Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med 2013;368:2355-65. DOI: 10.1056/NEJMoa1214609

Rapid blood pressure lowering in intracerebral haemorrhage: the INTERACT2 study

TABLE OF CONTENTS

Study Investigators

The INTERACT2 investigators are as follows: **Executive Committee:** C.S. Anderson (Principal Investigator), J. Chalmers (Chair), H. Arima, S. Davis, E. Heeley, Y. Huang, P. Lavados, B. Neal, M.W. Parsons, R. Lindley, L. Morgenstern, T. Robinson, C. Stapf, C. Tzourio, and J.G. Wang. **National Leaders:** *China - Steering Committee:* Y. Huang (Chair), S. Chen, X.Y. Chen, L. Cui, Z. Liu, C. Lu, J. Wang, S. Wu, E. Xu, Q. Yang, C. Zhang, J. Zhang. *Europe - Austria*: R. Beer, E. Schmutzhard; *Belgium:* P. Redondo; *Finland*: M. Kaste, L. Soinne, T. Tatlisumak; *France*: C. Stapf; *Germany*: K. Wartenberg; *Italy*: S. Ricci; *The Netherlands:* K. Klijn; *Portugal*: E. Azevedo; *Spain*: A. Chamorro; *Switzerland*: M. Arnold, U. Fischer; *India:* S. Kaul, J. Pandian, H. Boyini, S. Singh; *North America* – A.A. Rabinstein; *South America - Argentina* – C. Estol; *Brazil* – G. Silva; *Chile* – P. Lavados, V.V. Olavarria; and *United Kingdom* – T.G. Robinson. **Data Safety and Monitoring Committee:** R.J. Simes (Chair), M.-G. Bousser, G. Hankey, K. Jamrozik (deceased), S.C. Johnston, and S. Li. **Project Office Operations Committee:** E. Heeley (Study Director), C.S. Anderson, K. Bailey, J. Chalmers, T. Cheung, C. Delcourt, S. Chintapatla, E. Ducasse, T. Erho, J. Hata, B. Holder, E. Knight, R. Lindley, M. Leroux, T. Sassé, E. Odgers, R. Walsh, and Z. Wolfowicz. **Endpoint Adjudication Committee:** C.S. Anderson, G. Chen, C. Delcourt, S. Fuentes, R. Lindley, B. Peng, H.-M. Schneble, and M.-X. Wang. **Statistical Analysis:** H. Arima, L. Billot, S. Heritier, Q. Li, and M. Woodward. **CT Analyses:** C. Delcourt (Chair), S. Abimbola, S. Anderson, E. Chan, G. Cheng, P. Chmielnik, J. Hata, S. Leighton, J.-Y. Liu, B. Rasmussen, A. Saxena, and S. Tripathy. **Data Management and Programming:** M. Armenis, M.A. Baig, B. Naidu, G. Starzec, and S. Steley. **Coordinating Centres:** *International* (The George Institute for Global Health, Sydney, Australia) – C.S. Anderson, E. Heeley, M. Leroux, C. Delcourt, T. Sassé, E. Knight, K. Bailey, T. Cheung, E. Odgers, E. Ducasse, B. Holder, Z. Wolfowicz, R. Walsh, S. Chintapatla, T. Erho; *Argentina, Buenos Aires* (STAT Research) – C. Estol, A. Moles, A. Ruiz, M. Zimmermann; *Brazil, Fortaleza* (Medicamenta MRS) – J. Marinho, S. Alves, R. Angelim, J. Araujo, L. Kawakami; *Chile, Santiago* (Clínica Alemana, Universidad del Desarrollo) – P. Lavados, V.V. Olavarria, C. Bustos, F. Gonzalez, P. Munoz Venturelli; *China, Beijing* (The George Institute China incorporating George Clinical, and Peking University First Hospital) – Y. Huang, X. Chen, Y. Huang, R. Jia, N. Li, S. Qu, Y. Shu, A. Song, J. Sun, J. Xiao, and Y. Zhao; *China, Shanghai* (The Centre for Epidemiological Studies and Clinical Trials, The Shanghai Institute of Hypertension, Rui Jin Hospital, Shanghai Jiaotong University School of Medicine) - J.-G. Wang, Q. Huang; *Europe, Paris* (Unité de Recherche Clinique, APHP - Hôpital Lariboisière)

– C. Stapf, E. Vicaut, A. Chamam, M.-C. Viaud, C. Dert, U. Fiedler, V. Jovis, S. Kabla, S. Marchand, A. Pena, V. Rochaud; *India, Hyderabad* (The George Institute India) – K. Mallikarjuna H. Boyini, N. Hasan; *Norway, Oslo* (Oslo University Hospital) – E. Berge, E.C. Sandset, A. S. Forårsveen; *United Kingdom* (Department of Cardiovascular Sciences, University of Leicester) – T. Robinson, D. Richardson, T. Kumar, S. Lewin; *United Kingdom* (London, Imperial Clinical Trials Unit) - N. Poulter, J. Field, A. Anjum, A. Wilson,. **Principal Investigators and Coordinators (according to country and center, with numbers of patients in parentheses)**: *Argentina (4)* - Clínica Instituto Medico Adrogue (1): H. Perelmuter, A.M. Agarie; Hospital Central de Mendoza (3): A.G. Barboza, L.A. Recchia, I.F. Miranda, S.G. Rauek, R.J. Duplessis; *Australia (73)* - Austin Hospital (5): H. Dewey, L. Walker, S. Petrolo; Box Hill (3): C. Bladin; Gosford Hospital (22): J. Sturm, D. Crimmins, D. Griffiths, A. Schutz, V. Zenteno; John Hunter Hospital (10): M.W. Parsons, F. Miteff, N. Spratt, E. Kerr, C.R. Levi; Monash Medical Centre (5): T.G. Phan, H. Ma, L. Sanders, C. Moran, K. Wong; Royal Brisbane and Women's Hospital (3): S. Read, R. Henderson, A. Wong, R. Hull, G. Skinner; Royal Melbourne Hospital (13): S. Davis, P. Hand, B. Yan, H. Tu, B. Campbell; Royal Prince Alfred Hospital (4): C.S. Anderson, C. Delcourt; Sir Charles Gairdner Hospital (4): D.J. Blacker; Western Hospital (4): T. Wijeratne, M. Pathirage, M. Jasinararchchi, Z. Matkovic, S. Celestino; *Austria (63)* - Allgenmeines Krankenhaus Linz (9): F. Gruber, M.R. Vosko, E. Diabl, S. Rathmaier; Innsbruck Medical University - Department of Neurology (34): R. Beer, E. Schmutzhard, B. Pfausler, R. Helbok; Medical University of Graz, Department of Neurology (20): F. Fazekas, R. Fischer, B. Poltrum, B. Zechner, U. Trummer; *Belgium (12)* - Cliniques De L'Europe (Europe Clinic) (1): M.P. Rutgers; UCL St Luc (5): A. Peeters, A. Dusart, M.-C. Duray, C. Parmentier, S. Ferrao-Santos; Universitair Ziekenhuis Brussel (6): R. Brouns, S. De Raedt, A. De Smedt, R.-J. Van Hooff, J. De Keyser; *Brazil (17)* - Hospital das Clínicas de Porto Alegre (5): S.C.O. Martins, A.G. de Almeida, R. Broudani, N.F. Titton; Hospital Quinta D'Or (1): G.R. de Freitas, F.M. Cardoso, L.M. Giesel, N.A. Lima Junior; Hospital Santa Marcelina (3): A.C. Ferraz de Almeida, R.B. Gomes, T.S. Borges dos Santos, E.M. Veloso Soares, O.L.A. Neto; Universidade Federal de São Paulo (7): G.S. Silva, D.L. Gomes, F.A. de Carvalho, M. Miranda, A. Marques; Universidade Federal do Paraná (1): V.F. Zétola, G. de Matia, M.C. Lange; *Chile (29)* - Clinica Alemana de Santiago (8): J. Montes, A. Reccius, P. Munoz Venturelli, V.V. Olavarria, A. Soto; Clínica Alemana de Temuco, Chile (3): R. Rivas, C. Klapp; Clínica Dávila (5): S. Illanes, C. Aguilera, A. Castro; Complejo Asistencial Dr. Víctor Ríos Ruiz (12): C. Figueroa, J. Benavides, P. Salamanca, M.C. Concha, J. Pajarito; Hospital Naval Almirante Nef (1): P. Araya, F. Guerra; *China (1926)* - Baotou Central Hospital (225):

