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Sex differences in treatment, radiological features and outcome after intracerebral haemorrhage: Pooled analysis of Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage trials 1 and 2

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Abstract

Introduction: Reports vary on how sex influences the management and outcome from acute intracerebral haemorrhage. We aimed to quantify sex disparities in clinical characteristics, management, including response to blood pressure lowering treatment, and outcomes in patients with acute intracerebral haemorrhage, through interrogation of two large clinical trial databases.

Patients and Methods: Post-hoc pooled analysis of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage trials 1 and 2, where patients with a hypertensive response (systolic, 150–220 mmHg) after spontaneous intracerebral haemorrhage (<6 h) were randomised to intensive (target <140 mmHg <1 h) or guideline-recommended (<180 mmHg) blood pressure lowering treatment. The interaction of sex on early haematoma growth (24 h), death or major disability (modified Rankin scale scores 3–6 at 90 days), and effect of randomised treatment were determined in multivariable logistic regression models adjusted for baseline confounding variables.

Results: In 3233 participants, 1191 (37%) were women who were significantly older, had higher baseline National Institutes of Health Stroke Scale scores and smaller haematoma volumes compared to men. Men had higher three-month mortality (odds ratio 1.48, 95% confidence interval 1.10–2.00); however, there was no difference between women and men in the combined endpoint of death or major disability. There were no significant sex differences on mean haematoma growth or effect of randomised blood pressure lowering treatment.

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Discussion: Men included in the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage trials had more comorbidities, larger baseline haematoma volumes and higher mortality after adjustment for age, as compared with women.
Conclusion: Men included in the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage trials had a greater odds of dying after intracerebral haemorrhage than women, which could not be readily explained by differing casemix or patterns of blood pressure management.
Clinical trial registration: The Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage trials studies are registered with ClinicalTrials.gov (NCT00226096 and NCT00716079).

Keywords
Sex differences, intracerebral haemorrhage, blood pressure, haematoma growth, perihaematomal oedema

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Introduction

Spontaneous intracerebral haemorrhage (ICH) is the most serious type of stroke,[1,2] where age and ethnicity are recognised predisposing risk factors. However, sex-related biological and social factors may also influence the pathophysiology, response to treatments, and thus prognosis for recovery from ICH. Although a recent individual patient data meta-analysis found no differences in the outcomes of death or major disability after ICH,[3] there is some evidence for a lobar location of the haematoma to be more common in women.[4,5] While haematoma volume and its expansion appears similar in women and men, perihaematomal oedema volume may be smaller in women[6] while better control of blood pressure (BP) may influence the chances of survival but not overall functional outcome in men rather than women.[7,8] Herein, we undertook a post-hoc analysis of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage trials (INTERACT 1 and 2) to determine sex differences in clinical characteristics, management and outcome of patients with acute ICH. In addition, we undertook analyses to determine sex differences in the effect of intensive versus guideline BP lowering treatment on outcome in patients with acute ICH.

Methods

The INTERACT 1 (n = 404) and 2 (n = 2829) studies were international, multicentre, open, blinded endpoint assessed, randomised controlled trials.[9–12] In brief, a total of 3243 patients with spontaneous ICH within 6 h of onset and elevated systolic BP (SBP 150–220 mmHg) were randomly assigned to receive intensive (target BP <140 mmHg within 1 h) or contemporary guideline recommended (target SBP <180 mmHg) BP lowering therapy, according to standardised protocols. Patients were excluded if they had a structural cerebral cause for the ICH, were in deep coma (Glasgow coma scale (GCS) scores 3–5), had massive haematoma with poor prognosis or if early surgery to evacuate the haematoma was planned. Written informed consent was obtained from all participants (or approved surrogates) and the study protocol was approved by the ethics committee of each participating hospital. The INTERACT studies are registered with ClinicalTrials.gov, numbers NCT00226096 and NCT00716079.

