RESEARCH PAPER

Early blood pressure lowering in patients with intracerebral haemorrhage and prior use of antithrombotic agents: pooled analysis of the INTERACT studies

Lili Song,[1] Else Charlotte Sandset,[2,3] Hisatomi Arima,[3] Emma Heeley,[3] Candice Delcourt,[3] Guofeng Chen,[4] Jie Yang,[5] Guojun Wu,[6] Xia Wang,[3] Pablo M Lavados,[7] Yining Huang,[8] Christian Stapf,[9] Jiguang Wang,[10] Thompson G Robinson,[11] John Chalmers,[3] Richard I Lindley,[3] Craig S Anderson,[3] for the INTERACT2 Investigators

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jnnp-2016-313246).

For numbered affiliations see end of article.

Correspondence to
Professor Craig S Anderson, The George Institute for Global Health, Royal Prince Alfred Hospital and the University of Sydney, P.O. Box M201, Missenden Road, Sydney, NSW 2050, Australia; canderson@george.org.au

Received 1 February 2016
Revised 8 April 2016
Accepted 22 April 2016
Published Online First 13 May 2016

To cite: Song L, Sandset EC, Arima H, *et al*. *J Neurol Neurosurg Psychiatry* 2016;**87**:1330–1335.

ABSTRACT

Objective Antithrombotic agents increase risks of intracerebral haemorrhage (ICH) and associated adverse outcomes. We determined differential effects of early blood pressure (BP) lowering in patients with/without antithrombotic-associated ICH in the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trials (INTERACT1 and 2).

Design Post hoc pooled analyses of the INTERACT studies—international, multicentre, prospective, open, blinded end point trials of patients with ICH (<6 h) and elevated systolic BP (SBP 150–180 mm Hg) randomly assigned to intensive (target SBP <140 mm Hg) or guideline-based (SBP <180 mm Hg) BP management. Associations of antithrombotic use and (1) death or dependency (modified Rankin scale scores 3–6) were analysed using logistic regression, and (2) of increased haematoma+intraventricular haemorrhage volume (IVH) with/without intraventricular haemorrhage (IVH) over 24 h were estimated in analyses of covariance.

Results In all, 3184 patients were included in these analyses. Antithrombotic-associated ICH (364 patients, 11%) was not associated with a significantly increased risk of death or dependency (OR 1.38, 95% CI 0.93 to 2.04). There was no heterogeneity in the BP-lowering treatment effect on death or dependency. Among 1309 patients who underwent follow-up CT after 24 h, absolute increase in haematoma±IVH volume was larger (5.2/5.0 mL) in those with compared to those without prior antithrombotics (2.2/0.9 mL; p=0.022/0.031). Intensive BP lowering reduced haematoma±IVH growth by 4.7/7.1 mL in patients on antithrombotics versus 1.3/1.4 mL in those without, although these differences did not reach statistical significance (p homogeneity=0.104/0.059).

Conclusions In patients with ICH, prior antithrombotic therapy is associated with greater haematoma growth, which may be reduced by early intensive BP-lowering treatment.

Trial registration number NCT00226096, NCT00716079.

Acute intracerebral haemorrhage (ICH) is a major cause of global disease burden,[1 2] with outcome determined by the initial volume and subsequent growth of the underlying haematoma.[3–5] Antithrombotic (antiplatelet and/or anticoagulant) therapy not only increases the risk of ICH,[6] but also worsens the severity of haemorrhage, and increases the risk of death[7 8] due to enhanced bleeding and extension of intraventricular haemorrhage (IVH).[9 10] Although the number of patients with ICH related to prior use of antithrombotic therapy is increasing in ageing populations,[11 12] there are no proven treatments despite guidelines emphasising rapid reversal of anticoagulation using vitamin K, fresh-frozen plasma (FFP), or prothrombin complex concentrate (PCC).[13 14] The benefits of controlling elevated blood pressure (BP) in this patient group are uncertain. Our objective was to determine whether early intensive BP-lowering treatment can attenuate haematoma growth in the subset of patients with antithrombotic-associated ICH who participated in the pilot and main phases of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trials (INTERACT1 and 2).