Y. Li, G. Liu, B. Wang, J. Zhang, Y. Chong; Beijing Shijitan Hospital (19): M. He, L. Wang, J. Liu; Beijing Tongren Hospital (11): X. Zhang, C. Lai, H. Jiang, Q. Yang, S. Cui; Chang Ning District Central Hospital (25): Q. Tao, Y. Zhang, S. Yao, M. Xu, Y. Zhang; Changsha Central Hospital (42): Z. Liu, H. Xiao, J. Hu, J. Tang; Gongli Hospital, Pudong New Area, Shanghai (11): J. Sun, H. Ji, M. Jiang; Haidian Hospital, Beijing (9): F. Yu, Y. Zhang, X. Yang, X. Guo; Hejian City People's Hospital (158): Y. Wang, L. Wu, Z. Liu, Y. Gao, D. Sun; Hunan Province Brain Hospital (14): X. Huang, Y. Wang, L. Liu, Y. Li, P. Li; Jiangsu Province Hospital of Traditional Chinese Medicine (9): Y. Jiang, H. Li, H. Lu; Nanjing First Hospital (10): J. Zhou, C. Yuan; Navy General Hospital (2): X. Qi, F. Qiu, H. Qian, W. Wang, J. Liu; Peking University First Hospital (4): Y. Huang, W. Sun, F. Li, R. Liu, Q. Peng; Peking University Shougang Hospital (8): Z. Ren, C. Fan, Y. Zhang, H. Wang, T. Wang; People's Hospital of Beijing Daxing District (60): F. Shi, C. Duan, S. Chen, J. Wang, Z. Chen; Pinggu County Hospital, Beijing (60): X. Tan, Z. Zhao, Y. Gao, J. Chen, T. Han; Qinghai Province People's Hospital (12): S. Wu, L. Zhang, L. Wang, Q. Hu, Q. Hou; Qinghai University Affiliated Hospital (41): X. Zhao, L. Wang, G. Zeng, L. Ma, F. Wang; Ruijin Hospital Affiliated to Shanghai Jiaotong University School of Medicine (4): S. Chen, L. Zeng, Z. Guo, Y. Fu, Y. Song; Second Hospital of Hebei Medical University (83): L. Tai, X. Liu, X. Su, Y. Yang, R. Dong; Shijiazhuang 260 Hospital (25): Y. Xu, S. Tian, S. Cheng, L. Su, X. Xie; The Affiliated Hospital of Xuzhou Medical College (39): T. Xu, D. Geng, X. Yan, H. Fan, N. Zhao; The Branch Hospital of the First People's Hospital (52): S. Wang, J. Yang; The Chinese PLA No. 263 Hospital (108): J. Zhang, M. Yan, L. Li; The Fifth Affiliated Hospital Sun Yat-Sen University (26): Z. Li, X. Xu, F. Wang; The First Affiliated Hospital of Baotou Medical College (81): L. Wu, X. Guo, Y. Lian, H. Sun, D. Liu; The First Affiliated Hospital of Fujian Medical University (12): N. Wang, Q. Tang; The First Affiliated Hospital of Wenzhou Medical College (68): Z. Han, L. Feng; The Fourth Hospital of Jilin University (73): Y. Cui, J. Tian, H. Chang, X. Sun, J. Wang; The Second Affiliated Hospital Suzhou University (31): C. Liu, Z. Wen; The Second Affiliated Hospital of Guangzhou Medical College (38): E. Xu, Q. Lin; The Second Affiliated Hospital of Wenzhou Medical College (21): X. Zhang, L. Sun, B. Hu, M. Zou, Q. Bao; The Second Hospital of Qinghuangdao (51): X. Lin, L. Zhao, X. Tian, H. Wang, X. Wang; The Second Hospital of Tianjin Medical University (12): X. Li, L. Hao, Y. Duan, R. Wang, Z. Wei; Third Hospital of Hebei Medical University (20): J. Liu, S. Ren, H. Ren, Y. Wang, Y. Dong; Tianjin Medical University General Hospital (27): Y. Cheng, M. Zou, W. Liu, J. Han, C. Zhang; Tianjin Third Central Hospital (14): Z. Zhang, J. Zhu, Y. Wang, Q. Li; Traditional Chinese Medicine Hospital, Zhangjiagang (10): J. Qian, Y. Sun, K. Liu, F. Long; Wangcheng County People's Hospital of

