Quality of stroke care and outcomes by sex: a pooled analysis including 19,000 participants

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Supplemental tables (available from Dryad): **Figure e-1** Functional outcomes and vascular endpoints of patients with ischemic stroke who have undergone thrombolysis by study, **Figure e-2** Functional outcomes and vascular endpoints of patients with ischemic stroke without thrombolysis (Headpost study), **Figure e-3** Functional outcomes and vascular endpoints of patients with stroke by study, **Figure e-4** Odds ratio of being prescribed preventatives on admission and at 90-day follow up by study, **Figure e-5** Functional outcomes and vascular endpoints of patients with ischemic stroke by study, **Figure e-6** Functional outcomes and vascular endpoints of patients with intracerebral hemorrhage by study, **Figure e-7** Health related quality of life outcomes categorised into the five dimensions of EQ5D stratified by study, **Figure e-8** Ischemic stroke health related quality of life outcomes categorised into the five dimensions of EQ5D stratified by study, **Figure e-9** Intracerebral hemorrhage health related quality of life outcomes categorised into the five dimensions of EQ5D stratified by study, **Figure e-10** Hospital management by sex

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Abstract

Objective: To explore the sex differences in outcomes and management after stroke using a large sample with high-quality international trial data.

Methods: Individual participant data were obtained from five acute stroke randomized controlled trials. Data were obtained on demographics, medication use, in-hospital treatment and functional outcome. Study-specific crude and adjusted models were used to estimate sex differences in outcomes and management, and then pooled using random-effects meta-analysis.

Results: There were 19,652 participants of whom 7721 (40%) were women. After multivariable adjustments, women with ischemic stroke had higher survival at 3 to 6 months (odds ratio [OR] 0.82; 95% confidence interval [CI] 0.70-0.97), higher likelihood of disability (OR 1.20; 95% CI 1.06-1.36) and worse quality of life (weighted mean difference -0.07, 95% CI -0.09—0.04). For management, women were more likely admitted to an acute stroke unit (OR 1.17, 95% CI 1.01-1.34), but less likely intubated (OR 0.72, 95% CI 0.53-0.99), treated for fever (OR 0.82, 95% CI 0.70-0.95) and admitted to an intensive care unit (OR 0.86, 95% CI 0.76-0.98). For pre-admission medications, women had higher odds of being prescribed antihypertensive agents (OR 1.22, 95% CI 1.13-1.31) and lower odds of being prescribed antiplatelets (OR 0.86; 95% CI 0.79-0.93), glucose lowering (OR 0.86; 95% CI 0.78-0.94) and lipid lowering agents (OR 0.85; 95% CI 0.77-0.94).

Conclusions: This analysis suggest that women who had ischemic stroke had better survival but were also more disabled and had poorer quality of life. Variations in hospital and out-of-hospital management may partly explain the disparities.

Clinical Trial Registration Information: URL: http://www.clinicaltrials.gov. Unique identifier: INTERACT 1 NCT00226096, INTERACT 2 NCT00716079, ENCHANTED NCT01422616, HeadPoST NCT02162017, SCAST NCT00120003.

Introduction

Sex differences in disease risk, management and outcome, are an increasing focus of health services and research. Regarding stroke, women are generally older at the time of onset, and a higher proportion have hypertension and atrial fibrillation (AF) than men, but there are ongoing uncertainties over differing aspects of management and outcomes. Studies of ischemic stroke have shown that women are less likely to receive full etiologic assessment and proven therapies for secondary prevention.[1] Despite having a higher burden of AF, women are less likely to receive oral anticoagulation,[2] especially in those at high risk.[3] Studies consistently find that women have poorer survival after stroke than men,[4,5] but data on functional outcome and health-related quality of life, overall and according to stroke subtype, are lacking. Better understanding of the type and degree of inequities in stroke management and outcomes are important for improving health outcomes, and an initial step towards personalized medicine. We aimed to determine sex differences in the management and outcomes of stroke in a pooling analysis of international randomized clinical trial populations.

Materials and Methods

Design

A pooled analysis of five large, international, multicentre, randomized controlled trials was conducted that included: the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage trials (INTERACT 1[6] and 2[7] studies; referred to as INTERACT studies), the alteplase-dose arm of the Enhanced Control of Hypertension and Thrombolysis Stroke study (ENCHANTED),[8] the Head Position in acute Stroke Trial (HeadPoST),[9] and the Scandinavian Candesartan Acute Stroke Trial (SCAST).[10] All participants in these studies had provided informed consent and approval from relevant ethics committees. These acute

stroke studies were suitable for pooling because of their similar pragmatic design features and ready availability of individual participant data (IPD) (Table 1).

