RESEARCH PAPER

Prognostic significance of delayed intraventricular haemorrhage in the INTERACT studies

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ABSTRACT

Background and purpose Intraventricular extension of intracerebral haemorrhage (ICH) predicts poor outcome, but the significance of delayed intraventricular haemorrhage (dIVH) is less well defined. We determined the prognostic significance of dIVH in the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trials (INTERACT 1 and 2).

Methods Pooled analyses of the INTERACT CT substudies—international, multicentre, prospective, open, blinded end point, randomised controlled trials of patients with acute spontaneous ICH and elevated systolic blood pressure (SBP)—randomly assigned to intensive (<140 mm Hg) or guideline-based (<180 mm Hg) SBP management. Participants had blinded central analyses of baseline and 24 h CTs, with dIVH defined as new intraventricular haemorrhage (IVH) on the latter scan. Outcomes of death and major disability were defined by modified Rankin Scale scores at 90 days.

Results There were 349 (27%) of 1310 patients with baseline IVH, and 107 (11%) of 961 initially IVH-free patients who developed dIVH. Significant associations of dIVH were prior warfarin anticoagulation, high (≥15) baseline National Institutes of Health Stroke Scale score, larger (≥15 mL) ICH volume, greater ICH growth and higher achieved SBP over 24 h. Compared with those who were IVH-free, dIVH had greater odds of 90-day death or major disability versus initial IVH (adjusted ORs 2.84 (95% CI 1.52 to 5.28) and 1.87 (1.36 to 2.56), respectively (p trend <0.0001)).

Conclusions Although linked to factors determining greater ICH growth including poor SBP control, dIVH is independently associated with poor outcome in acute small to moderate-size ICH.

Trial registration numbers NCT00226096 and NCT00716079.

INTRODUCTION

Intraventricular haemorrhage (IVH) complicates approximately 45% of cases of acute spontaneous intracerebral haemorrhage (ICH) and is an important prognostic factor,[1–6] being associated with increasing age, larger ICH volume, deep ICHs and elevated blood pressure (BP) at presentation.[1 2] Common sequelae of IVH include obstructive hydrocephalus and neurological deterioration,[2–4] resulting in poor clinical outcomes.[1–5] Delayed IVH (dIVH), ascribed to IVH observed on follow-up brain imaging when the initial diagnostic scan was free of IVH (figure 1), occurs in 10–20% of cases at 24 h and is associated with ICH growth,[7 8] a process recognised to confer a poor prognosis.[9] Other reported associations of dIVH include an earlier time to CT scan, atrial fibrillation and use of warfarin with high international normalised ratio (INR).[7 8] However, data regarding the prognostic significance of dIVH are limited and conflicting.[7 8]

We aimed to determine the significance of dIVH among participants of the CT substudies in the pilot and main phases of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trials (INTERACT 1 and 2).[10 11] We examined associations of dIVH with ICH growth and level of achieved systolic BP (SBP) in the first 24 h, and with the key clinical outcomes at the end of follow-up at 90 days.

METHODS

Participants

INTERACT 1 and 2 were international, multicentre, prospective, open, blinded end point, randomised controlled trials, as outlined in detail elsewhere.[10 11] In summary, a total of 3243 adult patients (404 in INTERACT 1, 2839 in INTERACT 2) with spontaneous ICH within 6 hours of onset and elevated SBP (150–220 mm Hg) were randomly assigned to receive intensive (target SBP <140 mm Hg) or guideline-recommended (<180 mm Hg) BP management. In predefined CT substudies, 1310 consecutive patients (346 in INTERACT 1 and 964 in INTERACT 2) underwent repeat CT at 24±3 h. The study protocols were approved by the appropriate ethics committee at each participating site and written informed consent was obtained directly from either the patient or an appropriate surrogate.

Procedures

Achieved postrandomisation SBP in the hyperacute phase was an average of measurements taken at 1, 6, 12, 18 and 24 h postrandomisation. Clinical outcomes were the combined and separate end points of death and major disability, according to scores on the modified Rankin Scale (mRS) of 3–6, 6 and 3–5, respectively.[12]