Baseline demographic and clinical characteristics were recorded at the time of enrolment, including neurological severity assessed on the GCS and National Institutes of Health Stroke Scale (NIHSS).[13] After the diagnostic CT scan in all patients, 1313 participants (346 and 1967 in INTERACT1 and 2, respectively) underwent a repeat CT scan at 24 ± 3 h using similar procedures, with de-identified uncompressed digital images on Digital Imaging and Communications in Medicine format assessed centrally for haematoma and perihaematomal oedema volumes by trained neurologists blind to clinical, time and sequence data, using computer-assisted multi-slice planimetric and voxel threshold techniques (MIStar@, Apollo Medical Imaging Technology, Melbourne, Australia).[14] All patients were assessed by functional outcome by trained researchers blind to treatment allocation using the modified Rankin scale (mRS) at 90 days.

For these analyses, the primary clinical outcome was death at 90 days. Secondary outcomes were death or major disability (mRS scores 3–6), separately for major disability (mRS 3–5), achieved SBP over 24 h serious adverse events, and absolute growth over 24 h in haematoma and perihaematomal oedema volumes in the subgroup with repeat CT.

Baseline characteristics were summarised as mean (standard deviation) or median (interquartile range) for continuous variables, and number (%) for categorical variables, with sex differences tested using Wilcoxon and chi-square tests, respectively. Using women as the reference, associations between sex and outcomes were examined using logistic regression with adjustments for age, region of recruitment (China versus non-China), history of ischaemic stroke or other undifferentiated stroke, and antihypertensive treatment, baseline blood glucose (>6.5 versus ≤6.5 mmol/l), NIHSS score (<15 versus ≥15), haematoma volume, and randomised BP lowering treatment. In the CT substudies, associations of sex and baseline volumes of haematoma and perihaematomal oedema, and their absolute growth over 24 h, were assessed by analysis of covariance, with similar adjustment variables as above. Data are reported with odds ratios (OR) and 95% confidence intervals (CI). A P value <0.05 was indicative of statistical significance. All analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC).

Results

Of 3233 INTERACT studies participants, 1191 (37%) were women who were older, more likely to have taken prior antihypertensive medication, and present with higher blood glucose levels and greater neurological deficits than men (Table 1). However, men were more likely to have had prior ischaemic stroke and to be intubated during hospitalisation. There were no sex differences in other aspects of in-hospital management over seven days.

Men had greater odds of death compared to women, adjusted OR 1.38 (95% CI 1.05–1.83; P = 0.022) (Table 2), but there were no significant differences in functional outcomes.

Table 1. Patient characteristics by sex.

	Women (n = 1191)	Men (n = 2042)	*P* value
Age, years	64.9 (13.0)	62.5 12.6)	<0.0001
Chinese	859 (72.1)	1445 (70.8)	0.410
History of cardiac disease	139 (11.7)	202 (9.9)	0.112
Diabetes mellitus	115 (9.7)	224 (11.0)	0.234
History of intracerebral haemorrhage	95 (8.0)	180 (8.8)	0.403
History of ischaemic/undifferentiated stroke	110 (9.2)	259 (12.7)	0.003
History of hypertension	902 (75.7)	1446 (70.9)	0.003
Use of antihypertensive therapy	574 (48.2)	875 42.9)	0.004
Use of antithrombotic agents	122 (10.2)	246 (12.1)	0.119
Lipid lowering therapy	69 (5.8)	140 (6.9)	0.232
Clinical features			
Systolic BP (mmHg)	179.8 (16.9)	179.0 17.3)	0.130
NIHSS score	11 (7–16)	10 (6–15)	0.002
NIHSS score ≥15	371 (31.3)	544 (26.8)	0.006
GCS score	14 (12–15)	14 (13–15)	0.002
GCS <13	340 (28.6)	481 (23.6)	0.002
Hyperglycaemia. >6.5 mmol/l	600 (52.7)	889 (46.4)	0.001
Haematoma volume (ml)	9.9 (5.3–17.7)	11.3 (5.8–19.9)	0.004
Left hemisphere	556 (50.3)	935 (50.5)	0.921
Deep location of haematoma	910 (82.3)	1560 (84.2)	0.176
Intraventricular extension	320 (28.9)	501 (27.0)	0.265
Randomised to intensive BP lowering	581 (48.8)	1021 (50.0)	0.504
Time from onset to randomisation	3.7 (2.8–4.7)	3.7 (2.8–4.7)	0.856
Any intravenous BP lowering treatment	549 (46.5)	994 (49.7)	0.084
Management over seven days			
Intensive care unit admission	380 (36.6)	681 (39.1)	0.178
Intubation	62 (5.3)	158 (7.9)	0.005
IV mannitol	763 (64.7)	1293 (64.7)	0.995
Any surgery	64 (5.4)	119 (5.9)	0.539
Venous thromboembolism prophylaxis	233 (19.8)	395 (19.8)	0.998
Haemostatic therapy	40 (3.4)	92 (4.6)	0.098