Study factors

Details on data collection and definitions have been discussed in detail elsewhere.[6, 8-11] In general, data were collected from the participant or a proxy at the time of their presentation to hospital ('baseline'), over several days after admission, and for at least several months of follow-up.

The factors analysed for significant sex differences in stroke[5] were considered under four separate headings: (a) sociodemographic (age, sex, ethnicity and region of study conduct); (b) premorbid condition (dependence, estimated according to the modified Rankin Scale [mRS],[12] comorbidities of hypertension, diabetes mellitus, AF, hypercholesterolemia, prior stroke and serious cardiovascular [CV] events); and health behaviors such as current cigarette use; (c) clinical data (admission BP and heart rate), type of stroke (ischemic or intracerebral hemorrhage [ICH]), and severity (according to scores on either the National Institutes of Health Stroke Scale [NIHSS] or Scandinavian Stroke Scale [SSS]).[13]

Outcomes

This IPD examined the following: (i) in-hospital management (including the use of intubation, antipyretics, venous thromboembolism [VTE] prophylaxis, admission to an acute stroke unit (ASU) or intensive care unit, neurosurgery, inpatient rehabilitation, and early withdrawal of medical care), (ii) out of hospital management (including pre-admission CV prevention and secondary CV prevention medication recorded on 3 month follow-up); (iii) death or disability, defined by scores 3-6 on the mRS, stratified by stroke type, (iv) CV endpoints (myocardial infarction and recurrent stroke), (v) health-related quality of life

(HRQoL) assessed directly or by proxy, using the EuroQoL Group 5-Dimension self-report questionnaire (EQ-5D),[14]

Management details were available for all studies except SCAST. For pre-admission CV prevention, four of the studies (INTERACT studies, ENCHANTED, and HeadPoST), had data on antihypertensives, anticoagulants, antiplatelet, and glucose-lowering medications available for analysis; for secondary CV prevention at follow up, data on antihypertensives (INTERACT studies, ENCHANTED, and HeadPoST), and aspirin (ENCHANTED and HeadPoST), were available. In four of the studies (INTERACT studies, ENCHANTED and HeadPoST) death and disability were assessed at 3 months, in SCAST the mRS was assessed at 6 months, post-randomization.

Statistical analysis

IPD were analysed using the two stage method for meta-analyses.[15] The first stage involved building study-specific crude and adjusted models to estimate the differences in outcomes for women compared to men. Consistent with the pre-defined analysis plans of these studies, logistic regression was used in four studies (INTERACT studies, ENCHANTED and SCAST), and a generalised linear mixed model with fixed randomised intervention, fixed period, random cluster, and random cluster-period effects, was used to adjusted for the cluster crossover design in HeadPoST. *A priori*, the following rules were applied to determine the covariates for inclusion in the study-specific multivariable models: (i) the covariate was missing in <20% of cases; (ii) the covariate was associated with death or disability in unadjusted analysis ($P < 0.1$); (iii) the covariate was associated with sex ($P < 0.1$); and (iv) the inclusion of the covariate in a model with only sex changed the magnitude of the sex coefficient by ≥10% (Figure e1-e10). Age and stroke severity were forced into the final multivariable models because of their established association with poor outcomes and sex.

The second stage of analyses involved combining the crude and adjusted study-specific association estimates in a random-effects, inverse-variance weighted, meta-analysis. Statistical heterogeneity was evaluated using I^2 statistics. SAS version 9.3 (SAS Institute, Cary, NC) was used in all analyses.

Data availability statement

This pooled analysis involves trial data shared amongst investigators. It is not a data repository and any requests for the source data should be made to the relevant chief investigator of each study.

Results

There were 19,652 participants included in the five studies, and 7721 (40%) were women. The INTERACT studies enrolled the smallest proportion of women (37%), whilst SCAST enrolled the most (42%)(Table 1). Tables 2 show the baseline characteristics of participants in each study population stratified by sex. Women were significantly older at the time of stroke in all studies, and more so for those recruited from Europe/Australia and South America. Women also had higher systolic BP, heart rate, and neurological impairment (NIHSS scores), and were more likely to have a history of hypertension and AF on admission. Conversely, men were more like to be Asian, smokers, had higher diastolic BP, prior stroke, coronary artery disease, diabetes mellitus, and pre-morbid independence (mRS scores).

