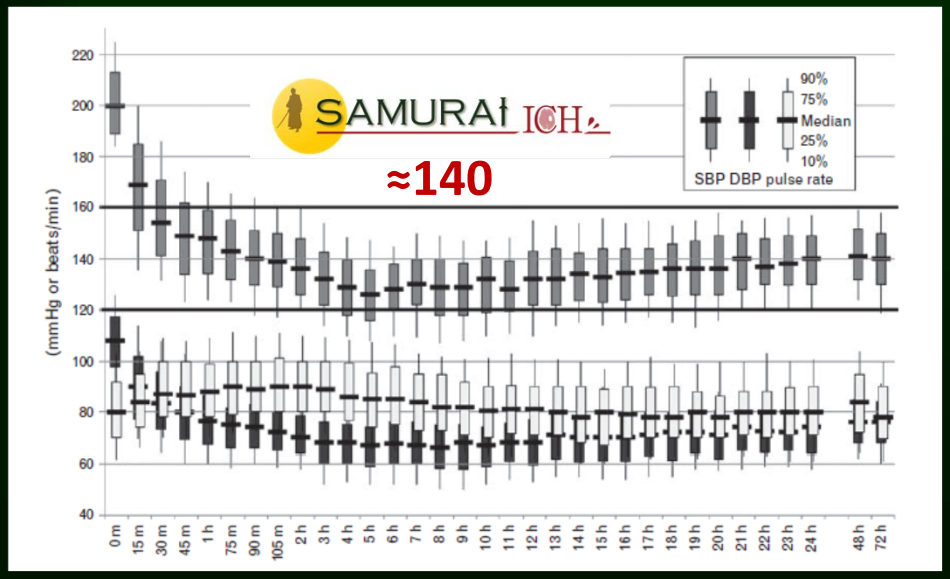
Comparison: Underlying features

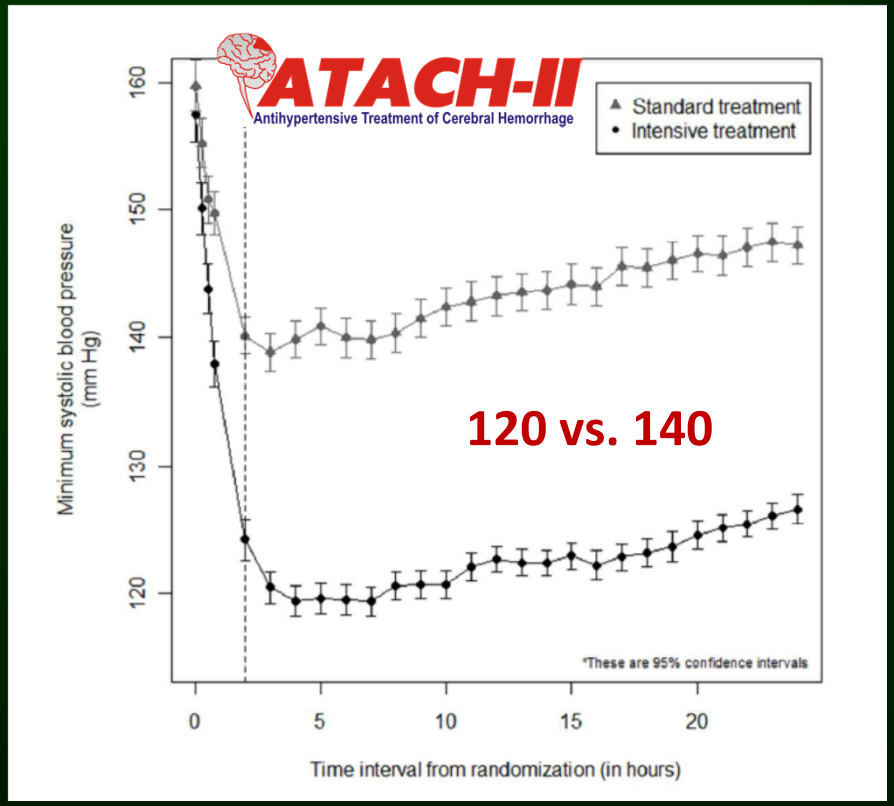
	interact2	ATACH-II Antihypertensive Treatment of Cerebral Hemorrhage	SAMURAI ICH
Patient Number	1399 (intensive)	500 (intensive)	211
Women, %	35.8%	39.2%	38.4%
Age, y	63.0±13.1	62.0±13.1	65.6±12.0
Asian, %	67.7% (China)	55.4%	100%
NIHSS (median)	10	11	13
bSBP, mmHg	179±17	200.0±27.1	201.8±15.7
Hematoma volume, mL (median)	11	10.3	10.2
Left hematoma, %	49.8%	48.1%	-
Target SBP, mmHg	<140	110 - 140	120 - 160
CCB as study drugs	16.2%	100%	100%
Onset-to-Tx, h (criterion)	<6	<4.5	<3
Onset-to-Tx	4.0 h	149±65 m	101.5±35.0 m