METHODS

The INTERACT studies were international, multicentre, open, blinded end point, randomised controlled trials, as described in detail elsewhere.[15–17] Briefly, 404 (INTERACT1) and 2829 (INTERACT2) patients with spontaneous ICH within 6 hours of onset and elevated systolic BP (SBP, 150–220 mm Hg) were randomised to receive intensive (target SBP <140 mm Hg within 1 h) or guideline-recommended (target SBP <180 mm Hg) BP-lowering treatment. CT substudies included 345 (INTERACT1) and 964 (INTERACT2) patients who underwent a repeat CT at 24 h using the same procedures as the baseline CT as a part of routine practice or where patients provided consent for an additional scan for research. The study protocols were approved by appropriate ethics committees at each site and written informed consent was obtained from each patient or, where appropriate, an approved surrogate. The INTERACT studies are registered with ClinicalTrials.gov (numbers NCT00226096 and NCT00716079).

Procedures

Demographic and clinical characteristics, and medical history including current medications, were recorded at the time of enrolment. Stroke severity was measured using the Glasgow coma scale (GCS) and National Institutes of Health Stroke Scale (NIHSS) at baseline, 24 h and at day 7 (or earlier on discharge from hospital). Antithrombotic therapy included the use of an antiplatelet agent (eg, aspirin) or oral anticoagulants (eg, warfarin).

For each CT scan, uncompressed digital images were sought by the core analysis laboratory in DICOM format on a CD-ROM identified only with the patient's unique study number. Haematoma volumes with and without inclusion of any IVH component were calculated independently by trained scientists who were blind to the clinical data, treatment and date and sequence of scan. This calculation was performed with computer-assisted multislice planimetric and voxel threshold techniques in MIStar software (V.3.2) (Apollo Medical Imaging Technology, Melbourne, Australia). Inter-reader reliability was checked by periodic re-analysis of the scans (10% in INTERACT1 and 15% in INTERACT2) throughout the study to avoid drift (intraclass correlation coefficients, 0.97 for INTERACT1 and 0.92 for INTERACT2).

Statistical analysis

Association of prior antithrombotic therapy on the primary clinical outcome was death or dependency at 90 days (modified Rankin scale score 3–6), and assessed using multivariable binary logistic regression adjusting for age, sex, region, prior ischaemic stroke, acute coronary syndrome, diabetes mellitus, currently treated hypertension, use of lipid lowering therapy, systolic BP, NIHSS score, time from onset to CT, location and volume of haematoma, and randomised treatment as recorded at baseline. The effect of intensive BP lowering on death or dependency is reported as an OR with associated 95% CI, and significance was tested using a standard χ^2 test of proportion (as prespecified in the protocol). Comparisons of randomised BP-lowering treatment effects between participants with and without prior use of antithrombotic therapy were estimated by adding an interaction term to the statistical model.

Associations of prior use of antithrombotic therapy on absolute increase in haematoma volume (±IVH) over 24 h were

Table 1 Characteristics of patients with acute intracerebral haemorrhage according to antithrombotic use at presentation