Figure 1 shows that women were more likely to be admitted to an ASU whilst in hospital (odds ratio [OR] 1.17, 95% confidence interval [CI] 1.01-1.34) but were less likely to be intubated (OR 0.72, 95% CI 0.53-0.99), given treatment for fever (OR 0.82, 95% CI 0.70-0.95) and be admitted to an intensive care unit (OR 0.86, 95% CI 0.76-0.98).

On admission to hospital, women had higher odds of having received antihypertensive medication (OR 1.22, 95%CI 1.13-1.31) and lower odds of having an antiplatelet(s) (OR 0.86, 95% CI 0.79-0.93), glucose lowering (OR 0.86, 95% CI 0.78-0.94) and lipid lowering therapy (OR 0.85, 95% CI 0.77-0.94) (Figure 2). There was no difference in the prescription of anticoagulants between sexes (OR 0.97, 95% CI 0.84-1.12). For secondary prevention, there were no sex differences in the prescription of antihypertensive medication (OR 0.92, 95% CI 0.84-1.01) or antiplatelet agents (OR 1.00, 95% CI 0.90-1.10) at 3 month follow-up (Figure 2).

After multivariable adjustments, women were significantly less likely to die within 3-6 months after an ischemic stroke (OR 0.82, 95% CI 0.70-0.97), though this lower likelihood was not significant for ICH (OR 0.87, 95% CI 0.66-1.13) (Figure 3). With respect to disability, women had greater disability (mRS score 3-6) (OR 1.20, 95% CI 1.06-1.36) after ischemic stroke than men, but there was no difference between the sexes for ICH (OR 0.97, 95% CI 0.81-1.16). There were no clear sex differences in the risk of recurrent vascular events, for ischemic stroke or ICH (Figure 3). The results were consistent in a subgroup analyses on thrombolyzed and non-thrombolyzed patients with ischemic stroke (Figure e-1 and e-2). Overall, women experienced worse HRQoL (weighted mean difference -0.07, 95% CI -0.09—0.04). Across all five dimensions of health-related quality of life, women had higher scores (ie more problems) than men after ischemic stroke (Figure 4). For ICH, conclusions are similar except there was no evidence of a sex difference in mobility (OR 1.06, 95% CI 0.79- 1.44) or ability to perform usual activities (OR 0.95, 95% CI 0.79-1.14).

Discussion

In this pooled analysis of 19,652 patients with acute stroke, survival among women with ischemic stroke was significantly higher than in men ischemic stroke but not in those with

ICH. In those who survived, women lived with greater disability than men after ischemic stroke, and experienced poorer HRQoL despite adjustments for age and severity. There were important sex-specific differences in management which may have influenced the disparities in these outcomes.

Our findings are broadly consistent with other studies overall and across the major stroke types.[16-22] An analysis on sex differences in mortality rates found that men have considerably higher mortality for various causes (including CV disease) across age groups due to interactions with culture and environment.[23] Our findings supports this analysis with women having better survival after stroke. Moreover, in our study, women were more likely to be admitted to an acute stroke unit which have known benefits in improving outcomes.[24] Regarding disability, a potential explanation is sex-specific differences in brain injury and repair after stroke.[25] Pre-clinical studies of ischemic stroke suggest that aging brain in females is more sensitive to ischemia than males, in relation to declining estrogen, increased systemic inflammation, and an alteration in gene expression.[16, 26] Other studies report that disparities in functional outcome may be influenced by differences in muscle strength[27] or motor cortex affected by stroke.[28]

Differing access to evidence-based treatment may also be a determinant of sex differences in functional outcome after stroke.[29] Our study supports this hypothesis, as women were less likely to receive intubation, treatment for fever or intensive care unit admission but were more likely to be admitted to acute stroke units. However, we acknowledge that clinical trial participants are likely to receive high standards of care[30] in line with contemporaneous advances in guideline recommendations for ischemic[31, 32] and hemorrhagic stroke.[33, 34]

Older studies have reported sex differences in diagnostic evaluations, such as lipid testing,[35] and therapeutic interventions such as carotid surgery;[36] whereas more recent publications have shown no sex differences in hospital stroke care.[37-40] Several studies have also indicated

that the use of preventative medication for stroke differs between men and women. The PINNACLE (Practice Innovation and Clinical Excellence) registry, [2] for example, showed that women were less likely to receive oral anticoagulant treatment compared with men. Our other findings of women being less likely to be prescribed an antiplatelet agent, glucose lowering, and lipid lowering medications, is also consistent with previous studies.[41, 42] More research is needed to better understand the reasons for such disparities in the recommended use and uptake of medications for stroke prevention, and how this influences outcomes.