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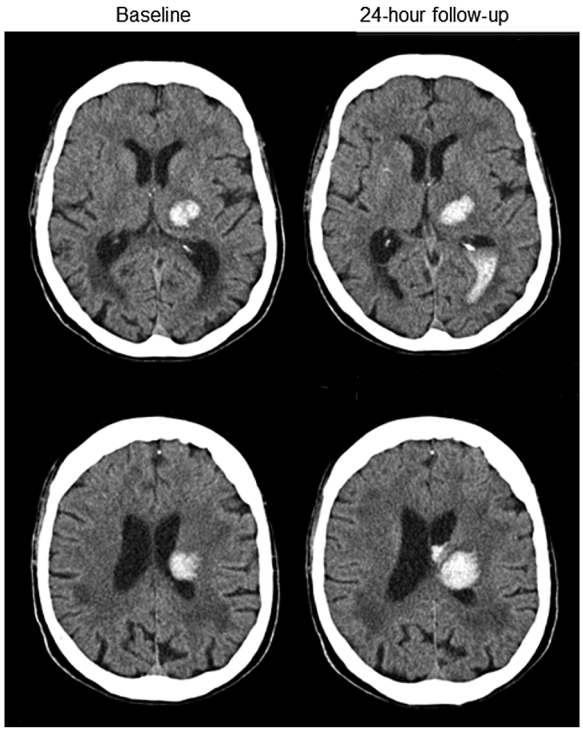

Figure 1 Baseline and 24 h follow-up CT images from a selected patient to demonstrate delayed intraventricular haemorrhage.

For each CT scan, uncompressed digital CT images collected in the Digital Imaging and Communications in Medicine (DICOM) format identified only with the patient's unique study number were analysed centrally by trained staff blind to the clinical data, treatment and sequence of the scan. ICH volume and growth were calculated using computer-assisted multislice planimetric and voxel threshold techniques in MIStar software (V.3.2).[13] Manual measurements were used to calculate ICH volumes on an extreme minority of CT scans that were received as digital images or plain films.

All CT images were analysed for the presence of blood in the ventricular system, and ICH location was defined as the presumed origin of the primary ICH. Patients with IVH were classified as having either (1) initial IVH, defined as the presence of IVH on the baseline CT, or (2) dIVH, defined as the presence of new IVH on a 24 h CT scan, where IVH was previously absent (figure 1). ICH parameters were absolute and percentage growth over 24 h. The location of ICH was classified by its major component (more than half of the total ICH volume by visual inspection). The presence of hydrocephalus was rated by visual inspection of ventricular size.

Statistical analysis

Baseline characteristics were summarised as mean (SD), median (IQR) and per cent according to three groups (no IVH, initial IVH and dIVH). Associations of dIVH and key outcomes were examined in multivariable logistic regression models, for the total patient group and in those free of IVH at baseline. These models included adjustment for significant variables in univariate analyses as well as key demographic variables (ie, age, sex, China region), time to diagnostic CT scan and randomised BP-lowering treatment. Clinical variables were categorised around the median for ICH volume (≥15 mL vs <15 mL), clinical severity (baseline National Institutes of Health Stroke Scale (NIHSS) scores ≥15 vs <15) and time to diagnostic CT scan (≤2 h vs >2 h), as defined previously.[11] ICH location was categorised as either deep hemispheric versus other location. ICH growth and mean achieved BP over 24 h were continuous variables. Prior warfarin and antiplatelet use were combined into a single variable termed 'antithrombotic use.' Collinearity and interaction between variables were checked. Data are reported with ORs and 95% CI. A two-sided p value <0.05 was set as the level for statistical significance. All statistical analyses were performed using SAS V.9.3 (SAS institute, Cary, North Carolina, USA).

RESULTS

Table 1 outlines baseline characteristics of the 1310 CT substudy participants, where 349 (27%) had IVH at presentation. In the remaining 961 patients without initial IVH, 107 (11%) had dIVH on 24 h repeat CT. Nearly half (42%) of the patients with dIVH had a lenticular origin of ICH, as compared with 13% of those with initial IVH. Conversely, 19% of dIVH was associated with thalamic ICH location as compared with 52% in those with initial IVH. There was near even distribution with respect to lobar ICH, occurring in 11%, 11% and 15% of patients with no IVH, initial IVH and dIVH, respectively. There were relatively small numbers of cerebellar and brainstem ICHs across all groups: 22 (3%), 12 (3%) and 4 (4%) patients had cerebellar ICHs, and 32 (4%), 0 (0%) and 2 (2%) had brainstem ICHs in the no IVH, initial IVH and dIVH groups, respectively. Hydrocephalus was more frequent in the initial IVH group at both baseline (89, 27%) and 24 h (94, 27%) compared with those without IVH (70, 8% and 65, 8%) or dIVH (20, 19% and 21, 20%) (p<0.0001). At 24 h, patients with initial IVH had higher IVH volumes than those with dIVH (p<0.0001).

