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ARTICLE

Sex differences in treatment and outcome after stroke

Pooled analysis including 19,000 participants

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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 5 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 7,721 (40%) were women. After multivariable adjustments, women with ischemic stroke had higher survival at 3–6 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 to 0.04). For management, women were more likely to be admitted to an acute stroke unit (OR 1.17, 95% CI 1.01–1.34), but less likely to be intubated (OR 0.58, 95% CI 0.36–0.93), treated for fever (OR 0.82, 95% CI 0.70–0.95), or admitted to an intensive care unit (OR 0.83, 95% CI 0.74–0.93). For preadmission 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 agents (OR 0.86, 95% CI 0.78–0.94), or lipid-lowering agents (OR 0.85, 95% CI 0.77–0.94).

Conclusions

This analysis suggests 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.

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Glossary

AF = atrial fibrillation; **ASU** = acute stroke unit; **BP** = blood pressure; **CI** = confidence interval; **CV** = cardiovascular; **ENCHANTED** = Enhanced Control of Hypertension and Thrombolysis Stroke study; **HeadPoST** = Head Position in Acute Stroke Trial; **HRQoL** = health-related quality of life; **ICH** = intracerebral hemorrhage; **ICU** = intensive care unit; **INTERACT** = Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial; **IPD** = individual participant data; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **SCAST** = Scandinavian Candesartan Acute Stroke Trial; **SSS** = Scandinavian Stroke Scale.

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] In studies that have not adjusted for key confounders, women were observed to have poorer poststroke survival than men, which was reversed after adjustment for age, prestroke function, and stroke severity. However, much data on disability and health-related quality of life (HRQoL), overall and according to stroke subtype, are lacking.[4,5] 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.

Methods

Design

A pooled analysis of 5 large, international, multicenter, randomized controlled trials was conducted that included the following: 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] 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 presentation to hospital (baseline), over several days after admission, and for at least several months of follow-up.

The factors analyzed for significant sex differences in stroke[5] were considered under 4 separate headings: (1) sociodemographic (age, sex, ethnicity, and region of study conduct); (2) 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; (3) clinical data (admission blood pressure [BP] and heart rate); and (4) type of stroke (ischemic or intracerebral hemorrhage [ICH]) and severity of stroke (according to scores on either the NIH Stroke Scale [NIHSS] or Scandinavian Stroke Scale [SSS]).[13]

Outcomes

These IPD examined the following in ischemic stroke and ICH: (1) in-hospital management (including the use of intubation, antipyretics, venous thromboembolism prophylaxis, admission to an acute stroke unit [ASU] or intensive care unit [ICU], neurosurgery, inpatient rehabilitation, and early withdrawal of medical care); (2) out of hospital management (including preadmission CV prevention and secondary CV prevention medication recorded on 3 months follow-up); (3) death or disability, defined by scores 3–6 on the mRS, stratified by stroke type; (4) CV endpoints (myocardial infarction and recurrent stroke); and (5) HRQoL assessed directly or by proxy, using the EuroQoL 5-Dimension self-report questionnaire.[14]

Management details were available for all studies except SCAST. For preadmission CV prevention, 4 of the studies (INTERACT studies, ENCHANTED, and HeadPoST) had data on antihypertensives, anticoagulants, antiplatelets, 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 4 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 postrandomization.

Standard protocol approvals, registrations, and patient consents

Clinical trial registration information: clinicaltrials.gov, unique identifier: INTERACT-1, NCT00226096; INTERACT-2, NCT00716079; ENCHANTED, NCT01422616; HeadPoST, NCT02162017; SCAST, NCT00120003. All participants in these studies provided informed consent and received approval from relevant ethics committees.

Table 1 Design of the included trials

Study	Design	Setting	Stroke type	N	Women, n (%)	Men, n (%)	Intervention
Overall				19,652	7,721	11,931	
INTERACT-1 and INTERACT-2 studies	Prospective, randomized, open-treatment, blinded endpoint	International, multicenter (188 hospitals)	Intracerebral hemorrhage	3,233	1,191 (36.8)	2,042 (63.1)	Intensive vs guideline-recommended blood pressure lowering
ENCHANTED, rtPA dose arm	Prospective, randomized, open-label trial with blinded outcome evaluation	International, multicenter (111 hospitals)	Ischemic stroke	3,297	1,248 (37.9)	2,049 (62.1)	Low vs standard dose alteplase
HeadPoST	Prospective, cluster-randomized, crossover, open-label	International, multicenter (114 hospitals)	Ischemic stroke, intracerebral hemorrhage	11,093	4,429 (39.9)	6,664 (60.1)	Lying-flat position vs sitting-up position, initiated soon after a stroke and maintained for 24 h
SCAST	Prospective, randomized, placebo-controlled, double-blind	North European, multicenter (146 hospitals)	Ischemic stroke, intracerebral hemorrhage	2,029	853 (42.0)	1,176 (58.0)	Candesartan vs placebo for 7 d