ATACH-II Antihypertensive Treatment of Cerebral Hemorrhage

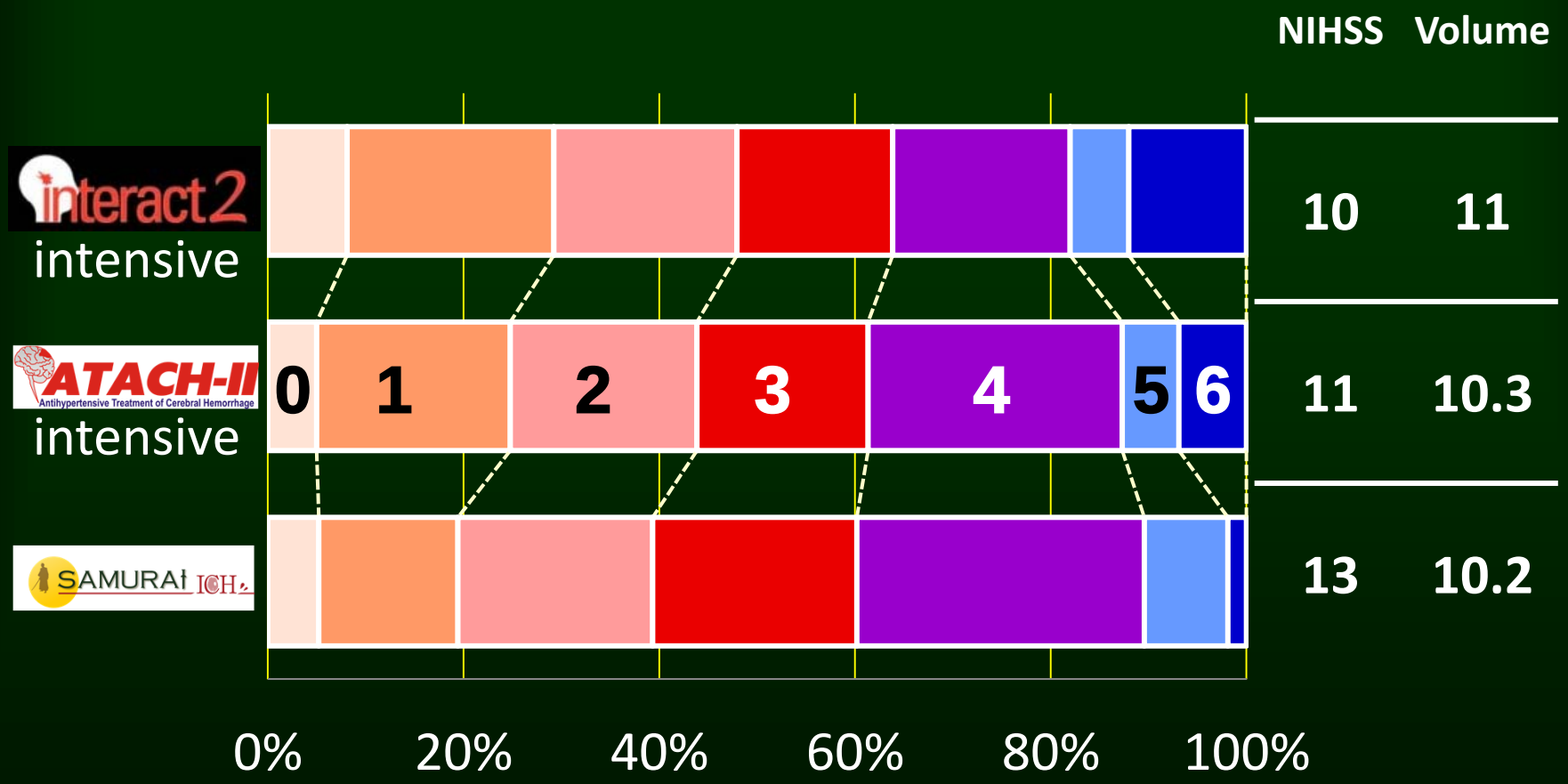
SBP course


interact2
Mean Systolic Blood Pressure (mm Hg)
200
190
180
170
160
150
140
130
120
110
0
164
153
150
139
Target level
P <0.0001
for times >15 min
R 15 30 45 60 6 12 18 24 am 2 pm am 3 pm am 4 pm am 5 pm am 6 pm am 7 pm
Minutes
Hours
Days / Time
140 vs. 150


SAMURAI ICH
≈140
90%
75%
Median
25%
10%
SBP DBP pulse rate
(mmHg or beats/min)
220
200
180
160
140
120
100
80
60
40
0 m 15 m 30 m 45 m 1 h 75 m 90 m 105 m 2 h 3 h 4 h 5 h 6 h 7 h 8 h 9 h 10 h 11 h 12 h 13 h 14 h 15 h 16 h 17 h 18 h 19 h 20 h 21 h 22 h 23 h 24 h 48 h 72 h


ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage
Standard treatment
Intensive treatment
Minimum systolic blood pressure (mm Hg)
160
150
140
130
120
120 vs. 140
*These are 95% confidence intervals
0 5 10 15 20
Time interval from randomization (in hours)