Hunan Province (8): X. Peng, Q. Zhang, Z. Yuan, C. Wang, M. Huang; Wuxi People's Hospital (5): J. Zhang, F. Wang, P. He, Y. You, X. Wang; Xiangya Hospital Central-South University (8): Q. Yang, H. Wang, J. Xia, L. Zhou, Y. Hou; Xining First People's Hospital (21): Y. Wang, L. Liu, Y. Qi, L. Mei, R. Lu; Xuzhou Central Hospital (128): G. Chen, L. Liu, L. Ping, W. Liu, S. Zhou; Yutian County Hospital, Hebei Province (225): J. Wang, L. Wang, H. Li, S. Zhang, L. Wang; Zengcheng People's Hospital (15): R. Zou, J. Guo, M. Li, W. Wei; *Finland (36)* - Helsinki University Central Hospital (36): L. Soinne, S. Curtze, M. Saarela, D. Strbian, F. Scheperjans; *France (221)* - Centre Hospitalier de Saint Denis - Hôpital Delafontaine (11): T. De Broucker, C. Henry, R. Cumurciuc, N. Ibos-Augé; Centre Hospitalier de Versailles André-Mignot (16): A.-C. Zéghoudi, F. Pico; CH Calais (12): O. Dereeper, M.-C. Simian, C. Boisselier, A. Mahfoud; CHRU de Brest (6): S. Timsit, F.M. Merrien; CHU de Nantes - Hôpital G&R Laënnec (13): B. Guillon, M. Sevin, F. Herisson, C. Magne; Hôpital de Meaux (12): A. Ameri, C. Cret, S. Stefanizzi, F. Klapzcynski; Hôpital Kremlin Bicêtre (7): C. Denier, M. Sarov-Riviere; Hôpital Lariboisière (37): C. Stapf, P. Reiner, J. Mawet, D. Hervé, F. Buffon; Hôpital Ste-Anne (9): E. Touzé, V. Domigo, C. Lamy, D. Calvet, M. Pasquini; Hôpital Tenon (12): S. Alamowitch, P. Favrole, I.-P. Muresan; Pitié Salpêtrière (37): S. Crozier, C. Rosso, C. Pires, A. Leger, S. Deltour; Roger Salengro Lille (30): C Cordonnier, H. Henon, C. Rossi; Service de Neurologie et Neurovasculaire, Groupe Hospitalier Paris Saint Joseph (19): M. Zuber, M. Bruandet, R. Tamazyan, C. Join-Lambert; *Germany (141)* - Charité-University Medicine Berlin - Center for Stroke Research Berlin (CSB) (46): E. Juettler, T. Krause, S. Maul, M. Endres, G.J. Jungehulsing; Department of Neurology University of Heidelberg UMM Mannheim (23): M. Hennerici, M. Griebe, T. Sauer, K. Knoll; Department of Neurology, University of Ulm (8): R. Huber, K. Knauer, C. Knauer, S. Raubold; Dresden University of Technology, University Hospital, Department of Neurology (27): H. Schneider, H. Hentschel, C. Lautenschläger, E. Schimmel, I. Dzialowski; Goethe University Hospital Frankfurt (10): C. Foerch, M. Lorenz, O. Singer, I.M. R. Meyer dos Santos; Klinikum Frankfurt (Oder) (1): A. Hartmann, A. Hamann, A. Schacht, B. Schrader, A. Teíchmann; Martin Luther University (21): K.E. Wartenberg, T.J. Mueller; University Hospital Düsseldorf (3): S. Jander, M. Gliem, C. Boettcher; University Medical Center Hamburg – Eppendorf (2): M. Rosenkranz, C. Beck, D. Otto, G. Thomalla, B. Cheng; *Hong Kong (1)* - Prince of Wales Hospital, Chinese University of Hong Kong (1): K.S. Wong, T.W. Leung, Y.O.Y. Soo; *India (97)* - Apollo Hospitals (1): S. Prabhakar, S.R. Kesavarapu, P.K. Gajjela, R.R. Chenna; Baby Memorial Hospital (13): K. Ummer, M. Basheer, A. Andipet; CARE Hospital, Nampally (10): M.K.M. Jagarlapudi, A.U.R. Mohammed, V.G. Pawar, S.S.K. Eranki; Christian Medical College & Hospital (17): J.

Pandian, Y. Singh, N. Akhtar; GNRC Hospitals (16): N.C. Borah, M. Ghose, N. Choudhury; Jehangir Clinical Development Centre Pvt Ltd (2): N.R. Ichaporia, J. Shendge, S. Khese; Lalitha Super Specialities Hospital (27): V. Pamidimukkala, P. Inbamuthaiah, S.R. Nuthakki, N.M.R. Tagallamudi, A.K. Gutti; Postgraduate Institute of Medical Education & Research (10): D. Khurana, P. Kesavarapu, V. Jogi, A. Garg, D. Samanta; St. John's Medical College & Hospital (1): G.R.K. Sarma, R. Nadig, T. Mathew, M.A. Anandan; *Italy (47)* - Central follow up for Italy: E. Caterbi; Nuovo Ospedale Civile, AUSL Modena (15): A. Zini, M. Cavazzuti, F. Casoni, R. Pentore, F. Falzone; Ospedale di Branca (6): S. Ricci, T. Mazzoli, L.M. Greco, C. Menichetti, F. Coppola; Ospedale di Città di Castello (16): S. Cenciarelli, E. Gallinella, A. Mattioni, R. Condurso, I. Sicilia; San Giovanni Battista (4): M. Zampolini, F. Corea, M. Barbi, C. Proietti; Sapienza University Unità di Trattamento Neurovascolare (6): D. Toni, A. Pieroni, A. Anzini, A. Falcou, M. Demichele; *The Netherlands (2)* - University Medical Center Utrecht (2): C.J.M. Klijn; *Norway (5)* - Sørlandet Sykehus HF Kristiansand (2): A. Tveiten, E.T. Thortveit, S. Pettersen; Sykehuset Innlandet HF Lillehammer (2): N. Holand, B. Hitland; University Hospital North Norway (1): S.H. Johnsen, A. Eltoft; *Pakistan (9)* - Aga Khan University (9): M. Wasay, A. Kamal, A. Iqrar, L. Ali, D. Begum; *Portugal (22)* - Centro Hospitalar Sao Joao (21): G. Gama, E. Azevedo, L. Fonseca, G. Moreira; Centro Hospitalar Vila Nova de Gaia (1): L.M. Veloso, D. Pinheiro, L. Paredes, C. Rozeira, T. Gregorio; *Spain (50)* - Complejo Hospitalario Universitario de Albacete (6): T. Segura Martin, O. Ayo, J. Garcia-Garcia, I. Feria Vilar, I. Gómez Fernández; Hospital Clinico de Barcelona (10): A. Chamorro, S. Amaro, X. Urra, V. Obach, A. Cervera; Hospital Universitari de Girona, Dr Josep Trueta (34): Y. Silva, J. Serena, M. Castellanos, M. Terceno, C. Van Eendenburg; *Switzerland (3)* - University of Bern, Inselspital (3): U. Fischer, M. Arnold, A. Weck, O. Findling, R. Lüdi; *United Kingdom (70)* - Addenbrookes Hospital (1): E.A. Warburton, D. Day, N. Butler, E. Bumanlag; Bristol Royal Infirmary (1): S. Caine, A. Steele, M. Osborn, E. Dodd, P. Murphy; County Durham & Darlington NHS Foundation Trust (1): B. Esisi, E. Brown, R. Hayman, V. K.V. Baliga, M. Minphone; John Radcliffe Hospital (3): J. Kennedy, I. Reckless, G. Pope, R. Teal, K. Michael; King's College Hospital (8): D. Manawadu, L. Kalra, R. Lewis, B. Mistry, E. Cattermole; Leeds General Infirmary (2): A. Hassan, L. Mandizvidza, J. Bamford, H. Brooks, C. Bedford; Musgrove Park Hospital (1): R. Whiting, P. Baines, M. Hussain, M. Harvey; New Cross Hospital (4): K. Fotherby, S. McBride, P. Bourke, D. Morgan, K. Jennings-Preece; Northumbria Healthcare - Wansbeck and North Tyneside General Hospitals (2): C. Price, S. Huntley, V.E. Riddell, G. Storey, R.L. Lakey; Nottingham University Hospital (2): G. Subramanian; Royal Bournemouth Hospital (3): D. Jenkinson, J. Kwan, O. David, D. Tiwari; Royal Devon and Exeter Hospital (3): M.