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

Statistical analysis

IPD were analyzed using the 2-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 predefined analysis plans of these studies, logistic regression was used in 4 studies (INTERACTstudies, ENCHANTED, and SCAST), and a generalized linear mixed model with fixed randomized 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: (1) the covariate was missing in <20% of cases; (2) the covariate was associated with death or disability in unadjusted analysis ($p < 0.1$); (3) the covariate was associated with sex ($p < 0.1$); and (4) the inclusion of the covariate in a model with only sex changed the magnitude of the sex coefficient by ≥10% (figures e-1–e-10, doi.org/10.5061/dryad.4qt8510).

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.

The adjusted analyses performed in each study used different sets of covariates according to the rules set in the first stage of the IPD, and their availability in each study. Randomized treatment was forced into the models. Hospital management and medication covariates were included in the models for death, disability, recurrent stroke, myocardial infarction, and HRQoL.

INTERACT studies

INTERACT studies reported age, country of origin, ethnicity, history of hypertension, history of stroke, history of myocardial infarction, glucose-lowering treatment, baseline NIHSS score, baseline systolic BP, randomized treatment, baseline hematoma volume, intubation, and ventilation.

ENCHANTED

ENCHANTED reported age, country of origin, ethnicity, history of hypertension, presence of AF, history of myocardial infarction, current smoking, baseline NIHSS score, baseline systolic BP, baseline glucose, randomized treatment, prestroke function, final diagnosis, nasogastric feeding given, subcutaneous heparin used, ASU admission, and any rehabilitation given.

HeadPoST

HeadPoST reported age, country of origin, history of hypertension, presence of AF, history of stroke, history of diabetes, current smoking, baseline NIHSS score, baseline systolic BP, prestroke function, intubation and ventilation, nasogastric feeding given, subcutaneous heparin used, mannitol given, ASU admission, ICU admission, and any rehabilitation given. However, due to a small sample, and to enable model fit, only age and stroke severity were adjusted for the following in HeadPoST: total stroke in intubation, neurosurgery, ICU admission, and all ischemic stroke and ICH in-hospital management and medication outcomes. Fixed intervention (lying flat vs sitting up) and fixed period, random cluster, and random cluster period effects were incorporated into generalized linear mixed models to take into account the study design.

SCAST

SCAST reported age, history of hypertension, presence of AF, baseline SSS score, baseline systolic BP, prestroke function, and randomized treatment.

SAS version 9.3 (SAS Institute, Cary, NC) was used in all analyses.