3M-mRS



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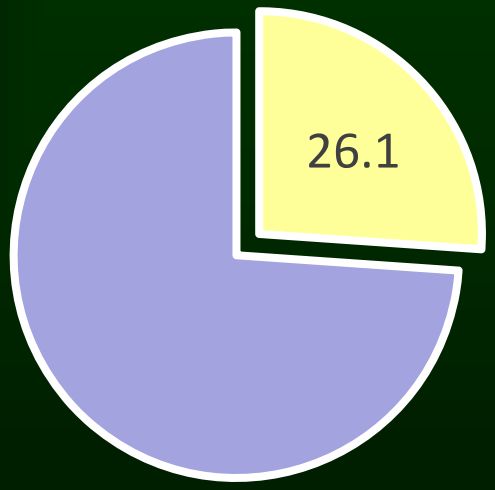
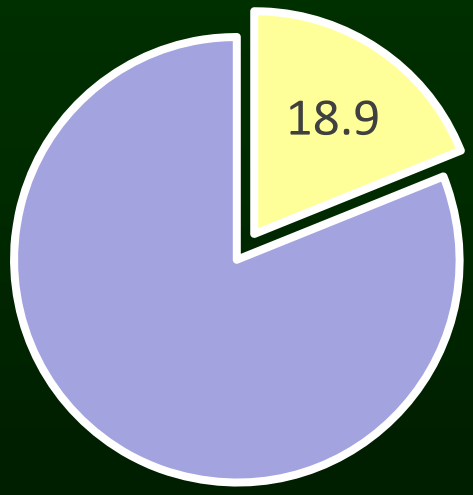
Hematoma enlargement