BP: blood pressure; GCS: Glasgow coma scale; IV: intravenous; NIHSS: National Institutes of Health stroke scale. Data are n (%), mean (SD) or median (IQR). P values are based on chi-square or Wilcoxon test.

Baseline haematoma volumes were smaller in women (9.9 versus 11.3 ml; P = 0.004), but haematoma location and intraventricular extension were similar in both sexes. Similarly, there was no sex difference in haematoma growth (2.6 versus 3.8 ml; P = 0.164) or perihaematomal oedema growth (3.8 versus 3.9 ml; P = 0.821) at 24 h (Table 3).

Although there was no significant sex difference in baseline SBP and at 1 h, SBP was marginally lower in women through 24 h (mean difference 1.6 mmHg;

Table 2. The effect of sex on clinical outcome at three months.

Outcome	Sex	n/N (%)	OR (95% CI)	P value	Adjusted OR (95% CI)[a]	P value
Death	F	126/1187 (10.6)	Reference			
	M	256/2030 (12.6)	1.22 (0.97–1.52)	0.092	1.38 (1.05–1.83)	0.022
Major disability[b]	F	520/1053 (49.4)	Reference			
	M	792/1752 (45.2)	0.85 (0.73–0.99)	0.032	0.93 (0.78–1.13)	0.471
Death or major disability[c]	F	646/1179 (54.8)	Reference			
	M	1048/2008 (52.2)	0.90 (0.78–1.04)	0.156	1.00 (0.83–1.19)	0.980
Shift on range of mRS scores	M versus F		1.09(0.96–1.23)	0.208	1.02 (0.88–1.17)	0.837

CI: confidence interval; F: female; M: male; mRS: modified Rankin scale; OR: odds ratio.
[a]Adjusted for age, region of recruitment (China versus non-China), history of ischaemic stroke or other undifferentiated stroke, baseline blood glucose (>6.5 versus ≤6.5) and prior use of antihypertension agent(s), National Institutes of Health stroke scale score (<15 versus ≥15), haematoma volume, and randomised BP lowering treatment.
[b]mRS scores 3–5.
[c]mRS scores 3–6.

Table 3. Radiological outcomes at 24 h.

Outcomes	Sex	Mean (95%CI)	P value	Adjusted P value[a]
Haematoma growth	F	2.6 (1.7–3.6)		
	M	3.8 (2.7–4.9)	0.164	0.122
Perihaematomal growth	F	3.8 (3.0–4.5)		
	M	3.9 (3.3–4.5)	0.821	0.819

F: female; M: male.
[a]Adjusted for age, region of recruitment (China versus non-China), history of ischaemic or other undifferentiated stroke, baseline blood glucose (>6.5 versus ≤6.5), prior use of antihypertensive(s), National Institutes of Health stroke scale score (<15 versus ≥15), haematoma volume and randomised BP lowering treatment.