Table 2 Patient characteristics by sex

	INTERACT studies		ENCHANTED		HeadPoST		SCAST	
Baseline characteristics	**Women (1,191)**	**Men (2,042)**	**Women (1,248)**	**Men (2,049)**	**Women (4,429)**	**Men (6,664)**	**Women (853)**	**Men (1,176)**
Age, y	64.9 (13.0)[a]	62.5 (12.6)	68.8 (13.3)[a]	65.2 (12.3)	71.1 (14.0)[a]	65.9 (13.2)	74.3 (10.5)[a]	68.4 (10.9)
Asian race	884/1,191 (74)	1,526/2,042 (75)	733/1,248 (58.7)	1,356/2,049 (66.2)[a]	1,876/4,429 (42.4)	3,546/6,664 (53.2)[a]	—	—
Country of origin								
Europe and Australia	285/1,191 (23.9)	488/2,042 (23.9)	367/1,248 (29.4)[a]	517/2,049 (25.2)	2,162/4,429 (48.8)[a]	2,599/6,664 (39.0)	—	—
China	859/1,191 (72.1)	1,445/2,042 (70.8)	481/1,248 (38.5)	938/2,049 (45.8)[a]	1,603/4,429 (36.2)	3,049/6,664 (45.8)[a]	—	—
Non-China Asian countries	25/1,191 (2.1)	81/2,042 (4.0)[a]	252/1,248 (20.2)	418/2,049 (20.4)	273/4,429 (6.2)	497/6,664 (7.5)[a]	—	—
South America	22/1,191 (1.8)	28/2,042 (1.4)	148/1,248 (11.9)[a]	176/2,049 (8.6)	391/4,429 (8.8)	519/6,664 (7.8)	—	—
Clinical features								
Systolic BP, mm Hg	179 (16)	179 (17)	149 (20)	149 (19)	157 (29)[a]	153 (26)	172.3 (20)	170.7 (18)
Diastolic BP, mm Hg	99 (13)	102 (15)[a]	83 (12)	85 (12)[a]	85 (17)	87 (16)[a]	88 (14)	92 (13)[a]
Heart rate, beats per minute	78 (13)	77 (14)	80 (16)[a]	78 (14)	79 (15)[a]	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)[a]	10 (6–15)	9 (5–15)[a]	8 (5–13)	5 (2–10)[a]	4 (2–8)	—	—
Medical history								
Hypertension	902/1,191 (75.7)[a]	1,446/2,039 (70.9)	854/1,245 (68.6)[a]	1,211/2,043 (59.3)	3,005/4,413 (68.1)[a]	4,146/6,648 (62.4)	597/827 (72.2)[a]	749/1,120 (66.9)
Previous stroke	194/1,191 (16.3)	404/2,042 (19.8)[a]	210/1,248 (16.8)	379/2,049 (18.5)	953/4,429 (21.5)	1,613/6,664 (24.2)[a]	192/838 (22.9)	264/1,151 (22.9)
Coronary artery disease	20/1,191 (1.7)	75/2,039 (3.7)[a]	160/1,245 (12.9)	319/2,043 (15.6)[a]	605/4,397 (13.8)	935/6,626 (14.1)	—	—
Atrial fibrillation	—	—	297/1,243 (23.9)[a]	339/2,042 (16.6)	568/4,370 (13.0)[a]	609/6,604 (9.2)	175/836 (20.9)	201/1,146 (17.5)
Diabetes mellitus	115/1,191 (9.7)	224/2,039 (11.0)	261/1,245 (21.0)	385/2,043 (18.8)	1,009/4,411 (22.9)	1,643/6,647 (24.7)[a]	137/837 (16.4)	183/1,161 (15.8)
Hypercholesterolemia	—	—	229/1,245 (18.4)	326/2,043 (16.0)	1,117/4,404 (25.4)	1,615/6,629 (24.4)	—	—
Current smoker	—	—	105/1,244 (8.4)	665/2,040 (32.6)[a]	329/4,385 (7.5)	1,796/6,590 (27.3)[a]	—	—
Prestroke function (mRS)								
No symptoms (mRS 0)	—	—	953/1,245 (76.5)	1,721/2,041 (84.3)[a]	2,484/4,414 (56.3)	4,264/6,657 (64.1)[a]	630/853 (73.8)	947/1,176 (80.5)[a]
With symptoms (mRS 1–5)	—	—	292/1,245 (23.5)[a]	320/2,041 (15.7)	798/4,414 (18.1)	1,189/6,657 (17.9)	223/853 (26.1)[a]	229/1,176 (19.4)

Continued

Table 2 Patient characteristics by sex *(continued)*

Baseline characteristics	INTERACT studies		ENCHANTED		HeadPoST		SCAST	
	Women (1,191)	Men (2,042)	Women (1,248)	Men (2,049)	Women (4,429)	Men (6,664)	Women (853)	Men (1,176)
Final diagnosis								
Ischemic stroke	—	—	954/1,248 (76.0)	1,654/2,049 (81.0)	3,726/4,426 (84.2)	5,759/6,656 (86.5)	758/853 (88.9)	975/1,174 (83.0)
Intracerebral hemorrhage	1,191 (100)	2,042 (100)	—	—	385/4,429 (8.7)	546/6,664 (8.2)	88/853 (10.3)	186/1,174 (15.8)
Other	—	—	294/1,248 (24.0)	395/2,049 (19.0)	315/4,426 (7.1)	351/6,656 (5.3)	7/853 (0.8)	13/1,174 (1.1)

Abbreviations: BP = blood pressure; ENCHANTED = Enhanced Control of Hypertension and Thrombolysis Stroke study; GCS = Glasgow Coma Scale; HeadPoST = Head Position in Stroke Trial; INTERACT = Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage; NIHSS = NIH Stroke Scale; SCAST = Scandinavian Candesartan Acute Stroke Trial.
Data are n (%), mean (SD), or median (IQR).
[a] Statistically significant results.