	Antithrombotics (n=364)	No antithrombotics (n=2820)	p Value
Demographic			
Age, years	71.6 (10.7)	62.4 (12.7)	<0.0001
Female sex	120 (33)	1059 (38)	0.088
Chinese region	96 (26)	2186 (78)	<0.0001
Medical history			
Prior intracerebral haemorrhage	27 (7)	243 (9)	0.439
Prior ischaemic stroke	89 (25)	236 (8)	<0.0001
Prior acute coronary syndrome	48 (13)	45 (2)	<0.0001
History of hypertension	309 (85)	2008 (71)	<0.0001
Diabetes mellitus	87 (24)	247 (9)	<0.0001
Medication history			
Antihypertensive therapy	297 (82)	1131 (40)	<0.0001
Oral anticoagulant	85 (23)	–	–
Antiplatelet therapy	293 (81)	–	–
Lipid-lowering therapy	131 (36)	73 (3)	<0.0001
Clinical features			
Time from onset to randomisation, hours	3.7 (2.9 to 4.8)	3.7 (2.8 to 4.7)	0.212
Systolic BP, mm Hg	177 (16)	179 (17)	0.004
Diastolic BP, mm Hg	94 (15)	102 (14)	<0.0001
NIHSS score*	13 (7 to 17)	10 (6 to 15)	<0.0001
NIHSS score ≥14	158 (44)	893 (32)	<0.0001
GCS score†	15 (13 to 15)	14 (12 to 15)	0.012
GCS score ≤8	20 (6)	117 (6)	0.559
CT findings			
Time from onset to CT	1.8 (1.3 to 2.7)	1.8 (1.2 to 2.7)	0.096
Baseline haematoma volume	10.2 (5.0 to 22.2)	10.8 (5.7 to 18.9)	0.699
Baseline haematoma+IVH volume	13.01 (5.54 to 29.4)	12.8 (6.4 to 23.2)	0.335
Haematoma location			
Lobar	57 (17)	228 (9)	0.001
Basal ganglia or thalamus	272 (79)	2162 (84)	
Cerebellar	11 (3)	90 (4)	
Brainstem	6 (2)	88 (3)	
Intraventricular extension	122 (34)	669 (24)	0.0002
Randomised intensive BP lowering	186 (51)	1394 (49)	0.550

Data are n (%), mean (SD) or median (IQR). p Values are based on χ^2 or Wilcoxon test.
*NIHSS scores can range from 0 (normal, no neurological deficit) to 42 (coma with quadriplegia).
†GCS scores can range from 3 (deep coma) to 15 (normal, alert).
BP, blood pressure; GCS, Glasgow coma scale; IVH, intraventricular haemorrhage; NIHSS, National Institutes of Health Stroke Scale.

assessed by an analysis of covariance (ANCOVA), adjusting for the same variables as above. The effects of intensive BP lowering on haematoma growth were also assessed by an ANCOVA including variables prespecified for the analysis of the effects of randomised treatment on haematoma outcomes in the statistical analysis plan[18] (time from onset to CT scan, location and baseline volume of haematoma). A sensitivity analysis was undertaken with significant haematoma growth without/with IVH defined as an absolute increase of ≥6 mL, using multivariable logistic regression. Comparisons of randomised BP-lowering treatment effects between participants with and without prior use of antithrombotic therapy were estimated by adding an interaction term to the statistical model. The present analysis was not prespecified. All data were analysed using SAS V.9.3 (SAS Institute).

RESULTS

There were 3184 patients with ICH included in the present analysis of whom 364 (11%) indicated prior use of antithrombotic therapy (279 with an antiplatelet agent only, 71 with anticoagulation only and 14 with both) (see online supplementary figure S1). These patients were older, less frequently recruited in China, and more often had a history of previous ischaemic stroke, acute coronary syndrome, hypertension and diabetes mellitus, and of using antihypertensive and lipid-lowering agents, as compared to those without prior antithrombotics (table 1). In addition, they presented with lower BP, greater clinical severity, and an ICH that was more often lobar in location and with IVH extension. Baseline haematoma volume was similar between patients with and without prior use of antithrombotics (median 10.2 vs 10.8 mL; p=0.699). There were no significant differences in the characteristics of patients between randomised groups for patients with and without prior use of antithrombotic therapy (data not shown).

Of the 3184 patients in this study, 1309 who underwent follow-up CT after 24 h were included in haematoma growth analysis. Baseline characteristics of the 1309 participants included and 1934 excluded in CT substudies are shown in online supplementary table S1. The included patients were older, less frequently recruited from China, and more often had a history of diabetes mellitus and of using antihypertensive, antithrombotic and lipid lowering medications.

