

SUPPLEMENTARY MATERIALS

Title: Early lowering of blood pressure after acute intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data

The Blood Pressure in Acute Stroke (BASC) Investigators*

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SUPPLEMENTARY TABLE 1 Comparison of one- and two-stage approaches to individual patient data (IPD) meta-analysis

One-stage approach	Two-stage approach
IPD from all studies are analysed together as if they belonged to a single study, adjusted for covariables. Statistical clustering can be addressed with multi-level modelling, where the source trial is treated as a random effect.	IPD from each study are analysed separately, adjusted for covariables. Then, similarly to aggregate-data meta-analysis, study-level estimates of effect are pooled in a random-effects meta-analysis model.

SUPPLEMENTARY TABLE 2 Design characteristics of eligible studies that provided individual patient data

Study (N=16)	Design	Phase	Sites (N)	ICH (N=6221)	SBP inclusion (mmHg)	Time window (hours)	Intervention	Length of treatment (days)	Primary outcome	Follow-up (days)	Outcome on mRS reported?
ICH only											
ATACH-II ¹	PROBE	III	109	1000	>180	<3	Nicardipine iv vs placebo	1	mRS 4-6	90	Yes
ICH ADAPT ²	PROBE	IIb	3	75	>150	<24	Target SBP <150 vs <180 mmHg	1	Perihaematomal blood flow at 2h	90	Yes
Gupta 2018 ³	PRO (not blind endpoint)	N/A	3	118	N/A	<72	Treat if MAP \geq 115 vs \geq 130	3	mRS 3-6	90	Yes
INTERACT1 ⁴	PROBE	IIc	44	404	150-220	<6	Target SBP <140 vs <180 mmHg	7	Proportional change in ICH volume at 24h	90	Yes
INTERACT2 ⁵	PROBE	III	170	2829	150-220	<6	Target SBP <140 vs <180 mmHg	1	mRS 3-6	90	Yes
Koch 2008 ⁶	PROBE	N/A	1	42	MAP >110	<8	Target MAP <110 vs 110-130	2	Neurological deterioration (NIHSS) within 48h	90	Yes
Mixed stroke											
CHHIPS ⁷	DBPC	III	6	25	>160	<36	Labetalol 50mg po/im or lisinopril po/sl 5mg vs placebo	14	mRS 4-6	14 (90)	Yes

Study (N=16)	Design	Phase	Sites (N)	ICH (N=6221)	SBP inclusion (mmHg)	Time window (hours)	Intervention	Length of treatment (days)	Primary outcome	Follow-up (days)	Outcome on mRS reported?
CHASE ⁸	PROBE	N/A	26	242	150-220	<72	10-15% reduction in SBP vs <180	7	mRS 3-6	90	Yes
ENOS (GTN) ⁹	SBBE	III	168	629	140-220	<48	GTN 5mg td vs none	7	mRS (ordinal)	90	Yes
GTN-1 ¹⁰	DBPC	IIa	1	4	N/A	<120	GTN 5mg td vs placebo	12	mRS 3-6	90	Yes
GTN-2 ¹¹	SBBE	IIb	1	5	100-230	<72	GTN 10mg vs 5mg td vs none	10	BP on day 1	90	Yes
SCAST ¹²	DBPC	III	146	274	>140	<30	Candesartan po vs placebo	7	Vascular death, MI, or stroke; mRS (ordinal)	180	Yes
VENUS ¹³	DBPC	III	?	35	130-220	<6	Nimodipine 120mg po vs placebo	10	mRS 4-6	90	Yes
Pre-hospital											
FAST-MAG ¹⁴	DBPC	III	45	387	N/A	<2	Magnesium * iv vs placebo	1	mRS (ordinal)	90	Yes
RIGHT-1 ¹⁵	SBBE	IIa	1	6	>140	<4	GTN 5mg td vs none	7	SBP at 2h	90	Yes
RIGHT-2 ¹⁶	DBPC	III	54	145	>120	<4	GTN 5mg td vs sham	4	mRS (ordinal)	90	Yes