Data availability

This pooled analysis involves trial data shared among 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

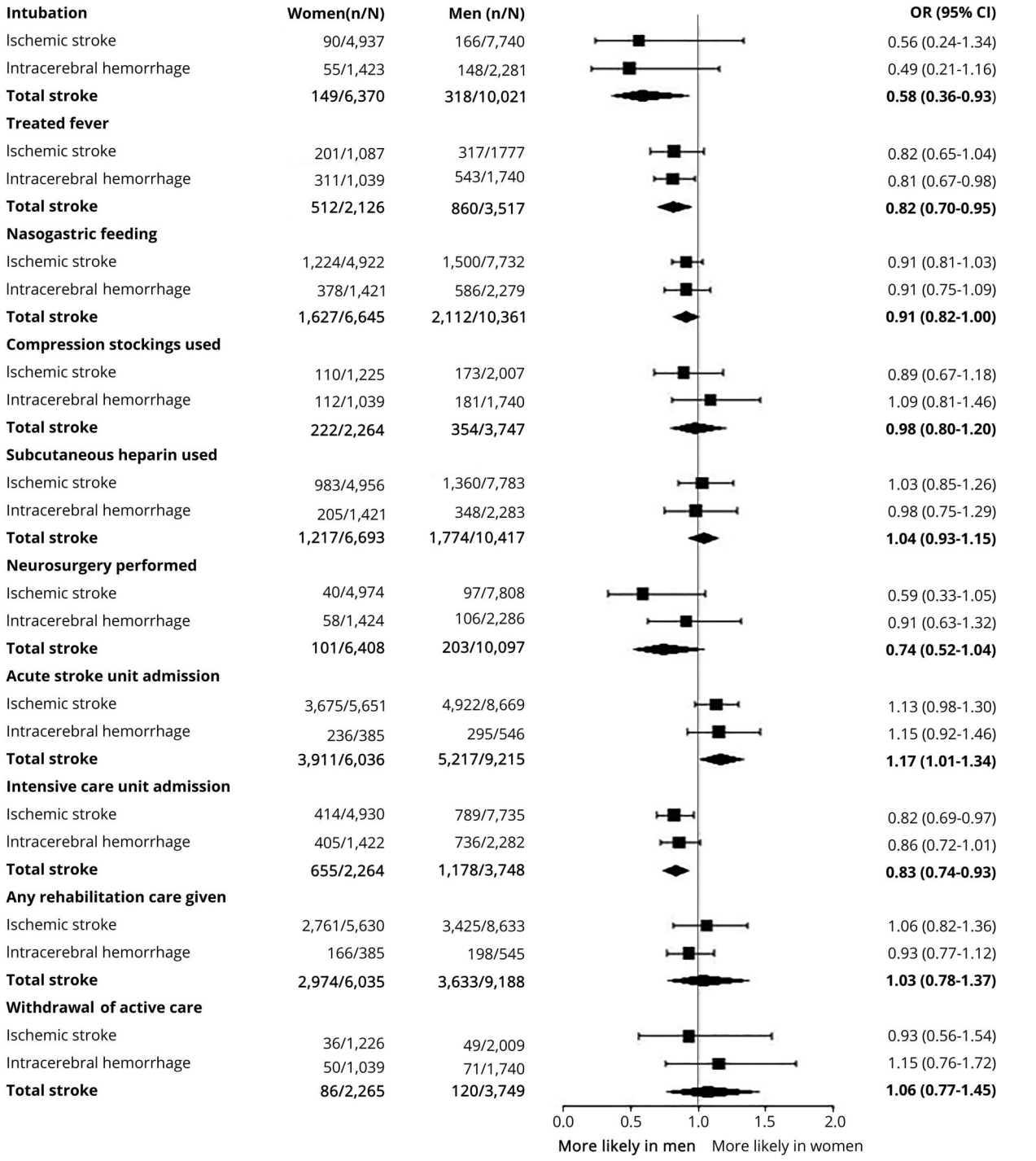
There were 19,652 participants included in the 5 studies, and 7,721 (40%) were women. The INTERACT studies enrolled the smallest proportion of women (37%), while SCAST enrolled the most (42%) (table 1). Table 2 shows the baseline characteristics of participants in each study population stratified by 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 neurologic 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 and to be smokers, and to have had higher diastolic BP, prior stroke, coronary artery disease, diabetes mellitus, and premorbid independence (mRS scores).