In unadjusted analysis, treatment with antiplatelets, anticoagulants or both, was associated with significant increased risks of both death and the combined end point of death or dependency (table 2). The risk of death was significantly higher in anticoagulated patients (OR 2.24, 95% 1.19 to 4.19; p=0.012) in the analysis adjusted for baseline difference, but not in patients defined by antithrombotic use. There was consistency of the effect of randomised BP-lowering treatment in patients with and without antithrombotics (table 3).

In the adjusted analysis, patients with ICH with prior use of antiplatelets, oral anticoagulants, or their combination, had larger absolute increases in haematoma volume without/with IVH as compared with those without antithrombotics, with differences ranging from 1.3 to 9.5 mL for haematoma only (p=0.022), and 2.0 to 12.5 mL for haematoma plus IVH (p=0.031; figure 1). Results were similar in the antiplatelet-treated and anticoagulant-treated patients (p=0.127 and p=0.248 for homogeneity), and also in sensitivity analyses using significant growth in haematoma volume without/with IVH as a binary variable (≥6 mL vs <6 mL) (multivariable-adjusted ORs of prior use of antithrombotics 1.48 (95% CI 0.94 to 2.32), p=0.091 without IVH and 1.76 (95% CI 1.14 to 2.72), p=0.011 with IVH) (see online supplementary table S2).

Figure 2 shows the effects of randomised intensive BP lowering on haematoma growth among patients with and without prior use of antithrombotic therapy. The mean differences in SBP between randomised groups during 1–24 h were 13.9 mm Hg (95% CI 10.6 to 17.3) for patients with antithrombotics and 13.1 mm Hg (95% CI 11.4 to 14.9) for those without (p=0.664 for homogeneity). Treatment-related reduction in absolute increase in haematoma volume without/with IVH tended to be larger in patients with antithrombotics (4.7 mL, 95% CI −0.8 to 10.3 mL; and 7.1 mL, 95% CI −1.5 to 15.7 mL) than in those without antithrombotics (1.3 mL, 95% CI −0.3 to 2.8 mL; and 1.4 mL, 95% CI −0.7 to 3.6 mL), although the difference did not reach statistical significance (p=0.104 and 0.059 for homogeneity). Similar results were obtained for the binary outcome of significant growth in haematoma volume without/with IVH (OR 0.72 (95% CI 0.51 to 1.01) vs 0.84 (95% CI 0.44 to 1.58), p=0.679 for homogeneity; and OR 0.77 (95% CI 0.55 to 1.08) vs 0.96 (95% CI 0.53 to 1.77), p=0.555 for homogeneity).

DISCUSSION

These secondary analyses of the INTERACT studies demonstrate that prior antithrombotic therapy was associated with significant

Table 2 Effects of antithrombotics versus no antithrombotics on death or dependency

	Previous antithrombotic treatment		Crude			Adjusted*		
	Yes n/N (%)	No n/N (%)	OR	95% CI	p Value	OR	95% CI	p Value
Death or dependency								
Antiplatelets	187/279 (67)	1437/2820 (51)	1.96	1.51 to 2.54	<0.0001	1.17	0.80 to 1.70	0.425
Anticoagulants	57/71 (79)	1437/2820 (51)	3.92	2.17 to 7.06	<0.0001	1.58	0.75 to 3.37	0.228
Combination	10/14 (71)	1437/2820 (51)	2.41	0.75 to 7.69	0.180	2.22	0.50 to 9.77	0.293
Overall	254/364 (70)	1437/2820 (51)	2.22	1.76 to 2.81	<0.0001	1.38	0.93 to 2.04	0.113
Death								
Antiplatelets	49/279 (18)	300/2820 (11)	1.79	1.29 to 2.49	0.0004	1.01	0.64 to 1.61	0.952
Anticoagulants	26/71 (37)	300/2820 (11)	4.85	2.95 to 7.98	<0.0001	2.24	1.19 to 4.19	0.012
Combination	5/14 (36)	300/2820 (11)	4.67	1.55 to 14.0	0.003	3.15	0.86 to 11.6	0.085
Overall	80/364 (22)	300/2820 (11)	2.37	1.80 to 3.12	<0.0001	1.24	0.86 to 1.75	0.223

*Values were adjusted for age, sex, region, prior ischaemic stroke, acute coronary syndrome, diabetes, currently treated hypertension, lipid-lowering therapy, systolic blood pressure, National Institutes of Health Stroke Scale score, time from onset to CT scan, location and baseline volume of haematoma, randomised treatment and trial.