James, S. Keenan, H. Eastwood; Royal United Hospital Bath NHS Trust (6): L. Shaw, P. Kaye, D. Button, B. Madigan, D. Williamson; Royal Victoria Infirmary Hospital NHS Foundation Trust (8): A. Dixit, J. Davis, M.O. Hossain, G.A. Ford; Salford Royal NHS Foundation Trust (12): A. Parry-Jones, V. O'Loughlin, R. Jarapa, Z. Naing; St George's Healthcare NHS Trust (1): C. Lovelock, J. O'Reilly, U. Khan; St. Thomas Hospital (1): A. Bhalla, A. Rudd, J. Birns; University College London Hospitals NHS Foundation Trust (6): D.J. Werring, R. Law, R. Perry, I. Jones, R. Erande; University Hospital of North Staffordshire (2): C. Roffe, I. Natarajan, N. Ahmad, K. Finney, J. Lucas; University Hospitals of Leicester NHS Trust (3): A. Mistri, D. Eveson, R. Marsh, V. Haunton, T. Robinson; *USA (11)* - Mayo Clinic (11): A.A. Rabinstein, J.E. Fugate, S.W. Lepore.

Methods

Training of Investigators

All INTERACT2 investigators were trained in the protocol, Good Clinical Practice (GCP) and use of the NIHSS and mRS scales if they had no recent certification.

Schedule for Monitoring of Sites

Regionally based research staff undertook quality control activities necessary for the conduct of the trial in accordance with the protocols, applicable guidelines and regulations. All participating sites had monitoring visits conducted after the third patient was randomized, then after the tenth and every 10 patients subsequently, to verify: consent, eligibility criteria and reported serious adverse events in 100% of patients; detailed source data verification in a minimum of 10% of patients; and for review of data that were outstanding or anomalous.

Sample Size Considerations

The sample size was set at 2800 to provide at least 90% power to detect a 14% relative risk reduction in the primary outcome for patients in the intensive BP lowering group compared to those in the guideline-recommended control group, using a two-sided significance test with 5% type I error. The following assumptions were made: a primary outcome of 50% in the control group will be reduced to 43% in the intensive group (i.e. 7% absolute decrease); and there will be 10% non-adherence to the intensive treatment and 3% overall loss to follow-up, as seen in INTERACT1. The 14% relative risk reduction is extrapolated from INTERACT1 where differences in systolic BP between randomized groups of 13 mm Hg and 11 mm Hg in the first 1 and 24 hours of treatment, respectively, resulted in approximately 2 ml absolute difference in hematoma growth at 24 hours. Further analysis of INTERACT1 cohort confirmed results of a meta-analysis of the recombinant activated clotting Factor VIIa studies

to indicate a 2-4 ml reduction in hematoma growth could translate into 10-20% better outcome in ICH. The expected magnitude of absolute benefit in terms of cases of death or dependency prevented being considered, which equates to a number needed-to-treat of 15, is considered a minimum clinically worthwhile benefit of the treatment, which could be applied widely as a standard care.

Terms of Reference of the Data Safety Monitoring Board (DSMB)

The DSMB was responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the intervention during the trial, and for monitoring the overall conduct of the clinical trial. The DSMB reviewed the recruitment of patients, separation in BP, dropout and event rates between groups, monitored safety, and examined the effects of treatment on the efficacy outcomes at twice-yearly intervals during conduct of the trial. The DSMB was charged with informing the study's Executive and Operational Committees if at any time there emerged either evidence beyond reasonable doubt of a difference between randomized groups in the primary outcome, or evidence that was likely to change clinical practice in the context of current knowledge. Two formal interim analyses after approximately 30% and 60% of the patients were followed up for 30 days were planned and conducted, using the Haybittle-Peto stopping rule (i.e. where a difference of 3 standard errors is considered as clear evidence of a treatment effect). The study was not terminated early and the committee did not request any additional analyses of the data. Professor R. John Simes, Chair of the DSMB, was invited to be an author on the manuscript only after the DSMB had submitted their final report.

Clinical Inclusion and Exclusion Criteria

Inclusion criteria

- Age is ≥18 years.
- Presentation with an acute stroke syndrome due to spontaneous ICH, defined as the sudden occurrence of bleeding into the parenchyma of the brain that may extend into the ventricles and/or in rare situations the subarachnoid space, that is confirmed by a CT scan (or MRI) of the brain. Patients with ICH whilst on antithrombotic treatment (antiplatelet agents or anticoagulation) are eligible.
- There are at least 2 systolic BP measurements of ≥150 and ≤220 mmHg, recorded 2 or more minutes apart. Patients with initial systolic BP levels outside of this range (<150 or >220 mmHg) may be randomised should the BP levels fulfil entry criteria on re-checking up to 6 hours after the onset of ICH. Patients with an initial systolic BP >220

mmHg may receive initial BP lowering and then be randomized, provided that the systolic BP is ≤220 mmHg within 6 hours of symptom onset.

- The randomly assigned BP lowering regimen is able to be commenced within 6 hours after the onset of ICH. If the precise timing of the onset of symptoms or signs of the qualifying event is unknown, then the time of onset will be taken as the last time the patient was known to be well.
- Active treatment and care will be provided to the patient in a suitable monitored facility (e.g. high dependency unit or intensive care unit) even if they are assigned with 'Not For Resuscitation (NFR)' or 'Do Not Resuscitate' (DNR) orders.
- Written informed consent is able to be obtained directly from the patient, or an appropriate surrogate based on local ethics committee recommendations