Figure 1 shows that women were more likely to be admitted to an ASU while in the hospital (odds ratio [OR] 1.17, 95% confidence interval [CI] 1.01–1.34) but were less likely to be intubated (OR 0.58, 95% CI 0.36–0.93), be given treatment for fever (OR 0.82, 95% CI 0.70–0.95), receive nasogastric feeding (OR 0.91, 95% CI 0.82–1.00), and be admitted to an ICU (OR 0.83, 95% CI 0.74–0.93). These results were attenuated after analyzing by stroke subtype due to reduced sample size.

On admission to the hospital, women had higher odds of having received antihypertensive medication (OR 1.22, 95% CI 1.13–1.31) and lower odds of having antiplatelet treatment (OR 0.86, 95% CI 0.79–0.93), glucose-lowering therapy (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). The treatment effect was attenuated for ICH (except for antihypertensive agents) but remained similar in ischemic stroke (with the exception of glucose-lowering agents). For secondary prevention, there were no sex differences in the prescription of antihypertensive agents (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

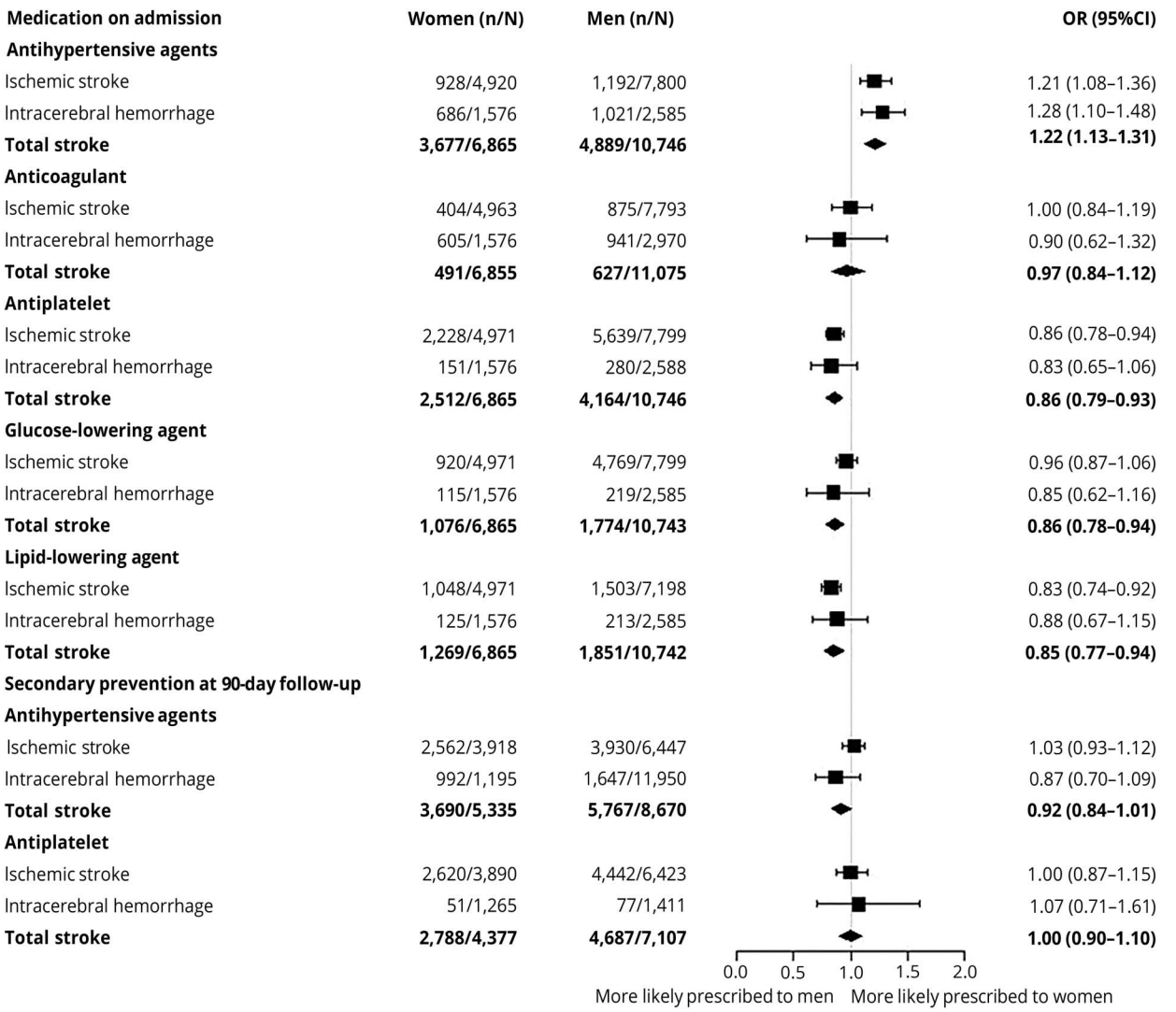
Figure 1 In-hospital stroke management



Total stroke numbers in women and men may not equate to the number of patients with ischemic and intracerebral hemorrhage. This is due to the inclusion of undifferentiated stroke and missing data in the total numbers. CI = confidence interval; OR = odds ratio.

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 subgroup analyses on thrombolyzed and nonthrombolyzed patients with ischemic stroke (figures e-1 and e-2, doi.org/10.5061/dryad.4qt8510). Overall, women experienced worse HRQoL (weighted mean difference −0.07, 95% CI −0.09 to 0.04). Across all 5 dimensions of HRQoL, women had higher scores (i.e., 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).

Figure 2 Prescription of cardiovascular prevention medication on admission and at 3-month follow-up after acute stroke