PROBE denotes prospective randomised open-label blinded-endpoint; DBPC, double-blind placebo-controlled; SBBE, single blind blinded endpoint, MAP, mean arterial pressure; SBP, systolic blood pressure; iv, intravenous; po, oral; sl, sublingual; td, transdermal; im: intramuscular; GTN, glyceryl trinitrate; ICH, intracerebral haemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes for Health Stroke Scale score

SUPPLEMENTARY TABLE 3 Design characteristics of eligible studies that did not provide individual patient data

Study (N=34)	Design	Phase	Sites (N)	ICH (N=5273)	SBP inclusion (mmHg)	Time window (hours)	Intervention	Length of treatment (days)	Primary outcome	Follow-up (days)	Outcome on mRS reported?
ICH only											
Chen 2010 ¹⁷	PROBE?	N/A	1	146	MAP >130	<6	MAP (150/90) 110 vs 130 (180/105) urapadil	1	Change in ICH volume at 24h	30	No
Dai 2005 ¹⁸	PROBE?	N/A	1	85	>180/100	<6	Nimodipine vs control	1	Nervous function defect	90	No
Duan 2011 ¹⁹	PROBE?	N/A	1	91	>180/100	<6	Target 130-150/90-100 vs 180/105	1	Proportional change in ICH volume at 24h	1	No
Gong 2013 ²⁰	PROBE?	N/A	1	120	>160	<4	Target SBP <140 vs <180 using GTN	1	Change in ICH volume at 24h	14	No
Gong FT 2015 ²¹	PROBE?	N/A	1	120	>160	<4	Target SBP 130-140 vs 160-180 using GTN	1	Change in ICH volume at 24h	14	No
Guo 2016 ²²	PROBE?	N/A	1	100	?	<3	Target SBP 130-140 vs 160-180	7	?	90	?
Huo 2012 ²³	PROBE?	N/A	1	124	NA	<6	SBP 120-150 vs 150-180	1	Change in ICH volume at 48h	30	No
Jiang AC 2013 ²⁴	PROBE?	N/A	1	106	>180 or MAP >140	<6	Target SBP <140 vs <180	1	Proportional change in ICH volume at 24h	14	No

Study (N=34)	Design	Phase	Sites (N)	ICH (N=5273)	SBP inclusion (mmHg)	Time window (hours)	Intervention	Length of treatment (days)	Primary outcome	Follow-up (days)	Outcome on mRS reported?
Jiang M 2013 ²⁵	PROBE?	N/A	1	96	>180/100	<6	160-180/90-100	1	Change in ICH volume at 24h	21	No
Kan 2020 ²⁶	PROBE?	N/A	?	1500	?	?	?	?	Several stated, without clear primary: ICH volume, adverse events, mRS	?	Yes
Lee JP 2011 ²⁷	PROBE?	N/A	1	138	>180/110	<24	160 -180 /90 - 100 vs ~180/105	1	Change in ICH volume at 24h	1	No
Lee L 2011 ²⁸	PROBE?	N/A	1	64	>170	<24	Target <140 vs 170-220	1	Change in ICH volume at 24h	28	No
Lee YB 2013 ²⁹	PROBE?	N/A	1	78	>180/100	<6	Target 130-150/90-100 vs 180/105	1	Change in ICH volume at 72h	30	No
Liang 2013 ³⁰	PROBE?	N/A	1	178	>170	<24	Target SBP <140 vs <170 mmHg	1	Change in ICH volume at 24h	28	No
Luo 2010 ³¹	PROBE?	N/A	1	122	N/A	<12	Target SBP <140 vs <180	1	Change in ICH and edema volume at 7, 28, and 90d	90	No
Ma 2013 ³²	PROBE?	N/A	1	160	>180/110	<24	130-150/80-90 vs 180/105	1	Change in ICH volume at 24h	1	No
Song 2010 ³³	PROBE?	N/A	1	256	>180/110	<24	intensive vs guideline	1	Change in ICH volume at 24h	21	No
Sun 2012 ³⁴	PROBE?	N/A	1	120	>180/110	<24	Target SBP <140 vs <180	1	Change in ICH volume at 24h	1	No