Exclusion criteria

- Known definite contraindication to intensive BP lowering (e.g. known severe carotid, vertebral or cerebral arterial stenosis, Moya Moya disease or Takayasu's arteritis, high-grade stenotic valvular heart disease, or severe renal failure).
- Known definite indication to intensive BP lowering (e.g. very high systolic level >220 mmHg, hypertensive encephalopathy, or aortic dissection).
- Definite evidence that the ICH is secondary to a structural abnormality in the brain (e.g. an arteriovenous malformation, intracranial aneurysm, tumour, or trauma), cerebral infarction within the last 30 days, or recent use of thrombolysis for ischemic stroke (or other vascular condition).
- A high likelihood that the patient will die within the next 24 hours on the basis of clinical and/or radiological criteria (e.g. massive hematoma with mid-line shift of a hemisphere or deep coma on presentation, defined by score of 3-5 on the GCS).
- Known existing dementia or pre-stroke disability (e.g. score 3-5 on the modified Rankin scale).
- Concomitant medical illness that would interfere with the outcome assessments and/or follow-up (e.g. advanced cancer or respiratory disease).
- Patients considered for early surgical evacuation of the hematoma.
- Patients who have previously participated in INTERACT2 or are currently participating in another investigational drug trial.
- Patients who are considered to have a high likelihood of not adhering to the study treatment or the follow-up regimen.
- Informed consent is not or cannot be obtained. For example, obtunded patients are not automatically excluded from the study. However, if the next of kin or legal guardian

(i.e. the individual legally empowered where the consent is obtained) cannot provide consent, randomization and entry into the study could not proceed.

Classification of Secondary Endpoints

All deaths and non-fatal cardiovascular events were adjudicated by blinded clinical experts through review of source data in their local language. Discrepancies in the serious adverse event reported by a clinician and an expert adjudicator were reviewed and resolved by a central expert committee after review of all available data. Since all patients had ICH, all deaths were classified as due to ICH unless an unequivocal non-cerebral cause was established. All deaths were categorized as:

- *Death from direct effects of initial ICH*, defined as any death after the onset of the randomised intracerebral hemorrhage event in a patient who had progressive neurological deterioration and either the baseline or follow-up brain scan shows hematoma with mass effect, midline shift, or significant extension of initial hematoma in the absence of a clear extra-cranial cause for the death.
- *Death from recurrent cardiovascular event*, defined by clear clinical evidence of a recurrent stroke (i.e. a new stroke event occurring after a period of at ≥24 hours of stability with clear clinical, biological, and if applicable, CT brain scan findings), a coronary vascular event, or sudden death, according to standard definitions;
- *Death due to other causes*, defined by clear evidence of death due to a non-neurological cause, including pneumonia, sepsis, or injury

Serious adverse events were reported according to standard definitions and coded using terminology of the Medical Dictionary for Regulatory Authorities (MedDRA). However, as this is a classification by System-Organ Class (SOC) and Preferred Term (PT) that is not necessarily relevant for this study, the following categories of serious adverse events derived from MedDRA and follow-up assessments were defined:

- neurological deterioration where declines from the baseline to 24 hours assessment of either ≥4 on the NIHSS or ≥2 on the GCS are reported;
- clinician-reported episode of severe hypotension including acute renal failure with clinical consequences which required corrective therapy with intravenous fluids, inotropes/vasopressors, or hemodialysis;
- acute coronary event according to standard definitions consistent with a typical clinical presentation, abnormal electrocardiogram, or abnormally elevated enzymes;

- acute renal failure as reported by the clinician confirmed by elevation of biochemistry with or without the need for dialysis;
- other sequelae as reported by clinicians.

CT Scan Analysis

CT brain scans (or MRIs if no CT scan) were conducted according to standardized techniques at baseline (to confirm the diagnosis) in all patients, and at 24±3 hours in a subset of patients where such repeat scanning was either part of routine practice or where patients provided consent for an additional scan for research. In China, the collection of 24 hour CT scans was stopped after a target of 400 consecutive patients was reached in 2009, as follow-up CT scanning for ICH is generally not routine and was an additional cost of medical care. Uncompressed digital CT images were collected in DICOM format on a CD-ROM identified only with the patient's unique study number and were analysed centrally for the measurement of hematoma volumes and other parameters. Hematoma volumes with and without the inclusion of any intraventricular component were calculated independently by several trained imaging scientists who were kept blind to clinical data, treatment, and date and sequence of scan. This calculation was done with computer-assisted multi-slice planimetric and voxel threshold techniques in MIStar software (version 3.2) (Apollo Medical Imaging Technology, Melbourne, Australia). Inter-reader reliability was checked by periodic re-analysis of 15% of the scans reviewed by each scientist against a 'gold standard' single neurologist throughout the study to avoid drift (intraclass correlation coefficient, 0.92 for total hematoma volume and 0.96 after removing outlier data with total volumes >50 mL). For the small number of CT scans received as digital images or plain films, hematoma volume was measured manually using the ABC/2 method.[5]

Supplementary Table S1. Primary and secondary outcomes according to different methods of analysis of scores on the mRS*

Characteristic of mRS outcome scores	Blood pressure lowering: Intensive (N=1399)	Blood pressure lowering: Guideline (N=1430)	OR (95% CI)	P Value	OR adjusted (95% CI)	P Value
Primary outcome - no. (%)†						
0 to 2	663 (48.0)	627 (44.4)	0.87 (0.75 to 1.01)	0.059	0.87 (0.73 to 1.04)	0.122
3 to 6	719 (52.0)	785 (55.6)				
Key secondary outcome, shift on scores – no. (%)†						
0 (no symptoms at all)	112 (8.1)	107 (7.6)	0.87 (0.77 to 1.00)	0.044	0.89 (0.78 to 1.02)	0.105
1 (no significant disability despite symptoms)	292 (21.1)	254 (18.0)				
2 (slight disability)	259 (18.7)	266 (18.8)				
3 (moderate disability requiring some help)	220 (15.9)	234 (16.6)				
4 (moderate-severe disability much help)	250 (18.1)	268 (19.0)				
5 (severe disability, requiring full care)	83 (6.0)	113 (8.0)				
6 (death by 90 days)	166 (12.0)	170 (12.0)				
Other outcomes – no. (%)						
0 to 1	404 (29.2)	361 (25.6)	0.83 (0.70 to 0.98)	0.030	0.85 (0.70 to 1.03)	0.092
2 to 6	978 (70.8)	1051 (74.4)				
0, 1, 2, and 3, shift in scores‡	883 (63.9)	861 (61.0)	0.87 (0.76 to 0.99)	0.038	0.88 (0.76 to 1.02)	0.079
4 to 6 combined	499 (36.1)	551 (39.0)				
Death or major disability at 7 days – no./total no. (%)§	1056 (76.5)	1087 (77.3)	0.95 (0.80 to 1.14)	0.597		
Death or major disability at 28 days – no./total no. (%)¶	913 (66.0)	965 (68.1)	0.91 (0.77 to 1.06)	0.219		

*mRS denoted modified Rankin Scale, OR odds ratio, CI confidence interval.

†Compared to 2794 participants in unadjusted analysis, there were 2570 participants included in an analysis adjusted for region (China versus non-China participants), age (quartiles in 4 categories), baseline National Institutes of Health Stroke Scale (NIHSS) score (<15 versus ≥15), time band from onset to randomization (<4 versus ≥4 hours), and baseline volume (<15 versus ≥15 ml) and location (3 categories of lobar, deep and other) of hematoma, and presence of intraventricular hemorrhage.