Table 2 shows that the independent associations of dIVH in IVH-free patients at baseline included prior warfarin anticoagulation (OR 3.97, 95% CI 1.60 to 9.87; p=0.003), high (≥15) NIHSS score (OR 3.54, 95% CI 2.21 to 5.66; p<0.0001), higher mean achieved SBP over 24 h (OR 1.24, 95% CI 1.08 to 1.44; p=0.003) and greater baseline ICH volume (≥15 mL) (OR 1.87, 95% CI 1.17 to 2.96; p=0.01). No covariate interaction was found. For collinearity, all correlation coefficients were less than 0.40 except for baseline ICH volume and NIHSS score (r=0.44), and mean achieved SBP over 24 h and randomised treatment (r=0.45). In addition, table 3 shows that patients with dIVH had significantly greater absolute and percentage ICH growth at 24 h when compared with patients who did not develop any IVH (both p<0.0001).

In regard to 90-day clinical outcomes, a total of 23 patients were lost to follow-up, with 17 (2%), 5 (1%) and 1 (1%) patient(s) from no IVH, initial IVH and delayed IVH groups, respectively. Table 4 shows that dIVH remained independently associated with death or major disability at 90 days after controlling for demographics, prior ischaemic stroke, antithrombotic use, NIHSS score, mean achieved SBP over 24 h, location and volume of ICH, randomised BP-lowering treatment and ICH growth at 24 h. Compared with those with no IVH, adjusted ORs were 2.84 (95% CI 1.52 to 5.28) for dIVH and 1.87 (95% CI 1.36 to 2.56) for initial IVH (p trend <0.0001). Similar associations were observed separately for death (p trend=0.03) and major disability (p trend<0.0001). In the light of the difference in 24 h ICH volumes between groups (14.2 vs 21.7 vs 39.7 mL in no IVH, initial IVH and dIVH groups, respectively), a further analysis adjusting for 24 h ICH volume was conducted. The results remained consistent (see online supplementary table S1).

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Table 1 Patient characteristics by presence of IVH

	No IVH (n=854)	Initial IVH (n=349)	Delayed IVH (n=107)*	p Value
Demographic				
Age, years	65 (13)	67 (13)	66 (13)	0.003
Male sex	544 (64)	212 (61)	72 (67)	0.414
China region	484 (57)	174 (50)	51 (48)	0.037
Medical history				
ICH	66 (8)	21 (6)	11 (10)	0.311
Ischaemic stroke	70 (8)	44 (13)	7 (7)	0.033
Acute coronary event	25 (3)	18 (5)	1 (1)	0.051
Diabetes mellitus	100 (12)	48 (14)	11 (10)	0.500
Hypertension	613 (72)	255 (73)	74 (70)	0.695
Current medication				
Antihypertensive therapy	407 (48)	185 (53)	52 (49)	0.222
Warfarin anticoagulation	22 (3)	22 (6)	10 (9)	0.0002
Aspirin or other antiplatelet agent	111 (13)	66 (19)	12 (11)	0.018
Lipid-lowering therapy	71 (8)	42 (12)	11 (10)	0.125
Clinical features				
Time to diagnostic CT scan, hours	1.8 (1.2–2.6)	1.8 (1.3–2.7)	1.6 (1.1–2.2)	0.164
Time to diagnostic CT scan ≤2 h	498 (58)	205 (59)	74 (69)	0.095
GCS score	15 (13–15)	14 (12–15)	13 (12–15)	<0.0001
NIHSS score	9 (5–14)	14 (9–18)	16 (10–19)	<0.0001
NIHSS score ≥15	193 (23)	152 (44)	63 (59)	<0.0001
Systolic BP, mm Hg	179 (17)	181 (17)	182 (18)	0.161
Diastolic BP, mm Hg	100 (15)	99 (15)	99 (17)	0.609
Mean achieved BP over 24 h, mm Hg	147 (15)	150 (16)	153 (17)	0.001
CT findings				
Deep ICH location†	703 (82)	300 (86)	85 (79)	0.181
ICH volume at baseline, mL	9.1 (4.1–16.6)	11.7 (7.3–22.7)	16.9 (7.5–31.6)	<0.0001
IVH volume at baseline, mL	–	6.3 (1.8–13.3)	–	
IVH volume at 24 h, mL	–	6.5 (1.8–15.5)	2.5 (0.9–9.2)	<0.0001
Randomised intensive BP lowering	417 (49)	171 (49)	57 (53)	0.683

Data are n (%), mean (SD) or median (IQR). p Values are based on χ^2 or Kruskal-Wallis test.
*Measurements taken between 1 and 24 h postrandomisation.
†Basal ganglia or thalamus.
BP, blood pressure; GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage; NIHSS, National Institutes of Health Stroke Scale.