Strengths of this study include the large sample of stroke participants from a variety of healthcare settings in countries across the world, which enhances the generalizability of the findings. Moreover, the consistency of the assessment procedures, high rates of follow-up, and rigorous outcomes measurements supports the internal validity of these data. However, we recognize that this work is limited by being post-hoc, observational and restricted in the range of variables assessed, raising the potential for confounding and bias.

In summary, sex differences exist regarding survival, disability and management after stroke. Continued reporting of treatment and outcomes by sex, as well as further study of risk factor control and secondary prevention in men and women, are required to better appreciate the reasons and solutions for such disparities.

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Figure Legends

Figure 1. In-hospital stroke management

Figure 2. Medication prescription of cardiovascular prevention medication on admission and at 3 month follow up after acute stroke

Figure 3. Functional outcomes and vascular endpoints, by stroke type

Figure 4. Health-related quality of life outcomes according to dimensions of the EuroQoL Group 5-Dimension self-report questionnaire, by stroke type

Appendix 1 List of names, locations, roles, and contributions of all authors

Name	Location	Role	Contribution
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Xia Wang	The George Institute for Global Health, New South Wales, Australia	Author	Study concept and design, statistical analysis and interpretation of data
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Candice Delcourt	The George Institute for Global Health, New South Wales, Australia	Author	Study concept and design, critical revision of manuscript for intellectual content
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Table 1. Design of the included trials

Study	Design	Setting	Stroke Type	N	Women	Men	Intervention
OVERALL				19652	7721	11931	
INTERACT 1 and 2 studies	Prospective, randomized, open-treatment, blinded end-point	International, multicentre (188 hospitals)	Intracerebral hemorrhage	3233	1191 (36.8%)	2042 (63.1%)	Intensive vs. guideline recommended blood pressure lowering
ENCHANTED-rtPA dose arm	Prospective, randomized, open-label trial with blinded outcome evaluation	International, multicentre (111 hospitals)	Ischemic stroke	3297	1248 (37.9%)	2049 (62.1%)	Low vs. standard dose alteplase
HeadPoST	Prospective, cluster-randomized, crossover, open-label	International, multicenter (114 hospitals)	Ischemic stroke, Intracerebral hemorrhage	11,093	4429 (39.9%)	6664 (60.1%)	Lying-flat position vs. sitting-up position, initiated soon after a stroke and maintained for 24 hours
SCAST	Prospective, randomized, placebo-controlled, double-blind	North European, multicentre (146 hospitals)	Ischaemic stroke, Intracerebral hemorrhage	2029	853 (42.0%)	1176 (58.0%)	Candesartan vs. placebo for 7 days

INTERACT-The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage; ENCHANTED- the Enhanced Control of Hypertension and Thrombolysis Stroke study; rtPA- recombinant tissue plasminogen activator; HeadPoST- the Head Position in Stroke Trial; SCAST- The Scandinavian Candesartan Acute Stroke Trial