‡In ordinal regression, a proportional odds model was fitted 2570 participants included in the analysis of scores on the mRS between 0 and 3 (i.e. shift in good physical function) against scores between 4 and 6 which were combined as a single poor outcome. Covariates in the adjusted analysis were region (China versus non-China participants), age (quartiles in 4 categories), time band from onset to randomization (<4 versus ≥4 hours), and baseline National Institutes of Health Stroke Scale (NIHSS) score (<15 versus ≥15), and baseline volume (<15 versus ≥15 ml) and location (3 categories of lobar, deep and other) of hematoma, and presence of intraventricular hemorrhage. Without adjusting for the CT scan variables, the OR was 0.88 (95% CI 0.77 to 1.01), P=0.073.

§Unadjusted analysis based on 1381 patients in the intensive group and 1406 in the guideline group

¶Unadjusted analysis based on 1384 patients in the intensive group and 1416 in the guideline group

Supplementary Table S2. Effects of early blood pressure lowering treatments on hematoma volume*

	Blood Pressure Lowering					
	Intensive Group (N = 491)		Guideline Group (N = 473)		Absolute (mL) or proportional (%) decrease in intensive group	
Hematoma volumes					**(95% CI)**	**P Value**
Baseline to 24 hours - ml	Baseline	24 hours	Baseline	24 hours		
Hematoma	15.7±15.7	18.2±19.1	15.1±14.9	20.6±24.9		
Growth of the hematoma volume– ml	24 hours minus baseline		24 hours minus baseline		Guideline minus intensive	
Absolute - mean (95% CI)	3.1 (2.1 to 4.1)		4.9 (3.1 to 6.6)		1.8 (-0.3 to 3.8)	0.091
- adjusted mean (95% CI)†	2.3 (0.2 to 4.4)		3.7 (1.6 to 5.8)		1.4 (-0.6 to 3.4)	0.180
Relative - mean, % (95% CI)	44.7 (10.3 to 79.0)		52.2 (33.5 to 70.8)		7.5 (-31.9 to 47.0)	0.708
- adjusted median, % (95% CI)†	17.2 (9.3 to 25.7)		21.7 (13.5 to 30.5)		4.5 (-3.1 to 12.7)	0.269
Proportion of patients with *substantial* growth of the hematoma						
Hematoma – no. (%)	128 (26.1)		125 (26.4)		0.4 (-5.4 to 6.1)	0.899

*CI denotes confidence intervals. ICC was 0.92 for total volume and 0.95 with extreme outliers removed, for inter-reader reliability checked by re-analysis of 15% of the scans by a single neurologist using intra-class correlation with and without removing outliers in 625 cases.
†Covariates in the adjusted analysis were baseline volume, location and time from onset of ICH to CT scan. 95% CI for difference in adjusted medians were calculated using the bootstrap percentile method. Because of skewed raw data, adjusted medians are reported with 95% CI obtained by back-transformation.

Supplementary Figure S1: Enrolment and Follow-up*

Footnote:

*ICH denotes intracerebral hemorrhage, BP blood pressure, mRS modified Rankin Scale, and CT computerized tomography

†Screening logs were collected at each site for 1 randomly allocated month per year. The number estimated by extrapolation projected number of potential patients with ICH screened, based on the number of patients screened over the number of months that at a site was open for recruitment.

‡Patients with BP levels that were <180 mm Hg at any of the times of randomization, and 15 mins, 30 mins, or 45 mins post-randomization