In total, eight patients died in the first 24 h (4 with initial IVH and 4 with dIVH). The four patients with dIVH had repeat imaging earlier than 24 h and died shortly afterwards. A sensitivity analysis was conducted to avoid potential survival bias given that dIVH was, by definition, a diagnosis established in survivors at 24 h; this again showed consistency of the prognostic significance of dIVH (see online supplementary table S2).

Finally, analysis of 90-day ordinal mRS scores demonstrates that dIVH was associated with a significant shift towards poor outcomes (figure 2). Compared with no IVH, adjusted OR were 2.42 (95% CI 1.61 to 3.63) for dIVH and 2.01 (95% CI 1.58 to 2.55) for initial IVH (p trend <0.0001).

DISCUSSION

This study shows that dIVH is independently associated with a poor clinical outcome in ICH when associated with significant ICH expansion. As well as reaffirming that dIVH is associated with greater absolute and percentage ICH growth, our study highlights the use of warfarin anticoagulation, greater initial clinical severity (NIHSS score) and larger ICH volumes at presentation as being key factors associated with dIVH. The finding that a higher mean achieved SBP in the first 24 h after presentation was independently associated with dIVH provides further support for the potential benefits of early and sustained BP control in ICH.

Previous studies report an association of dIVH with ICH growth,[7 8] but a relation has also been shown with atrial fibrillation and supratherapeutic anticoagulation (high INR) on warfarin.[7] Given that anticoagulants delay haemostasis and potentiate ICH growth over a more protracted period, such an association with dIVH is not surprising. The statistical power provided by the large sample size in our study allowed confirmation of the significance of warfarin as an independent risk factor for dIVH, while adding strength to the argument that dIVH and ICH growth are inter-related.

One study has shown interesting associations between IVH subtype and primary ICH location,[7] in particular between lenticular/thalamic ICH and dIVH. Our analysis shows that dIVH is more frequent in patients with lenticular ICH and initial IVH is more common in patients with thalamic ICH, perhaps because of a tissue barrier between the lentiform nucleus and ventricular system and the close proximity of the thalamus to the lateral and third ventricles. Lobar ICH cases also tended to have a higher frequency of dIVH, which again could be explained by the remoteness to the ventricular system. On a background of concurrent anticoagulation, however, dIVH may be associated with growth of peripheral ICH in any location.

In regard to clinical outcomes, one single-centre study revealed an independent relationship between dIVH and adverse outcomes among 23 cases of dIVH in 216 patients with

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Table 2 Factors associated with dIVH among IVH-free patients at baseline (n=961)

	Univariate analysis		Multivariable analysis	
	Crude OR (95% CI)	p Value	OR (95% CI)	p Value
Demographic				
Age (per 10 years increase)*	1.10 (0.94 to 1.29)	0.23	1.01 (0.99 to 1.03)	0.30
Sex (male vs female)*	1.17 (0.77 to 1.80)	0.47	1.14 (0.72 to 1.80)	0.58
China region (yes vs no)*	0.70 (0.47 to 1.04)	0.08	0.91 (0.57 to 1.45)	0.69
Medical history				
ICH (yes vs no) (yes vs no)	1.37 (0.70 to 2.68)	0.36		
Ischaemic stroke (yes vs no)	0.78 (0.35 to 1.75)	0.55		
Diabetes mellitus (yes vs no)	0.86 (0.45 to 1.67)	0.66		
Hypertension (yes vs no)	0.88 (0.57 to 1.36)	0.57		
Current medication				
Antihypertensive therapy (yes vs no)	1.04 (0.70 to 1.55)	0.85		
Warfarin anticoagulation (yes vs no)*	3.90 (1.79 to 8.48)	0.001	3.97 (1.60 to 9.87)	0.003
Aspirin or other antiplatelet agent (yes vs no)	0.85 (0.45 to 1.59)	0.60		
Lipid-lowering therapy (yes vs no)	1.26 (0.65 to 2.47)	0.49		
Clinical features				
Time to diagnostic CT scan, hours (≤2 vs >2)*	1.60 (1.04 to 2.47)	0.03	1.47 (0.92 to 2.33)	0.11
NIHSS score (≥15 vs <15)*	4.90 (3.23 to 7.43)	<0.0001	3.54 (2.21 to 5.66)	<0.0001
Mean achieved systolic BP over 24 h, mm Hg (per 10 increase)	1.26 (1.12 to 1.43)	0.002	1.24 (1.08 to 1.44)	0.003
CT findings				
Deep location of ICH	0.83 (0.50 to 1.37)	0.47		
ICH volume at baseline, mL (≥15 vs <15)*	3.11 (2.07 to 4.68)	<0.0001	1.87 (1.17 to 2.96)	0.01
Randomised intensive BP lowering (yes vs no)*	0.84 (0.56 to 1.25)	0.39	1.01 (0.63 to 1.63)	0.96