Study (N=34)	Design	Phase	Sites (N)	ICH (N=5273)	SBP inclusion (mmHg)	Time window (hours)	Intervention	Length of treatment (days)	Primary outcome	Follow-up (days)	Outcome on mRS reported?
Szczechowski 1994 ³⁵	?	N/A	?	17	?	<24	Nimodipine 1-2mg iv vs dextran 40,000	?	?	N/A	?
Tao 2014 ³⁶	PROBE?	N/A	1	54	N/A	<3	Acupuncture vs control	1	Change in ICH volume at 24h	10	No
Wang 2012 ³⁷	PROBE?	N/A	1	110	>180/110	<24	160-180/90-100	1	Change in ICH volume at 24h	21	No
Xian 2010 ³⁸	PROBE?	N/A	1	106	>180/105	<72	140/90 vs 170/100	1	Change in ICH volume at 24h	90	No
Xu Bo 2010 ³⁹	PROBE?	N/A	1	400	150-220	<6	Target SBP <140 vs <180 using urapidil	2	Change in ICH volume at 24h	3	No
Xu MY 2011 ⁴⁰	PROBE?	N/A	1	41	150-220	<6	Target SBP <140 vs <180	1	Change in ICH volume at 24h	90	No
Zang 2019 ⁴¹	PROBE?	N/A	1	121	150-220	<5	Target 135-140 where SBP>150 vs <140 where SBP>180	3	ICH volume at 24h	90	Yes
Zhang HX 2011 ⁴²	PROBE?	N/A	1	121	NA	<6	Target SBP <140 vs <180 using sodium nitroprusside	1	Change in ICH and edema volume at 24 and 72h, 7 and 14d	30	No
Zhang SJ 2011 ⁴³	PROBE?	N/A	1	112	>180/110 or MAP >130	<24	Target 130-150/80-90 vs 180/105	1	Change in ICH volume at 24h	21	No

Study (N=34)	Design	Phase	Sites (N)	ICH (N=5273)	SBP inclusion (mmHg)	Time window (hours)	Intervention	Length of treatment (days)	Primary outcome	Follow-up (days)	Outcome on mRS reported?
Zhang HT 2016 ⁴⁴	PROBE?			102		<48	Target 130-140 vs 170-180	1	Change in ICH volume at 48h	30	No
Zhao 2012 ⁴⁵	PROBE?	N/A	1	76	>180/100	<6	Target 150/90 vs 165-180/95-100	1	Change in ICH volume at 24h	1	No
Zheng 2017 ⁴⁶	PROBE	II	1	201	150-220	<24	Target 120-140 vs 140-180	7	rehaemorrhage at 7 days after surgery	90	No
Mixed											
IMAGES-pilot ⁴⁷	DBPC	Ib	1	6	N/A	<12	Magnesium 73 mmol iv vs placebo	1	Barthel <60	90	?
IMAGES ⁴⁸	DBPC	III	99	200	N/A	<12	Magnesium 81 mmol iv vs placebo	1	Barthel <60 or mRS >1	90	Yes
Uzuner (unpublished)	?	?	?	?	?	?	Nimodipine * iv vs *	?	?	?	?
Pre-hospital											
PIL-FAST ⁴⁹	DBPC	Ia	1	3	>160	<3	Lisinopril 5-10mg sl vs placebo	7	Feasibility data	7	No

PROBE denotes prospective randomised open-label blinded-endpoint; DBPC, double-blind placebo-controlled; SBBE, single blind blinded endpoint, MAP, mean arterial pressure; SBP, systolic blood pressure; iv, intravenous; po, oral; sl, sublingual; td, transdermal; im: intramuscular; GTN, glyceryl trinitrate; ICH, intracerebral haemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes for Health Stroke Scale score

SUPPLEMENTARY TABLE 4 Bias assessment

	Risk of bias domains						Overall
	D1	D2	D3	D4	D5	D6	
Anderson 2008 (INTERACT1)	+	+	-	+	+	-	+
Anderson 2013 (INTERACT2)	+	+	-	+	+	+	+
Ankolaker 2012 (RIGHT-1)	?	+	-	+	+	+	-
Bath 2001(GTN-1)	+	+	+	+	+	?	+
Bath 2015 (ENOS)	+	+	-	+	+	+	+
Bath 2019 (RIGHT-2)	+	+	+	+	+	+	+
Butcher 2013 (ICH-ADAPT)	+	+	-	+	+	+	+
Chen 2010	?	?	-	?	+	+	X
Dai 2005	?	?	-	?	+	?	X
Duan 2011	?	?	-	?	+	+	X
Gong 2013	+	?	-	?	+	+	X
Gong 2015	?	?	-	?	+	+	X
Guo 2016	+	?	-	+	+	?	-