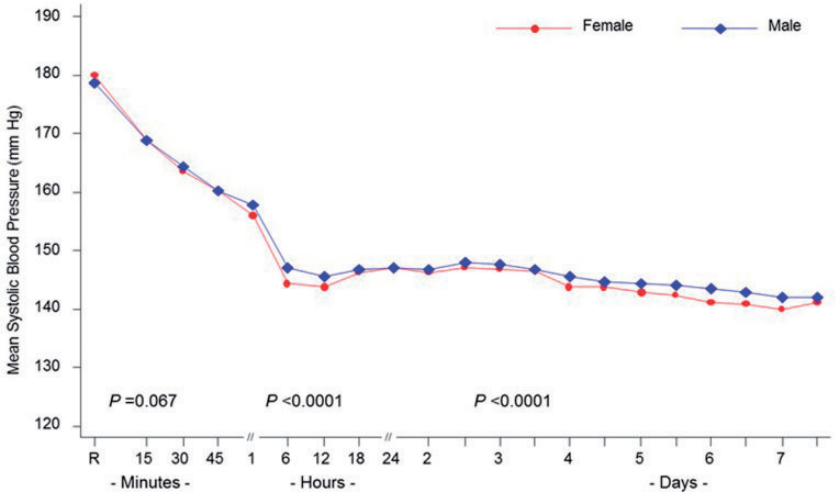

Figure 1. BP in women and men over seven days.

$P < 0.0001$) and seven days (mean difference 1.5 mmHg; $P < 0.0001$) (Figure 1). There was no heterogeneity in the effect of degree of BP lowering control between the sexes (Supplemental Table 1), nor of significant interactions between treatment and sex for any of the clinical endpoints (Table 2, Supplemental Tables 2–4).

Discussion

This study, derived from a large international clinical trial database, identified several sex-related differences in demography, risk profile and severity of acute ICH. Although women were older, the results suggest that men have a higher odds of dying compared to women after adjustment for age.

Previous studies are conflicting regarding sex disparities in the outcome from ICH. Some studies have reported increased mortality in men, whereas others report no differences or even higher deaths in women.[15] As most such data have been derived from single centres, there are multiple explanations for the differences covering change, bias, confounding and real differences in the biology, sociocultural factors and aspects of management.[15] While comorbid factors, such as vascular risk factors,[16] may contribute to higher case fatality after ICH in men than women, it may be that women are under-represented in stroke trials.[17] As women contributed to only about one-third of the data in the INTERACT studies, it is possible that frailer sicker women were excluded from participation.[17] While it has been proposed that men have a greater predisposition to haematoma expansion,[18] this was not confirmed in our analyses although men had slightly larger baseline haematoma volumes. Contrary to other studies, we found no differences in haematoma location.

Although more women than men were on prior antihypertensive therapy, men and women had comparable baseline SBP, but women were less likely to be treated with intravenous BP lowering medication which was reflected in significant, albeit small, differences in SBP between men and women in the first 24 h, and over the subsequent 7 days. These findings may reflect more treatment resistant BP or more severe ICH in women, where the natural decline in BP after ICH is less prominent in those with less severe illness.[19] Finally, despite greater BP control, there was higher case fatality in men than in women[7]; however, there was no heterogeneity in the effects of intensive versus guideline BP lowering on clinical outcomes.

Despite several strengths including the large and heterogeneous population, and systematic evaluation of outcomes, our study is limited by being post-hoc and selection bias related to a clinical trial population where the majority of participants were Chinese with mild ICH defined by small haematoma volumes and mild-moderate neurological deficits.

In summary, in our review of a large international clinical trial population, we have shown that men have a greater odds of dying after ICH than women, which could not be readily explained by differing casemix or patterns of BP management.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: ECS has received speaker fees from Bayer and Novartis. JC has received research grants from Servier, administered through the University of Sydney, as principal investigator for the ADVANCE trial and ADVANCE-ON post-trial study, and also received honoraria from Servier for speaking about those studies at scientific meetings. CSA holds a Senior Investigator Fellowship and grants from the National Health and Medical Research Council (NHMRC), and reports grants and honorarium travel reimbursement from Takeda China.

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Ethical approval

The INTERACT1 and INTERACT2 studies were approved centrally by the Ethics Review Committee of Royal Prince Alfred Hospital Zone in Sydney Local Health District, Sydney, Australia and Peking University Health Science Center, Beijing, PR China; and by the ethics committee at each participating hospital site.

Informed consent

Written informed consent was obtained from all patients or appropriate surrogates.

Guarantor

CSA.

Contributorship

CSA developed the concept and rationale for the study; ECS, CC and XW contributed to analyses, SS and CD undertook CT imaging analysis, and XW undertook analyses. All authors contributed to interpretation of the results, drafting and approval of the final manuscript, and take responsibility for the content and interpretation of this article.

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Supplemental material

Supplemental material for this article is available online.

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