Table 3 Effects of early intensive blood pressure-lowering treatment on death or dependency, by prior use of antithrombotics

	Intensive n/N (%)	Guideline n/N (%)	OR	95% CI	p Homogeneity
Death or dependency					
Antithrombotics	127/186 (68)	127/178 (71)	0.86	0.55 to 1.35	0.975
No antithrombotics	686/1349 (49)	751/1426 (53)	0.87	0.75 to 1.01	
Death					
Antithrombotics	40/186 (22)	40/178 (23)	0.95	0.56 to 1.55	0.895
No antithrombotics	147/1394 (11)	153/1426 (11)	0.98	0.77 to 1.25	

Unadjusted values as prespecified in the protocol.

increases in volume of haematoma with/without IVH during the first 24 h after the onset of acute ICH, and non-significantly increased risk of death or dependency. Furthermore, early intensive BP lowering may provide additional reduction in the volume of haematoma with/without IVH in patients with prior use of antithrombotic therapy and in those without. These analyses raise the possibility that intensive BP lowering is an effective treatment for haematoma/IVH growth related to prior use of antithrombotic therapy.

Previous observational studies of patients with ICH with prior use of oral anticoagulants have consistently demonstrated enlarged haematomas and greater IVH expansion compared with those who did not use anticoagulants before ICH onset.[9 10 19–21] Although studies of patients with ICH with prior use of antiplatelet agents are less consistent,[22–26] most have shown a positive relationship with haematoma growth.[23–26] Epidemiological data have also shown that ICH related both to antiplatelets and anticoagulants are more likely to be lobar.[27] While our analysis is limited by the small number of patients treated with antithrombotics, the results support the hypothesis generated from observational studies that prior use of antithrombotic therapy increases the risks of greater haemorrhage in acute ICH.

Limited strategies have been shown to attenuate haematoma growth in patients with ICH with prior use of antithrombotic therapy. Current guidelines in this patient group recommend rapid correction of International Normalised Ratio (INR) using vitamin K, FFP or PCCs for anticoagulant-related ICH.[13 14] However, one randomised trial of PCCs in combination with FFP compared to FFP alone in patients with anticoagulant-related ICH showed that PCCs did not improve functional outcomes and increased adverse events.[28] There is very limited randomised evidence supporting any of these approaches to treatment of antithrombotic-related ICH. Our analysis suggests that the early lowering of elevated BP could provide protection against growth of haematoma with/without IVH in patients with ICH with prior use of antithrombotics as well as in those without such premorbid treatment.

Despite a significant attenuation of haematoma, our adjusted analysis produced only a non-significant risk reduction of previous use of antithrombotics on death or dependency. As a strong correlation between increase in haematoma volume and poor functional outcome has been established, we believe the lack of statistical significance is likely to reflect the limited power provided by the small sample size of these subgroup data.[29]

Although this is the largest study to have investigated the effects of intensive BP lowering in patients with acute ICH with prior use of antithrombotic therapy, the number of subjects was still limited to provide power to detect an interaction between prior use of an antithrombotic and randomised intensive BP-lowering treatment. Moreover, because INTERACT studies were clinical trials that specifically excluded those patients who were likely to die within the next 24 h on the basis of clinical and/or radiological criteria, the present findings may not be applicable to patients with severe ICH.