D1: Randomisation method
 D2: Allocation concealment
 D3: Blinding of participants and personnel
 D4: Blinding of outcome assessment
 D5: Incomplete outcome data
 D6: Selective reporting

X High
 - Uncertain
 + Low
 ? No information

Gupta 2018	+	+	-	X	+	?	X
Kan 2020	?	?	?	?	?	?	?
Huo 2012	?	?	-	?	+	+	X
Horn 2001 (VENUS)	+	+	+	+	+	?	+
Jiang AC 2013	+	?	-	?	+	+	X
Jiang M 2013	?	?	-	?	+	+	X
Koch 2008	?	+	-	+	+	?	+
Lee JP 2011	?	?	-	?	+	+	X
Lee L 2011	?	?	-	?	+	+	X
Lee YB 2013	?	?	-	?	+	+	X
Lees 2004 (IMAGES)	+	+	+	+	+	+	+
Liang 2013	?	?	-	?	+	+	X
Luo 2010	+	?	?	?	+	+	X

D1: Randomisation method
 D2: Allocation concealment
 D3: Blinding of participants and personnel
 D4: Blinding of outcome assessment
 D5: Incomplete outcome data
 D6: Selective reporting

X High
 - Uncertain
 + Low
 ? No information

Ma 2013	?	?	-	?	+	+	X
Muir 1995 (IMAGES pilot)	+	+	+	+	+	?	+
Potter 2009 (CHHIPS)	+	+	+	+	+	+	+
Qureshi 2016 (ATACH-II)	+	+	-	+	+	+	+
Rashid 2003 (GTN-2)	+	+	-	+	+	?	+
Sandset 2011 (SCAST)	+	+	+	+	+	+	+
Saver 2015 (FAST-MAG)	+	+	+	+	+	+	+
Shaw 2013 (PIL-FAST)	+	+	+	+	X	+	-
Song 2010	?	?	-	?	+	+	X
Sun 2012	?	?	-	?	+	+	X
Szczechowski 1994	?	?	?	?	?	?	?
Tao 2014	+	?	-	?	+	+	X
Uzuner	?	?	?	?	?	?	?

D1: Randomisation method
 D2: Allocation concealment
 D3: Blinding of participants and personnel
 D4: Blinding of outcome assessment
 D5: Incomplete outcome data
 D6: Selective reporting

X High
- Uncertain
+ Low
? No information

Wang 2012	?	?	-	?	+	+	X
Xian 2010	?	?	-	?	+	+	X
Xu 2010	+	?	-	?	+	+	X
Xu MY 2011	+	?	-	?	+	+	X
Yuan 2020 (CHASE)	+	+	-	+	+	+	+
Zhang HX 2013	+	?	-	?	+	+	X
Zhang SJ 2011	?	?	-	?	+	+	X
Zhang HT 2016	?	?	-	?	+	+	X
Zang 2019	?	?	-	?	+	?	X
Zhao 2012	?	?	-	?	+	+	X
Zheng 2017	?	?	-	?	+	+	X

D1: Randomisation method
 D2: Allocation concealment
 D3: Blinding of participants and personnel
 D4: Blinding of outcome assessment
 D5: Incomplete outcome data
 D6: Selective reporting

 High
 Uncertain
 Low
 No information

SUPPLEMENTARY TABLE 5 Post-hoc sensitivity analysis: effect of active/intensive vs. placebo/guideline blood pressure lowering interventions on functional outcome after acute intracerebral haemorrhage adjusted for baseline Glasgow Coma Scale score.

Outcome: unfavourable shift in modified Rankin Scale scores at 90 days, adjusted for pre-specified covariables* and:	Adjusted OR* (95%CI)	p value
GCS score	0.97 (0.88 to 1.06)	0.50
NIHSS score	0.97 (0.88 to 1.06)	0.44

CI denotes confidence interval; OR, odds ratio.

*Age, sex, time from onset to randomisation and trial (random effect).

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