intensive

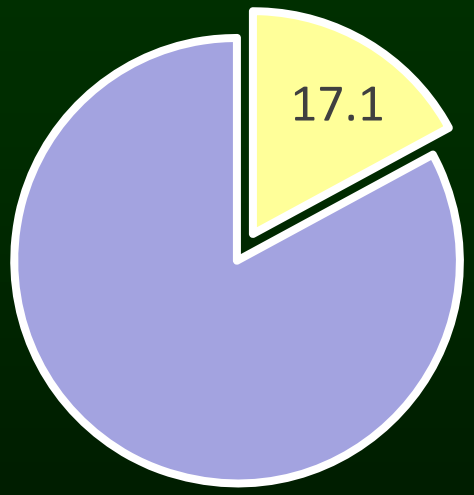


>33% or >12.5 mL

intensive

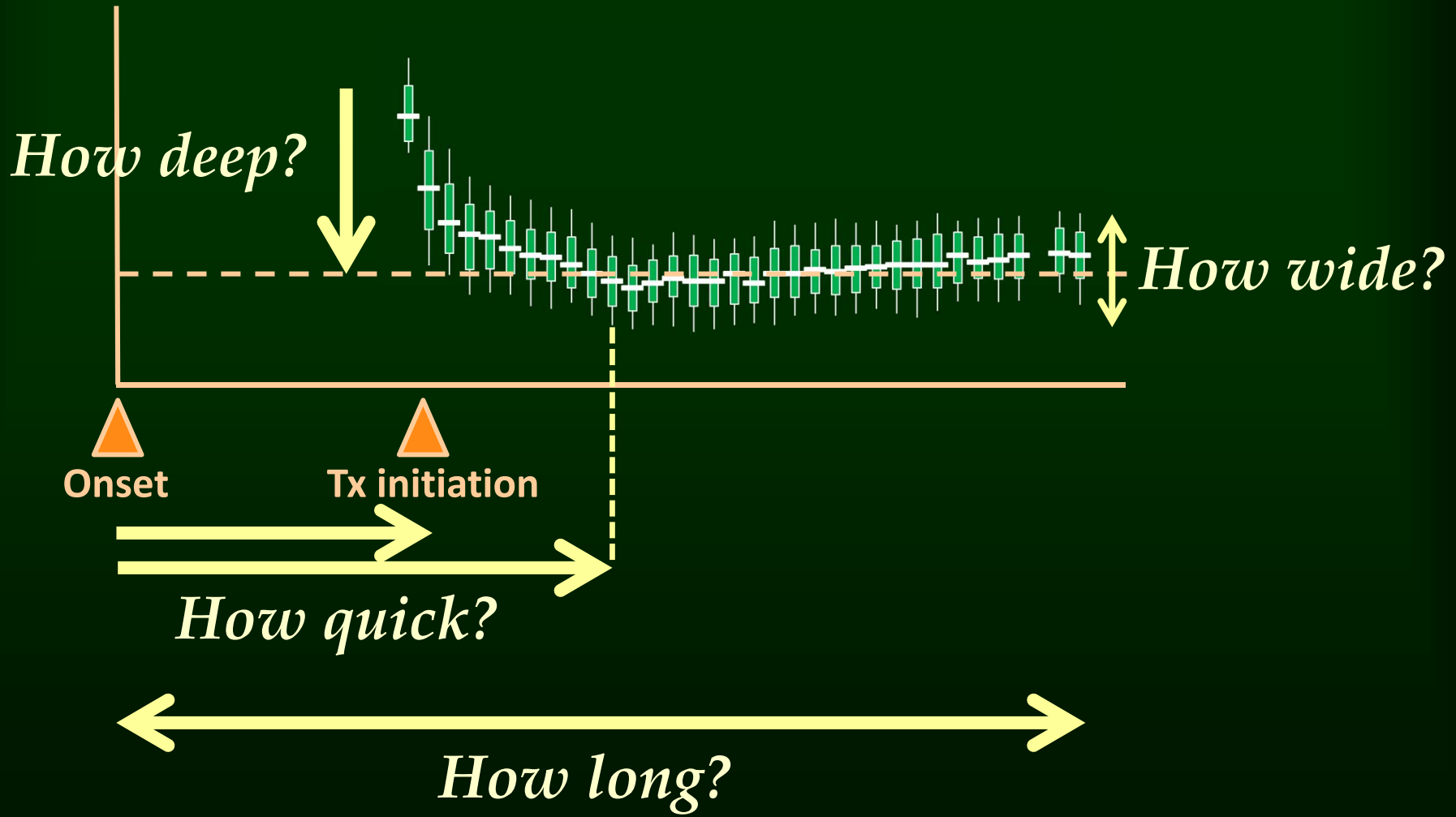


>33%



>33%

Keys to resolve differences



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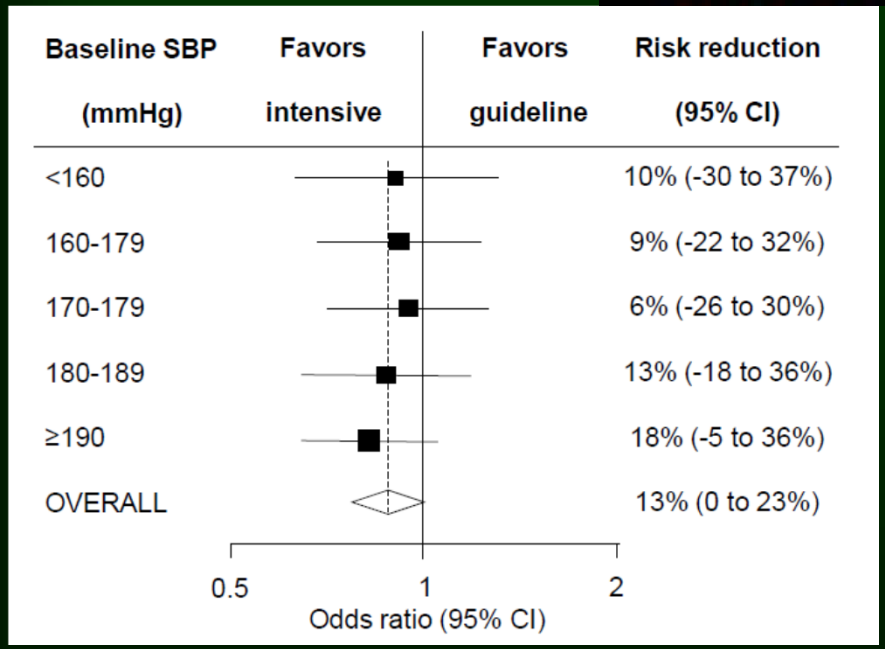
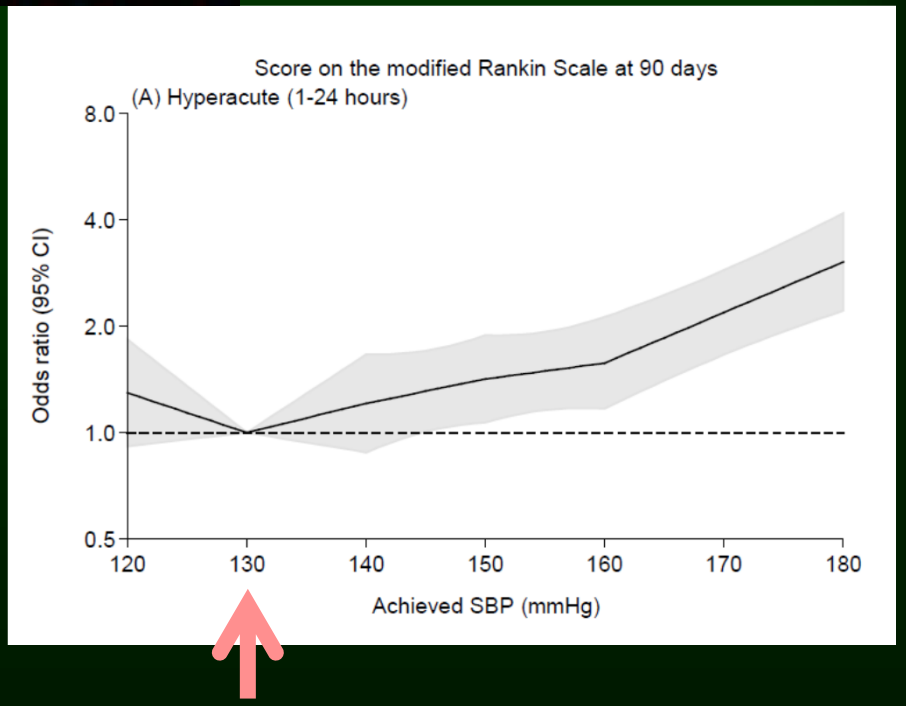
How deep? (the optimal SBP goal)