Table 2. Patient characteristics by sex

Baseline Characteristics	INTERACT studies		ENCHANTED		HeadPoST		SCAST	
	Women (1191)	Men (2042)	Women (1248)	Men (2049)	Women (4429)	Men (6664)	Women (853)	Men (1176)
Age, years [SD]	**64.9 [13.0]**	62.5 [12.6]	**68.8 [13.3]**	65.2 [12.3]	**71.1 [14.0]**	65.9 [13.2]	**74.3 [10.5]**	68.4 [10.9]
Asian race, n (%)	884/1191 (74)	1526/2042 (75)	733/1248 (58.7)	**1356 /2049 (66.2)**	1876 /4429 (42.4)	**3546 /6664 (53.2)**	-	-
Country of origin								
Europe and Australia, n (%)	285/1191 (23.9)	488/2042 (23.9)	**367/1248 (29.4)**	517 /2049 (25.2)	**2162/4429 (48.8)**	2599 /6664 (39.0)	-	-
China, n (%)	859/1191 (72.1)	1445/2042 (70.8)	481 /1248 (38.5)	**938/2049 (45.8)**	1603/4429 (36.2)	**3049 /6664 (45.8)**	-	-
Non-China Asian countries, n (%)	25/1191 (2.1)	**81 /2042 (4.0)**	252 /1248 (20.2)	418/2049 (20.4)	273/4429 (6.2)	**497/6664 (7.5)**	-	-
South America, n (%)	22/1191 (1.8)	28/2042 (1.4)	**148 /1248 (11.9)**	176/2049 (8.6)	391/4429 (8.8)	519/6664 (7.8)	-	-
Clinical features								
Systolic BP, mmHg [SD]	179 [16]	179 [17]	149 [20]	149 [19]	**157 [29]**	153 [26]	172.3 [20]	170.7 [18]
Diastolic BP, mmHg [SD]	99 [13]	**102 [15]**	83 [12]	**85 [12]**	85 [17]	**87 [16]**	88 [14]	**92 [13]**
Heart rate, beats per minute [SD]	78 [13]	77 [14]	**80 [16]**	78 [14]	**79 [15]**	76 [14]	-	-
GCS, Median (Q1 Q3)	14 (12 - 15)	14 (13- 15)	15 (13 - 15)	15 (14 - 15)	15 (14 - 15)	15 (14 - 15)	-	-
NIHSS, Median (Q1 Q3)	**11 (7 - 16)**	10 (6 - 15)	**9 (5 - 15)**	8 (5- 13)	**5 (2 - 10)**	4 (2 - 8)	-	-

Medical History								
Hypertension	**902/1191 (75.7)**	1446/2039 (70.9)	**854/1245 (68.6)**	1211/2043 (59.3)	**3005/4413 (68.1)**	4146/6648 (62.4)	**597/ 827 (72.2)**	749/1120 (66.9)
Previous stroke	194/1191 (16.3)	**404/2042 (19.8)**	210/1248 (16.8)	379/2049 (18.5)	953/4429 (21.5)	**1613/6664 (24.2)**	192/838 (22.9)	264/1151 (22.9)
Coronary artery disease	20/1191 (1.7)	**75/2039 (3.7)**	160/1245 (12.9)	**319/2043 (15.6)**	605/4397 (13.8)	935/6626 (14.1)	-	-
Atrial fibrillation	-	-	**297/1243 (23.9)**	339/2042 (16.6)	**568/4370 (13.0)**	609/6604 (9.2)	175/ 836 (20.9)	201/1146 (17.5)
Diabetes mellitus	115/1191 (9.7)	224/2039 (11.0)	261/1245 (21.0)	385/2043 (18.8)	1009/4411 (22.9)	**1643/6647 (24.7)**	137/ 837 (16.4)	183/1161 (15.8)
Hypercholesterolemia	-	-	229/1245 (18.4)	326/2043 (16.0)	1117/4404 (25.4)	1615/6629 (24.4)	-	-
Current smoker	-	-	105/1244 (8.4)	**665/2040 (32.6)**	329/4385 (7.5)	**1796/6590 (27.3)**	-	-
Pre-stroke function (mRS)								
No symptoms (mRS 0)	-	-	953/1245 (76.5)	**1721/2041 (84.3)**	2484/4414 (56.3)	**4264/6657 (64.1)**	630/853 (73.8)	**947/1176 (80.5)**
With symptoms (mRS 1-5)	-	-	**292/1245 (23.5)**	320/2041 (15.7)	798/4414 (18.1)	1189/6657 (17.9)	**223/853 (26.1)**	229/1176 (19.4)
Final diagnosis								
Ischemic stroke, n (%)	-	-	954/1248 (76.0)	1654/2049 (81.0)	3726/4426 (84.2)	5759/6656 (86.5)	758/ 853 (88.9)	975/1174 (83.0)
Intracerebral hemorrhage, n (%)	1191 (100)	2042 (100)	-	-	385/4429 (8.7)	546/6664 (8.2)	88/ 853 (10.3)	186/1174 (15.8)
Other	-	-	294/1248 (24.0)	395/2049 (19.0)	315/4426 (7.1)	351/6656 (5.3)	7/ 853 (0.8)	13/1174 (1.1)

Bold denotes statistically significant results, - denotes no available data. Data are n (%), mean (SD), or median (IQR). BP indicates blood pressure; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health stroke scale; CT, computed tomography. INTERACT-The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage; ENCHANTED- the Enhanced Control of Hypertension and Thrombolysis Stroke study; HeadPoST- the Head Position in Stroke Trial; SCAST- The Scandinavian Candesartan Acute Stroke Trial