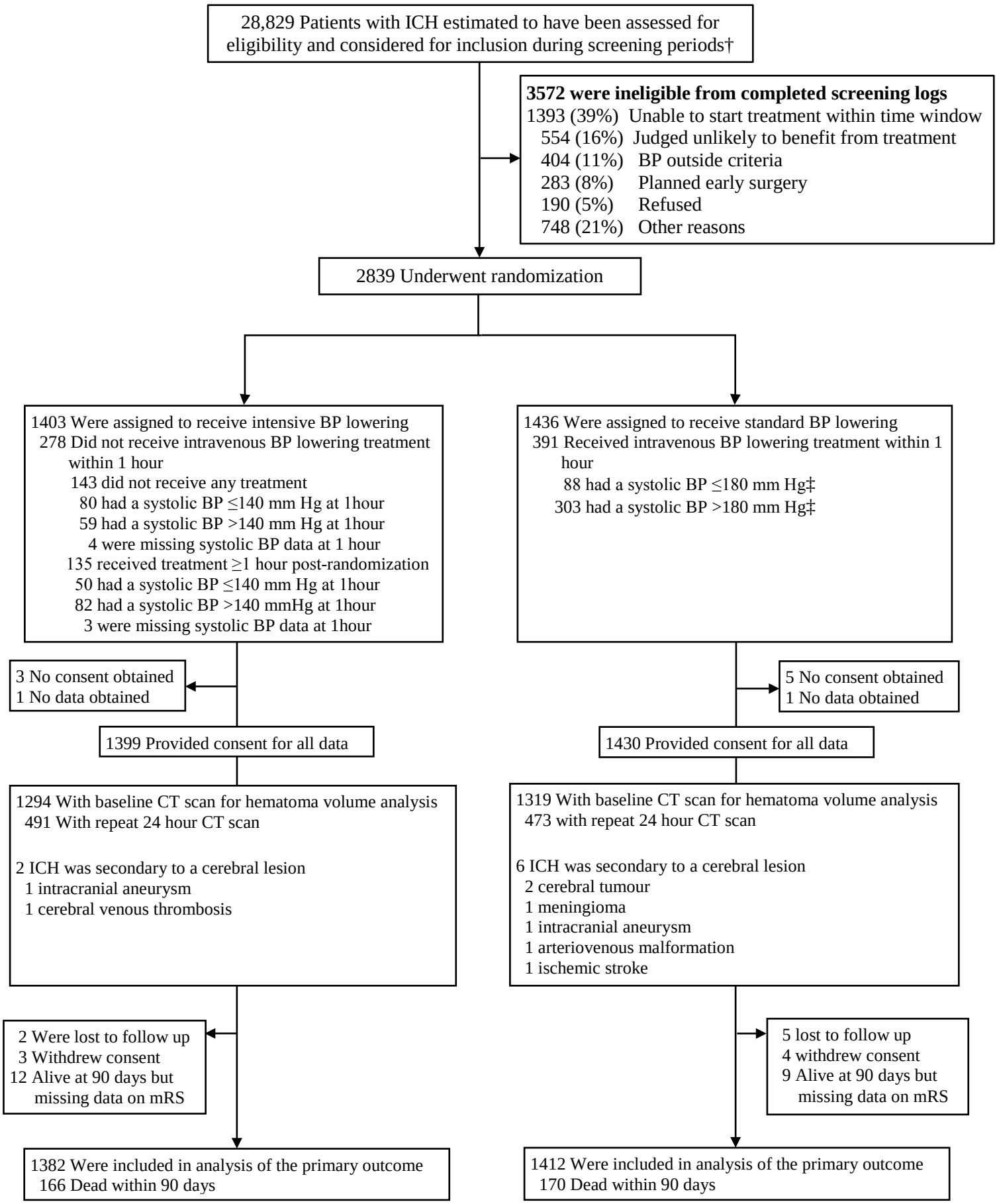
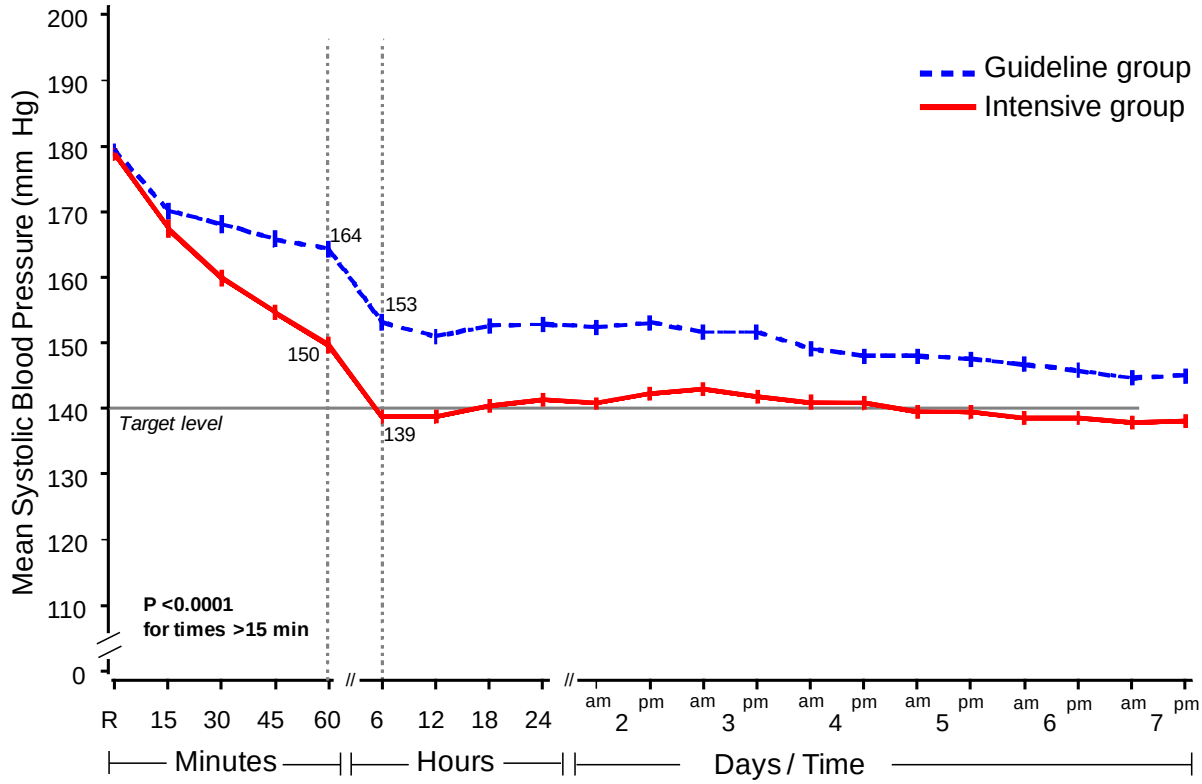
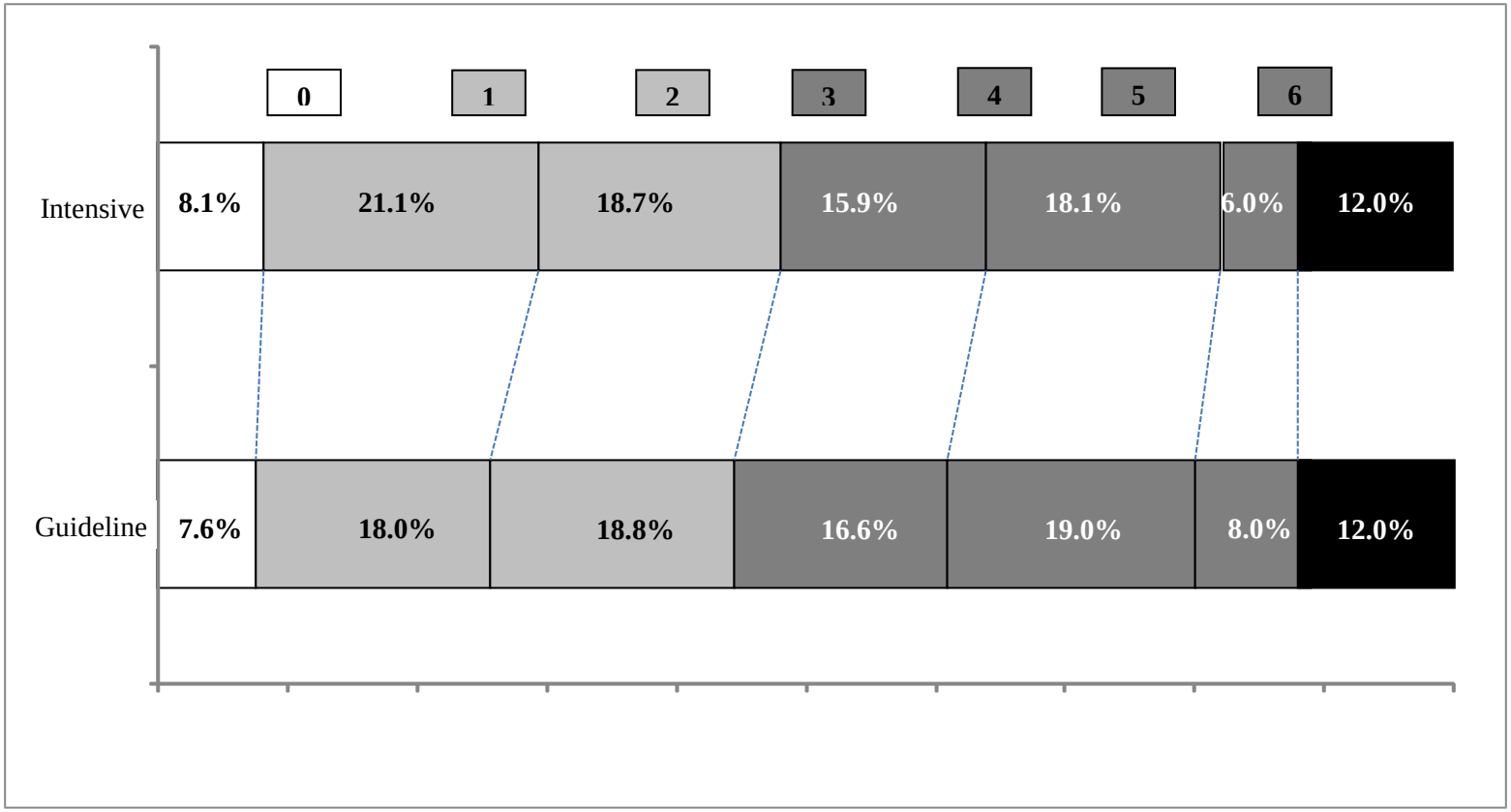