✓ bSBP

interact2

✓ Achieved SBP





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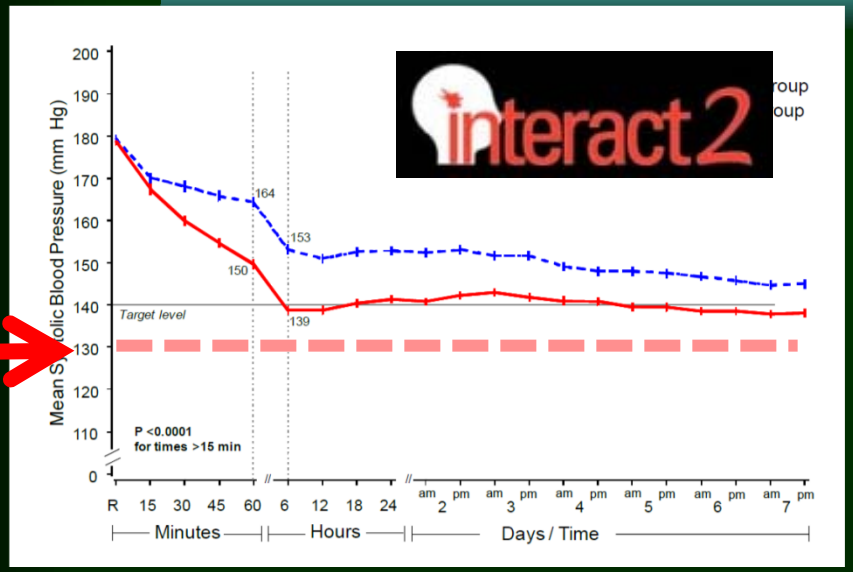
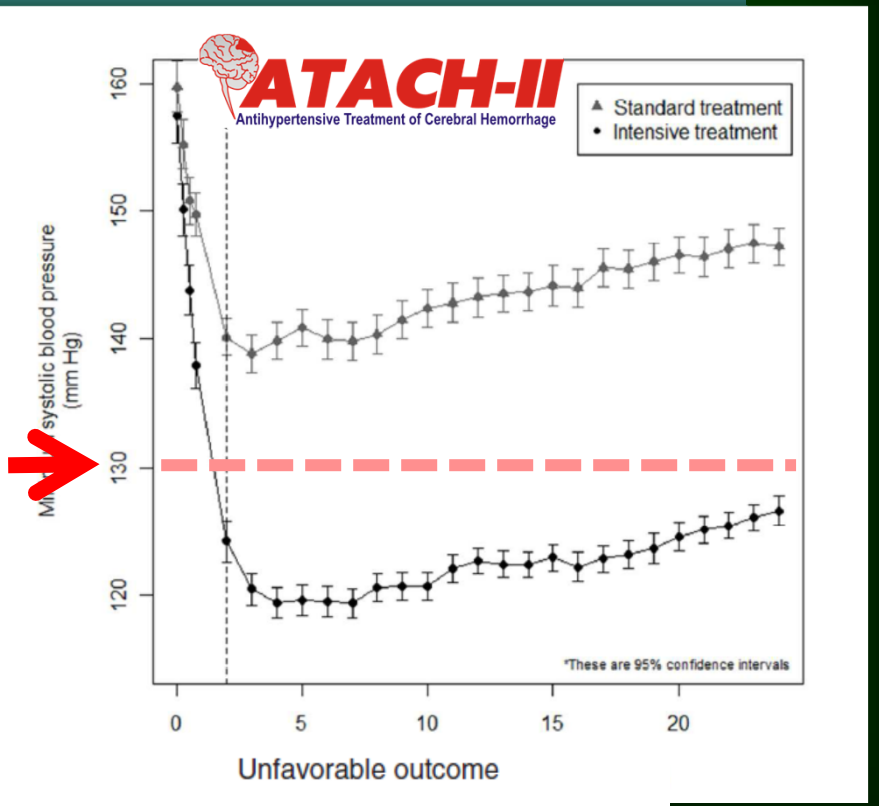
Arima H, et al: Neurology 2015;84:464–471.

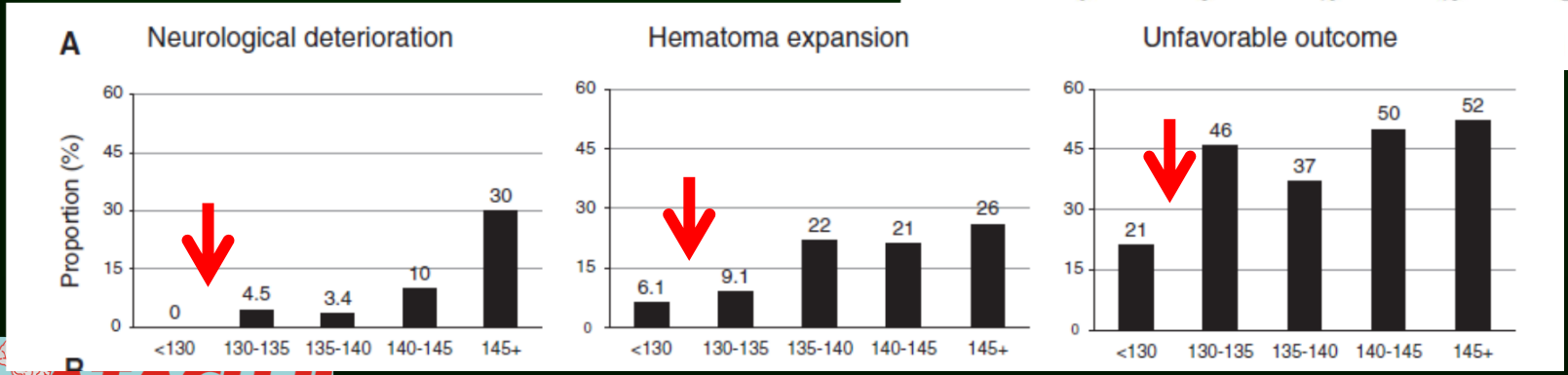
Is ≈130 mmHg optimal?