*Variables included in the multivariable analysis.
BP, blood pressure; dIVH, delayed intraventricular haemorrhage; ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage; NIHSS, National Institutes of Health Stroke Scale.

ICH.[7] Although this study showed that dIVH independently predicts mortality at 14 days (or at discharge, if this was earlier), there was no significant relation with functional outcomes at 90 days as compared with initial IVH. This study generated the hypothesis that dIVH represents a special clinical group at high risk of poor prognosis. An alternative interpretation was proposed by another study involving 19 cases of dIVH in 282 patients with ICH which concluded that differences in time to first imaging could account for the association of dIVH with worse outcome.[8] As in this study patients with dIVH had the first CT scan earlier than those with initial IVH (median time to diagnostic brain CT was 1.1 and 6 h, respectively), the diagnosis of dIVH could be explained by very early imaging, that is, before full ICH growth has occurred, and the worse prognosis could be related to the ICH growth rather than to the occurrence of dIVH per se. Although CT scan timing is likely to play a role in the diagnosis of dIVH, our study did not find that time to CT scan differed between IVH subtypes and it was not a factor independently associated with dIVH on multivariable analysis.

We are unable to define the reason for the association between dIVH and poor outcome independent of other factors such as ICH size and growth. One possible explanation is that the dIVH group experienced more ICH growth that extended beyond the first 24 h. An independent association between dIVH and higher mean SBP control during the first 24 h adds to the growing body of evidence that suggests beneficial effects of early intensive BP-lowering in acute ICH.[10 11 14 15] Intensive BP reduction may be especially relevant in high-risk patients such as those represented in dIVH. Specific monitoring for dIVH in patients with risk factors identified on admission may facilitate prompt diagnosis and early intervention with minimally invasive neurosurgical techniques, such as intraventricular thrombolysis should they be proven effective in the near future.[4 16] The presence of this simple radiographic marker may be useful for clinicians in their decisions about the need for aggressive early

Table 3 ICH growth by subtype of IVH

	ICH volume, mL, mean (SD)		Baseline to 24 h ICH growth, mL		Baseline to 24 h ICH growth, %	
	At baseline	At 24 h	Adjusted mean (95% CI)*	p Value	Adjusted mean (95% CI)*	p Value
No IVH (n=854)	12.4 (11.9)	14.2 (13.5)	2.5 (0.8 to 4.2)		15.2 (8.6 to 22.1)	
Initial IVH (n=349)	18.6 (18.0)	21.7 (24.4)	4.0 (2.0 to 6.0)	0.10†	14.2 (6.5 to 22.4)	0.77†
Delayed IVH (n=107)	22.8 (18.6)	39.7 (36.1)	17.9 (14.8 to 21.0)	<0.0001‡	78.5 (60.9 to 98.0)	<0.0001‡

*Adjusted by baseline variables of age, sex, China region, prior ischaemic stroke, antithrombotic use, time to diagnostic CT scan, baseline systolic blood pressure, location and volume of ICH and randomised blood pressure lowering.
†Comparison between no IVH and initial IVH.
‡Comparison between no IVH and delayed IVH.
ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage.