28,829 Patients with ICH estimated to have been assessed for eligibility and considered for inclusion during screening periods†
3572 were ineligible from completed screening logs
1393 (39%) Unable to start treatment within time window
554 (16%) Judged unlikely to benefit from treatment
404 (11%) BP outside criteria
283 (8%) Planned early surgery
190 (5%) Refused
748 (21%) Other reasons
2839 Underwent randomization
1403 Were assigned to receive intensive BP lowering
278 Did not receive intravenous BP lowering treatment within 1 hour
143 did not receive any treatment
80 had a systolic BP ≤140 mm Hg at 1hour
59 had a systolic BP >140 mm Hg at 1hour
4 were missing systolic BP data at 1 hour
135 received treatment ≥1 hour post-randomization
50 had a systolic BP ≤140 mm Hg at 1hour
82 had a systolic BP >140 mmHg at 1hour
3 were missing systolic BP data at 1hour
1436 Were assigned to receive standard BP lowering
391 Received intravenous BP lowering treatment within 1 hour
88 had a systolic BP ≤180 mm Hg‡
303 had a systolic BP >180 mm Hg‡
3 No consent obtained
1 No data obtained
5 No consent obtained
1 No data obtained
1399 Provided consent for all data
1430 Provided consent for all data
1294 With baseline CT scan for hematoma volume analysis
491 With repeat 24 hour CT scan
2 ICH was secondary to a cerebral lesion
1 intracranial aneurysm
1 cerebral venous thrombosis
1319 With baseline CT scan for hematoma volume analysis
473 with repeat 24 hour CT scan
6 ICH was secondary to a cerebral lesion
2 cerebral tumour
1 meningioma
1 intracranial aneurysm
1 arteriovenous malformation
1 ischemic stroke
2 Were lost to follow up
3 Withdrew consent
12 Alive at 90 days but missing data on mRS
5 lost to follow up
4 withdrew consent
9 Alive at 90 days but missing data on mRS
1382 Were included in analysis of the primary outcome
166 Dead within 90 days
1412 Were included in analysis of the primary outcome
170 Dead within 90 days

Figure S2. Systolic blood pressure levels at and after randomization



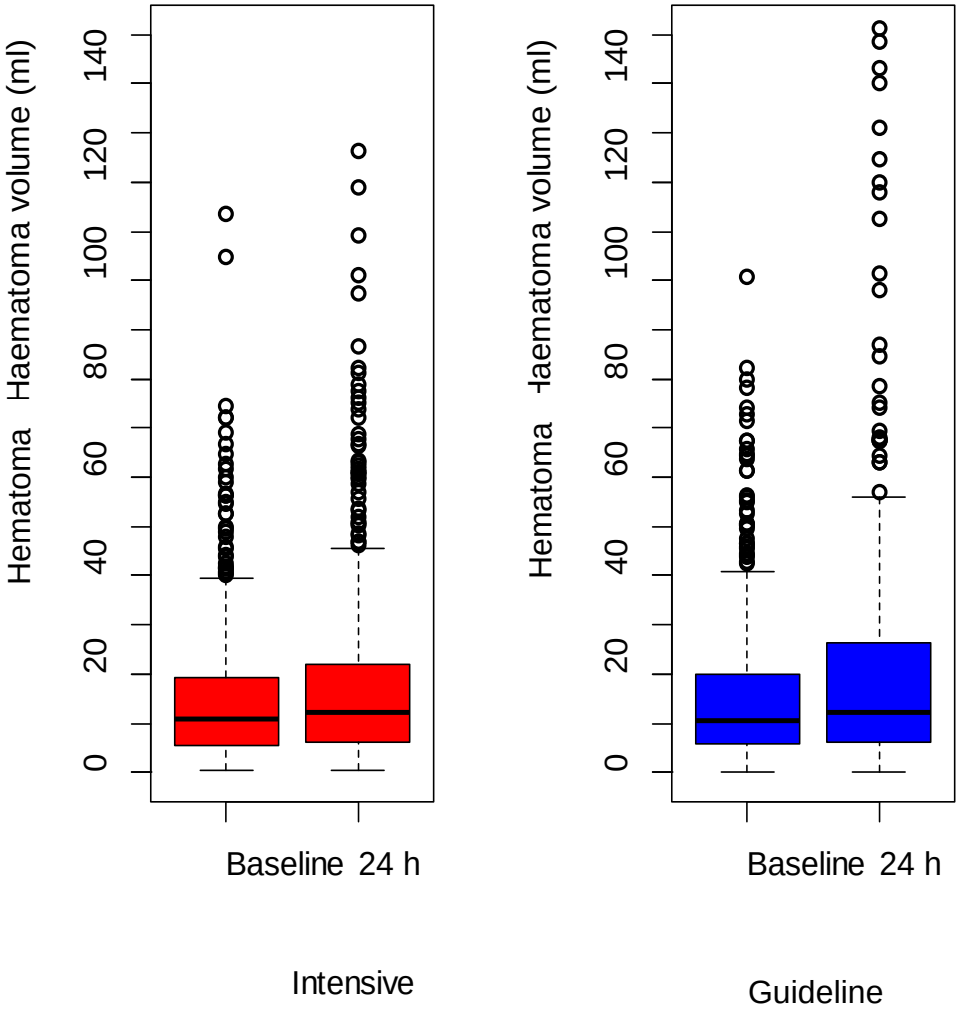
The lines incorporate blood pressure values with 95% confidence intervals represented by the vertical bars. The differences in mean systolic blood pressure are given for the intensive group as compared with the guideline-recommended group are given for 1 and 6 hours post-randomization. All between group blood pressures are significant (P<0.0001) from 15 minutes.

Figure S3. Distribution of scores on the modified Rankin scale at 90 days showing a 13% reduction in the odds of disability (P=0.044) from early intensive blood pressure lowering



The modified Rankin Scale evaluates global disability and handicap: scores range from 0 (no symptoms or disability) to 6 (death). There was significant difference between the groups receiving early intensive blood pressure lowering and guideline-recommended blood pressure lowering

Supplementary Figure S4 Change in hematoma volume from baseline to 24 hours, by randomized group



Footnote: Boxes represented interquartile range with enclosed solid line indicating median. Whiskers represent 90% of the range of values. Open circles represent 5% of outlier values.