SAMURAI ICH

Sakamoto Y, : Stroke 2013



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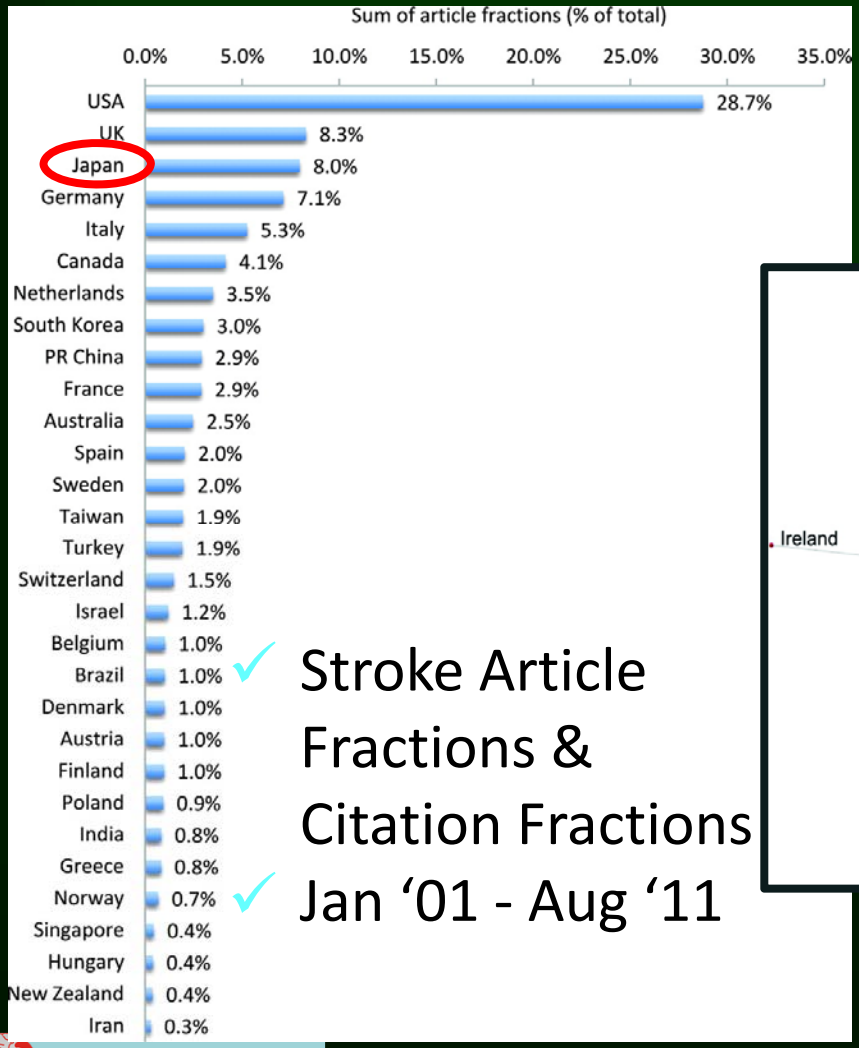
Another significance of ATACH-II in Japan

The ATACH-II Trial could be the seminal research project for stroke researchers in Japan to demonstrate themselves as effective contributors to investigator-initiated, international clinical trials.

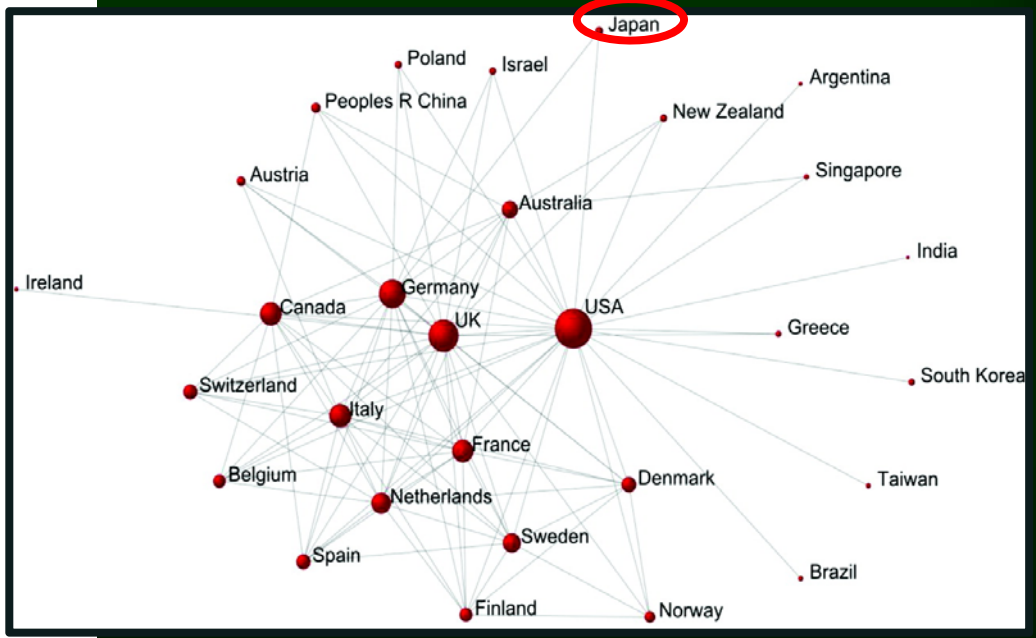
Toyoda K, et al: J Vasc Interv Neurol. 2012;5(supp):1-5