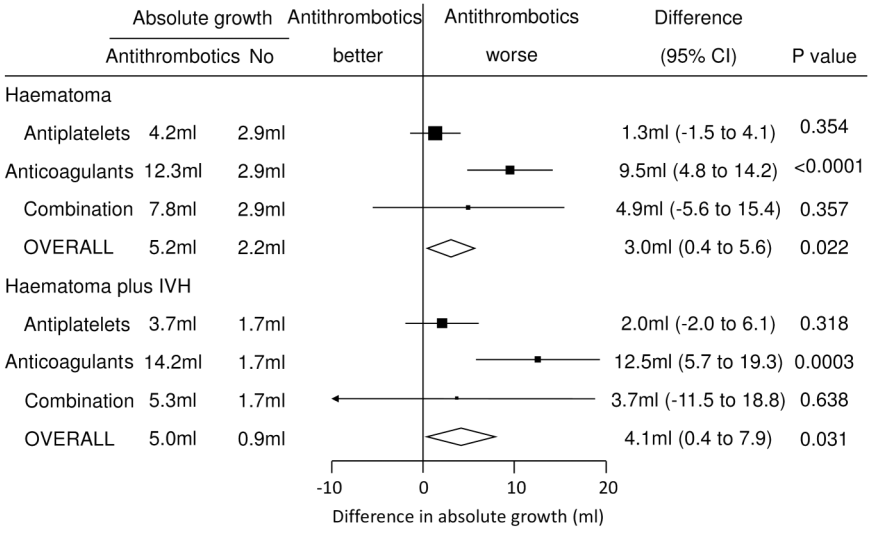

Figure 1 Haematoma growth according to prior use of antithrombotic therapy. Solid boxes represent estimates of the effects of prior use of antiplatelets, oral anticoagulants and their combination, and diamonds represent estimates and 95% CIs of overall antithrombotic therapy. Centres of the boxes are placed at the estimates of effect; areas of the boxes are proportional to the reciprocal of the variance of the estimates. Horizontal lines represent 95% CI. Values were adjusted for age, sex, region, prior ischaemic stroke, acute coronary syndrome, diabetes, currently treated hypertension, lipid-lowering therapy, systolic blood pressure, Glasgow coma scale score, time from onset to CT scan, location and baseline volume of haematoma, randomised treatment and trial.

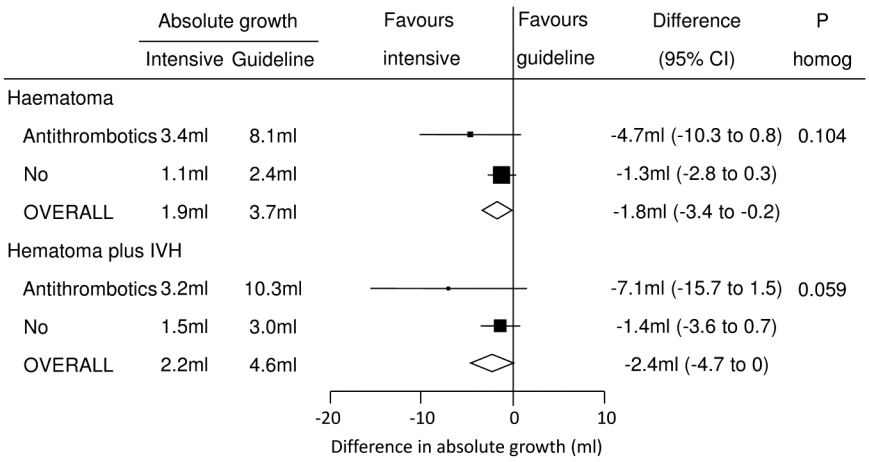

Figure 2 Effect of early intensive blood pressure-lowering treatment on haematoma growth, by prior use of antithrombotics. Solid boxes represent estimates of the effects of randomised intensive blood pressure-lowering treatment in subgroups defined by prior use of antithrombotic therapy, and diamonds represent estimates and 95% CIs of overall effects. Other conventions are similar to figure 1. Values were adjusted for time from onset to CT scan, location and baseline volume of haematoma and trial.