Total stroke numbers in women and men may not equate to the number of patients with ischemic and intracerebral hemorrhage. This is due to the inclusion of undifferentiated stroke and missing data in the total numbers. CI = confidence interval; OR = odds ratio.

Discussion

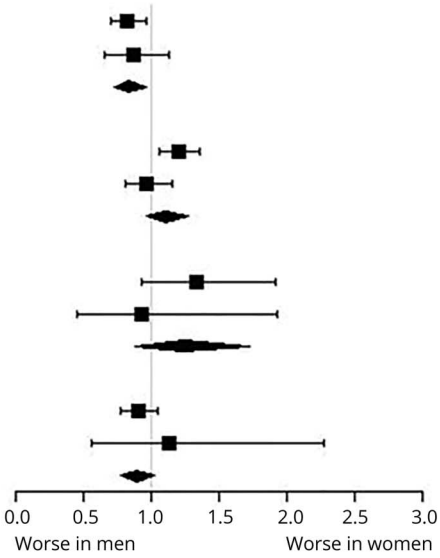
In this pooled analysis of 19,652 patients with acute stroke, survival among women with ischemic stroke was significantly higher than in men with ischemic stroke but not in those with ICH. In those who survived, women lived with greater disability than men after ischemic stroke, and experienced poorer 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 support 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] Preclinical studies of ischemic stroke suggest that aging brain in women is more sensitive to ischemia than in men, 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]

Our study found that in overall stroke, women were less likely to receive intubation, treatment for fever, nasogastric feeding, or ICU admission, but were more likely to be admitted to ASUs. While differing access to evidence-based treatment may be a determinant of sex differences in functional outcome after stroke,[29] these findings may also imply that the women in the study did not require these interventions. Additional research is

Figure 3 Functional outcomes and vascular endpoints by stroke type

Death	Women (n/N)	Men (n/N)	OR (95% CI)
Ischemic stroke	516/5,244	578/8,056	0.82 (0.70–0.97)
Intracerebral hemorrhage	194/1,600	329/2,677	0.87 (0.66–1.13)
Total stroke			**0.84 (0.73–0.96)**
Disability			
Ischemic stroke	2,407/4,728	3,064/7,478	1.20 (1.06–1.36)
Intracerebral hemorrhage	707/1,406	1,073/2,348	0.97 (0.81–1.16)
Total stroke			**1.11 (0.97–1.28)**
Myocardial infarction			
Ischemic stroke	73/5,732	71/8,783	1.33 (0.93–1.91)
Intracerebral hemorrhage	5/1,279	10/2,228	0.93 (0.45–1.93)
Total stroke			**1.24 (0.88–1.73)**
Recurrent stroke			
Ischemic stroke	475/5,732	655/8,783	0.91 (0.78–1.05)
Intracerebral hemorhage	18/1,279	30/2,228	1.13 (0.56–2.27)
Total stroke			**0.89 (0.78–1.03)**