Contribution to clinical stroke research



- ✓ Stroke Article Fractions & Citation Fractions Jan '01 - Aug '11

- ✓ Map of intl. collaboration in stroke research b/w countries



Asplund K, et al: Stroke. 2012;43:830-837

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Obstacles to investigator-initiated trials

- ✓ Repeatedly assembling the necessary personnel and infrastructure each time trials begin and their disassembly each time trials end has made for an inefficient environment for conducting trials.

Landis S, Fisher M. Stroke 2013

- ✓ Overwhelming shortages of study coordinators and research nurses for staff education, administration of test drugs, data management, adverse event collection, biostatistics, and other necessary tasks in Japan.

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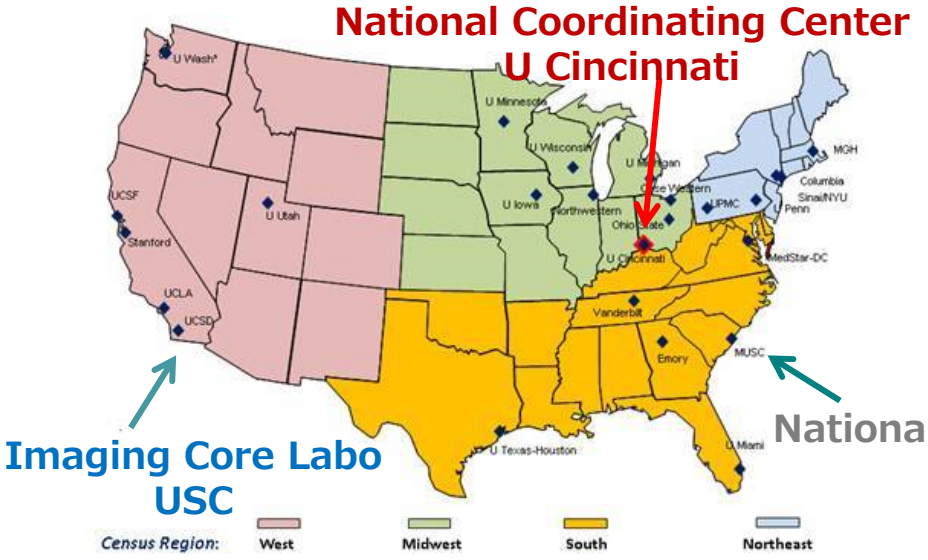
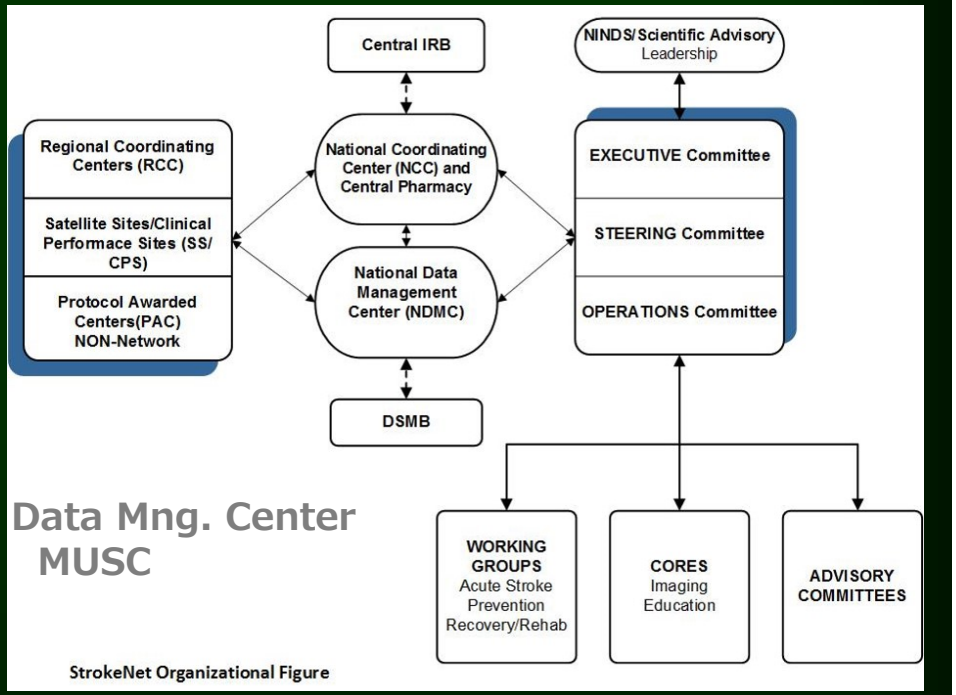
NIH StrokeNet
Prevention | Treatment | Recovery
NATIONAL COORDINATING CENTER