In summary, prior use of antithrombotic therapy was associated with larger haematoma growth. However, early intensive BP-lowering treatment may provide greater attenuation of haematoma growth among patients with ICH who have had prior use of antithrombotic therapy.

Author affiliations
[1]Department of Neurology, Shanghai 85th Hospital of PLA, Shanghai, China
[2]Department of Neurology, Oslo University Hospital, Oslo, Norway
[3]The George Institute for Global Health, Royal Prince Alfred Hospital and University of Sydney, Sydney, New South Wales, Australia
[4]Department of Neurology, Xuzhou Central Hospital, Xuzhou, China
[5]Department of Neurology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China
[6]Department of Neurology, Hebei Yutian Hospital, Yutian, China
[7]Servicio de Neurología, Departamento de Medicina, Clínica Alemana, Universidad del Desarrollo, and Universidad de Chile, Santiago, Chile
[8]Department of Neurology, Peking University First Hospital, Beijing, China
[9]Department of Neuroscience, CRCHUM, University of Montreal, Montreal, Quebec, Canada
[10]The Shanghai Institute of Hypertension, Rui Jin Hospital, Shanghai Jiaotong University, Shanghai, China
[11]Department of Cardiovascular Sciences and NIHR Biomedical Research Unit in Cardiovascular Disease, University of Leicester, Leicester, UK

Twitter Follow Else Sandset at @ECSandset

Contributors LS contributed to data interpretation and wrote the first draft of the report. ECS contributed to analyses and writing the report. HA supervised and conducted the analyses, and contributed to writing the report. TGR, JC, RIL and CSA obtained funding, and were responsible for planning of the study, supervision, data interpretation and writing of the report. EH, CD, XW, PML, YH, CS, RIL and TGR provided comments on data interpretation and the report.

Funding The INTERACT2 study was supported by Programme Grant (571281) and Project Grants (512402 and 1004170) from the National Health and Medical Research Council (NHMRC) of Australia. ECS holds a South-Eastern Norway Regional Health authority postdoctoral grant. HA held an Australian Research Council (ARC) Future Fellowship during much of these analyses. CSA holds a NHMRC Senior Principal Research Fellowship. All the authors had full access to the data.

Competing interests YH reports receiving reimbursement for travel expenses from Osaka Pharmaceuticals. CSA reports receiving reimbursement for travel expenses and honorarium from Takeda China, and is on Advisory Committees for Medtronic and Astra Zeneca.