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Table 4 IVH subtype and 90-day outcomes

Clinical outcome	IVH subtype	Event, n (%)	OR (95% CI)	p trend	Adjusted OR* (95% CI)	p trend
Death (n=1287)	No IVH (n=837)	56 (6.7)	1.00	<0.0001	1.00	0.03
	Initial IVH (n=344)	59 (17.2)	2.89 (1.96 to 4.26)		1.56 (1.00 to 2.45)	
	Delayed IVH (n=106)	33 (31.1)	6.31 (3.85 to 10.32)		1.74 (0.92 to 3.29)	
Major disability (n=1139)	No IVH (n=781)	331 (42.4)	1.00	<0.0001	1.00	<0.0001
	Initial IVH (n=285)	184 (64.6)	2.48 (1.87 to 3.28)		1.78 (1.29 to 2.46)	
	Delayed IVH (n=73)	56 (76.7)	4.48 (2.56 to 7.85)		2.90 (1.53 to 5.49)	
Death or major disability (n=1287)	No IVH (n=837)	387 (46.2)	1.00	<0.0001	1.00	<0.0001
	Initial IVH (n=344)	243 (70.6)	2.80 (2.14 to 3.66)		1.87 (1.36 to 2.56)	
	Delayed IVH (n=106)	89 (84.0)	6.09 (3.56 to 10.41)		2.84 (1.52 to 5.28)	

*Adjusted by baseline variables of age, sex, China region, prior ischaemic stroke, antithrombotic use, National Institutes of Health Stroke Scale score, time to diagnostic CT scan, mean achieved systolic blood pressure over 24 h, location and volume of ICH, randomised blood pressure lowering and ICH growth at 24 h.
ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage.

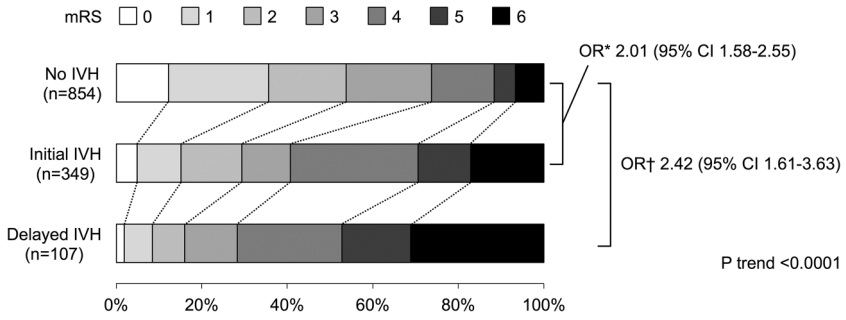

Figure 2 Distribution of mRS scores at 90 days by IVH subtype. *Comparison between no IVH and initial IVH. †Comparison between no IVH and delayed IVH. The model was adjusted by baseline variables of age, sex, China region, prior ischaemic stroke, antithrombotic use, NIHSS score, time to diagnostic CT scan, mean achieved systolic BP at 24 h, location and volume of ICH, randomised BP-lowering treatment, and ICH growth over 24 h (BP, blood pressure; ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale).

intervention and in their discussions about prognosis with patients and/or their relatives.

Prior studies of dIVH have been limited by their single-centre design and comparatively small cohorts. Strengths of our analysis include the data being derived from an international multicentre study that incorporated a large and heterogeneous population to allow adjustment for multiple potential confounders. However, we acknowledge that our study is prone to selection bias as it was based on a clinical trial population that was restricted to patients with ICH with initial hypertension and mild-to-moderately severe ICH without a major requirement for early neurosurgical intervention. We also recognise that this post hoc analysis is prone to chance association and incomplete adjustment for confounding variables, and that the collinearity of some variables may have influenced the strength of association of dIVH and some outcomes. Moreover, we had limited information on various management strategies other than those that have been reported in the main paper, where use of haemostatic therapy was limited.[11] Given the finding of a strong association between anticoagulant use and dIVH, an absence of data regarding admission INR and of the timing and adequacy of anticoagulation reversal strategies may be a source of bias. Another clear limitation of our study is in having CT data at only two time points, so we are unable to assess the dynamics of ICH and IVH volumes beyond 24 h after the onset of symptoms. In addition, we do not have data on the location of IVH. Thus, we are unable to provide clear conclusions regarding the potential biological mechanisms at play and, in particular, the impact of IVH dynamics on outcomes.

In summary, dIVH appears to be inextricably linked with ICH growth and is independently associated with a poor outcome in small to moderate-size ICH. Given that hypertension in the acute phase of ICH is associated with dIVH, early and sustained control of BP may have beneficial effects in such high-risk patients. Further prospective research in larger, unselected populations is warranted to confirm the significance of dIVH and, in particular, to determine the effects of BP reduction in patients with anticoagulation-related ICH.

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Contributors TJM, SS, AAR and CSA contributed to the study rationale and interpretation of the results. TJM was responsible for the first draft of the manuscript. XW and HA contributed to the data analysis. All the authors participated in the drafting of the manuscript and gave approval of its final version; and they also take responsibility for the content and interpretation of this manuscript.

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