脳国内循

National and Regional Coordinating Centers





National Data Mng. Center
MUSC

StrokeNet Organizational Figure

Broderick J, et al:
Stroke 2016;47:301-303

Editorial

The National Institutes of Health StrokeNet
A User's Guide

Joseph P. Broderick, MD; Yuko Y. Palesch, PhD; L. Scott Janis, PhD; for the National Institutes of Health StrokeNet Investigators

ATACH-II
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NeCST
Network for Clinical Stroke Trials

AMED
grants

National Stroke
Network Collaboration

NIH StrokeNet
Prevention | Treatment | Recovery
NATIONAL COORDINATING CENTER

ESO
EUROPEAN STROKE ORGANISATION

Korean Stroke Society

脳国内循

Participating stroke institutes from among the collaborators in our recent multicenter projects, including the SAMURAI THAWS, & the ATACH-II

NCVC= natl coordinating ctr.

- ☐ central coordination office
- ☐ data management center
- ☐ central pharmacy

etc.

日本脳卒中学会

Cooperation with the Japan Stroke Society

Iwate Medical University

☐ Central imaging laboratories

ATAC
Antihypertensive Treatment of

Editorial

Toyoda K, et al: Stroke 2016;47:304-305

Network for Clinical Stroke Trials (NeCST) for the Next Stroke Researchers in Japan

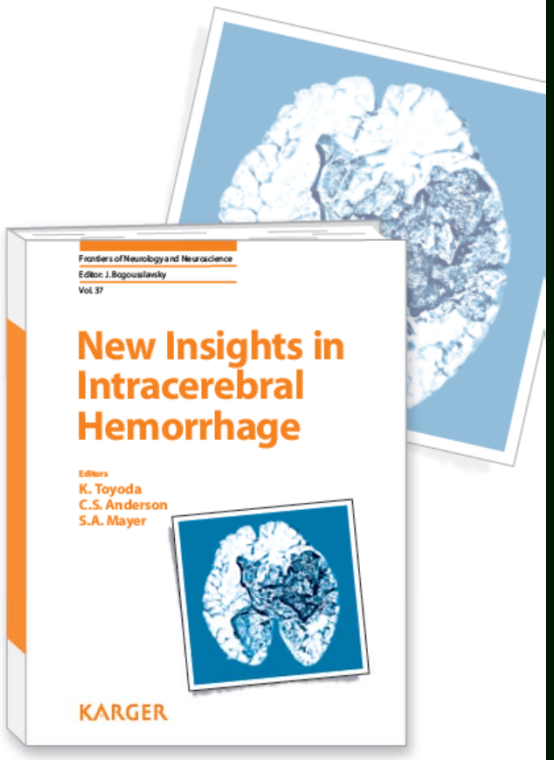
Kazunori Toyoda, MD, PhD; Haruko Yamamoto, MD, PhD; Masatoshi Koga, MD, PhD

Introducing a new era in acute stroke care

New Insights in Intracerebral Hemorrhage

Editors

Kazunori Toyoda
Craig S. Anderson
Stephan A. Mayer



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TTST, traditional international conferences on stroke therapy

1. 1990 @ Heidelberg
2. 1992 @ San Diego
3. 1994 @ Nara
4. 1996 @ Copenhagen
5. 1998 @ Washington DC
6. 2000 @ Queensland
7. 2002 @ Lyon
8. 2004 @ Whistler
9. 2006 @ Hong Kong
10. 2008 @ Budapest
11. 2011 @ New York City
12. 2014 @ Heidelberg/Mannheim

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

TTST, traditional international conferences on stroke therapy

Lecturers

Europe

- ✓ Werner Hacke
- ✓ Hans C Diener
- ✓ Rudger von Kummer
- ✓ Christian Gerloff
- ✓ Peter D. Schellinger
- ✓ Jochen B. Fiebach
- ✓ Kennedy Lees
- ✓ Peter Sandercock
- ✓ Phillip Bath
- ✓ Carlos Molina
- ✓ Markku Kaste
- ✓ Turgut Tatlisumak
- ✓ Valeria Caso
- ✓ Jean Marc Olivot

North America

- ✓ **Adnan Qureshi**
- ✓ **Yuko Palesch**
- ✓ Jeffrey Saver
- ✓ Gregory del Zoppo
- ✓ Wade Smith
- ✓ Raul G Nogueira
- ✓ Michael Hill
- ✓ Maarten G. Lansberg
- ✓ David S Liebeskind
- ✓ Satoshi Tateshima
- ✓ James Grotta
- ✓ Aquilla S Turk
- ✓ Tudor G Jovin
- ✓ Andrei V. Alexandrov
- ✓ Patric Lyden
- ✓ Pooja Khatri
- ✓ Opeolu Adeoye
- ✓ Johm Marler

Asia/Oseania

- ✓ Craig Anderson
- ✓ Stephen Davis
- ✓ Christopher Levi
- ✓ Bruce Campbell
- ✓ Jong S Kim
- ✓ Ji Hoe Heo
- ✓ Byung-Chul Lee
- ✓ Keun-Sik Hong
- ✓ Dong-Eog Kim
- ✓ Joung-Ho Rha
- ✓ KS Lawrence Wong
- ✓ Liping Liu
- ✓ Ruey–Tay Lin
- ✓ Chen-Ya Huang
- ✓ Deidre A. De Silva
- ✓ Kay Sin Tan

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