Ethics approval Regional health authorities of all sites involved.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Qureshi AI, Tuhrim S, Broderick JP, *et al*. Spontaneous intracerebral hemorrhage. *N Engl J Med* 2001;344:1450–60.
2 Krishnamurthi RV, Feigin VL, Forouzanfar MH, *et al*. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet Glob Health* 2013;1:e259–81.
3 van Asch CJ, Luitse MJ, Rinkel GJ, *et al*. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol* 2010;9:167–76.
4 Broderick JP, Brott TG, Duldner JE, *et al*. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. *Stroke* 1993;24:987–93.
5 Broderick JP, Diringer MN, Hill MD, *et al*. Determinants of intracerebral hemorrhage growth: an exploratory analysis. *Stroke* 2007;38:1072–5.
6 Flaherty ML, Kissela B, Woo D, *et al*. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. *Neurology* 2007;68:116–21.
7 Rosand J, Eckman MH, Knudsen KA, *et al*. The effect of warfarin and intensity of anticoagulation on outcome of intracerebral hemorrhage. *Arch Intern Med* 2004;164:880–4.
8 Thompson BB, Béjot Y, Caso V, *et al*. Prior antiplatelet therapy and outcome following intracerebral hemorrhage: a systematic review. *Neurology* 2010;75:1333–42.
9 Flibotte JJ, Hagan N, O'Donnell J, *et al*. Warfarin, hematoma expansion, and outcome intracerebral hemorrhage. *Neurology* 2004;63:1059–64.
10 Biffi A, Battey TW, Ayres AM, *et al*. Warfarin-related intraventricular hemorrhage: imaging and outcome. *Neurology* 2011;77:1840–6.
11 Lovelock CE, Molyneux AJ, Rothwell PM, *et al*. Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: a population-based study. *Lancet Neurol* 2007;6:487–93.
12 Bejot Y, Cordonnier C, Durier J, *et al*. Intracerebral haemorrhage profiles are changing: results from the Dijon population-based study. *Brain* 2013;136(Pt 2):658–64.
13 Hemphill JC 3rd, Greenberg SM, Anderson CS, *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;46:2032–60.
14 Steiner T, Al-Shahi Salman R, Beer R, *et al*. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. *Int J Stroke* 2014;9:840–55.
15 Anderson CS, Huang Y, Wang JG, *et al*. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. *Lancet Neurol* 2008;7:391–9.
16 Delcourt C, Huang Y, Wang J, *et al*. The second (main) phase of an open, randomised, multicentre study to investigate the effectiveness of an intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT2). *Int J Stroke* 2010;5:110–16.
17 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.
18 Anderson C, Heeley E, Heritier S, *et al*. Statistical analysis plan for the second INTEnsive blood pressure Reduction in Acute Cerebral hemorrhage Trial (INTERACT2): a large-scale investigation to solve longstanding controversy over the most appropriate management of elevated blood pressure in the hyperacute phase of intracerebral hemorrhage. *Int J Stroke* 2013;8:327–8.
19 Kuwashiro T, Yasaka M, Itabashi R, *et al*. Enlargement of acute intracerebral hematomas in patients on long-term warfarin treatment. *Cerebrovasc Dis* 2010;29:446–53.
20 Flaherty ML, Tao H, Haverbusch M, *et al*. Warfarin use leads to larger intracerebral hematomas. *Neurology* 2008;71:1084–9.
21 Huttner HB, Schellinger PD, Hartmann M, *et al*. Hematoma growth and outcome in treated neurocritical care patients with intracerebral hemorrhage related to oral anticoagulant therapy: comparison of acute treatment strategies using vitamin K, fresh frozen plasma, and prothrombin complex concentrates. *Stroke* 2006;37:1465–70.

22 Sansing LH, Messe SR, Cucchiara BL, *et al*. Prior antiplatelet use does not affect hemorrhage growth or outcome after ICH. *Neurology* 2009;72:1397–402.
23 Yildiz OK, Arsava EM, Akpinar E, *et al*. Previous antiplatelet use is associated with hematoma expansion in patients with spontaneous intracerebral hemorrhage. *J Stroke Cerebrovasc Dis* 2012;21:760–6.
24 Moussouttas M, Malhotra R, Fernandez L, *et al*. Role of antiplatelet agents in hematoma expansion during the acute period of intracerebral hemorrhage. *Neurocrit Care* 2010;12:24–9.
25 Saloheimo P, Ahonen M, Juvela S, *et al*. Regular aspirin-use preceding the onset of primary intracerebral hemorrhage is an independent predictor for death. *Stroke* 2006;37:129–33.
26 Toyoda K, Okada Y, Minematsu K, *et al*. Antiplatelet therapy contributes to acute deterioration of intracerebral hemorrhage. *Neurology* 2005;65:1000–4.
27 Lavados PM, Sacks C, Prina L, *et al*. Incidence of lobar and non-lobar spontaneous intracerebral haemorrhage in a predominantly Hispanic-Mestizo population—the PISCIS stroke project: a community-based prospective study in Iquique, Chile. *Neuroepidemiology* 2010;34:214–21.
28 Boulis NM, Bobek MP, Schmaier A, *et al*. Use of factor IX complex in warfarin-related intracranial hemorrhage. *Neurosurgery* 1999;45:1113–18; discussion 18–9.
29 Delcourt C, Huang Y, Arima H, *et al*. Hematoma growth and outcomes in intracerebral hemorrhage: the INTERACT1 study. *Neurology* 2012;79:314–19.