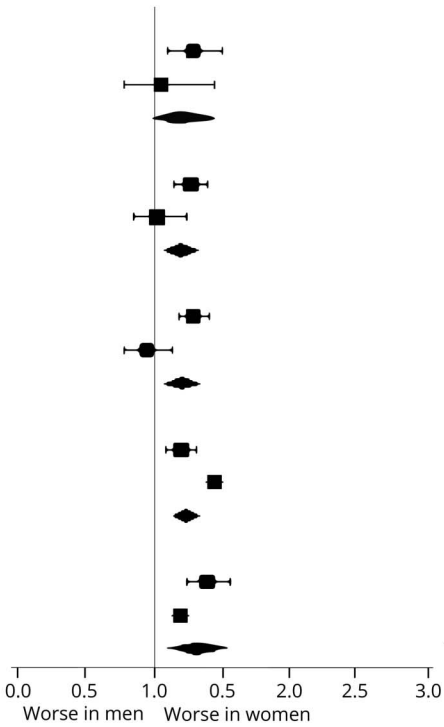
CI = confidence interval; OR = odds ratio.

needed to examine whether there are sex differences in intervention in women and men who have had stroke and experience similar complications.

Older studies have reported sex differences in diagnostic evaluations, such as lipid testing,[30] and therapeutic interventions, such as carotid surgery,[31] whereas more recent publications have shown no sex differences in hospital stroke care.[32–35]

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

Mobility	Women (n/N)	Men (n/N)	OR (95% CI)
Ischemic stroke	2,305/4,680	2,750/7,429	1.30 (1.11–1.51)
Intracerebral hemorrhage	892/1,411	1,377/2,350	1.06 (0.79–1.44)
Total stroke			**1.20 (1.00–1.45)**
Self care			
Ischemic stroke	1,884/4,680	2,227/7,428	1.28 (1.16– 1.40)
Intracerebral hemorrhage	745/1,410	1,044/2,349	1.03 (0.86–1.23)
Total stroke			**1.20 (1.09–1.33)**
Usual activities			
Ischemic stroke	2,567/4,679	3,252/7,428	1.30 (1.19–1.42)
Intracerebral hemorrhage	874/1,411	1,370/2,348	0.95 (0.79–1.14)
Total stroke			**1.21 (1.09–1.34)**
Pain/discomfort			
Ischemic stroke	1,733/4,677	2,178/7,418	1.21 (1.10–1.32)
Intracerebral hemorrhage	637/1,407	893/2,341	1.45 (1.10 –1.91)
Total stroke			**1.25 (1.16–1.35)**
Anxiety/depression			
Ischemic stroke	1,594/4,643	1,843/7,405	1.40 (1.25–1.57)
Intracerebral hemorrhage	533/ 1,406	784/2,330	1.20 (0.86–1.68)
Total stroke			**1.32 (1.11– 1.55)**



CI = confidence interval; OR = odds ratio.

Studies have indicated that the use of preventative medication for stroke may differ between men and women. The Practice Innovation and Clinical Excellence (PINNACLE) 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 medications, or lipid-lowering medications are also consistent with previous studies.[36,37] In addition, while we did not find any sex differences in the use of antihypertensive and antiplatelet agents at 90 days after stroke, the use of both is contingent on prescribing and adherence. 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 health care 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 support the internal validity of these data. However, we recognize that this work has limitations. First, it was post hoc, observational, and restricted in the range of variables assessed (including dose and amount of treatment and marital status), raising the potential for residual confounding. Second, clinical trial participants are likely to receive higher than average standards of care,[38] in line with contemporaneous advances in guideline recommendations for ischemic[39,40] and hemorrhagic stroke,[41,42] which may limit the generalizability of the findings. Third, the higher survival for women may explain their greater disability as a consequence of selection (survivor) bias. Finally, these data on the women and men who met exclusion criteria for the trials have not been analyzed in this pooled analysis.

Sex differences exist regarding survival, disability, and management after stroke. While in-hospital management does not appear to explain the sex differences in outcome, it is possible that the use of preventative medication may influence sex differences in outcome. 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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Appendix *(continued)*

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