ORIGINAL RESEARCH

Impact of Evidence-Based Stroke Care on Patient Outcomes: A Multilevel Analysis of an International Study

Paula Muñoz Venturelli, MD, PhD; Xian Li, PhD; Sandy Middleton, PhD; Caroline Watkins, PhD; Pablo M. Lavados, MD, MPH; Verónica V. Olavarría, MD, MSc; Alejandro Brunser, MD; Octavio Pontes-Neto, MD, PhD; Taiza E. G. Santos, PhD; Hisatomi Arima, MD, PhD; Laurent Billot, MRes; Maree L. Hackett, PhD; Lily Song, MD, PhD; Thompson Robinson, MD; Craig S. Anderson, MD, PhD; on behalf of the HEADPOST (Head Positioning in Acute Stroke Trial) Investigators*

***Background*—**The uptake of proven stroke treatments varies widely. We aimed to determine the association of evidence-based processes of care for acute ischemic stroke (AIS) and clinical outcome of patients who participated in the HEADPOST (Head Positioning in Acute Stroke Trial), a multicenter cluster crossover trial of lying flat versus sitting up, head positioning in acute stroke.

***Methods and Results*—**Use of 8 AIS processes of care were considered: reperfusion therapy in eligible patients; acute stroke unit care; antihypertensive, antiplatelet, statin, and anticoagulation for atrial fibrillation; dysphagia assessment; and physiotherapist review. Hierarchical, mixed, logistic regression models were performed to determine associations with good outcome (modified Rankin Scale scores 0–2) at 90 days, adjusted for patient and hospital variables. Among 9485 patients with AIS, implementation of all processes of care in eligible patients, or "defect-free" care, was associated with improved outcome (odds ratio, 1.40; 95% CI, 1.18–1.65) and better survival (odds ratio, 2.23; 95% CI, 1.62–3.09). Defect-free stroke care was also significantly associated with excellent outcome (modified Rankin Scale score 0–1) (odds ratio, 1.22; 95% CI, 1.04–1.43). No hospital characteristic was independently predictive of outcome. Only 1445 (15%) of eligible patients with AIS received all processes of care, with significant regional variations in overall and individual rates.

***Conclusions*—**Use of evidence-based care is associated with improved clinical outcome in AIS. Strategies are required to address regional variation in the use of proven AIS treatments.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov. Unique Identifier: NCT02162017. **(*J Am Heart Assoc*. 2019;8: e012640. DOI: 10.1161/JAHA.119.012640.)**

Key Words: acute stroke care • multilevel analysis • outcome • quality

Stroke is a major cause of death and disability, especially in low-resource regions.[1] Although considerable advances have been made in generating the evidence base that supports various treatments, particularly for acute ischemic stroke (AIS), their implementation is often limited by resource, organizational, and funding barriers in clinical practice.[2] For example, acute stroke unit (ASU) care is one of the most cost-effective treatments,[3–5] but many hospitals around the world do not have

From The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, Australia (P.M.V., X.L., L.B., M.L.H., L.S., C.S.A.); Centro de Estudios Clínicos, Instituto de Ciencias e Innovación en Medicina (P.M.V.), Servicio de Neurología, Departamento de Neurología y Psiquiatría (P.M.V., P.M.L., V.V.O., A.B.), and Departamento de Paciente Crítico, Clínica Alemana de Santiago (V.V.O.), Facultad de Medicina, Clínica Alemana Universidad del Desarrollo, Santiago, Chile; The George Institute for Global Health at Peking University Health Science Center, Beijing, China (X.L., L.S., C.S.A.); Nursing Research Institute, St Vincents Health Australia (Sydney) and Australian Catholic University, Sydney, Australia (S.M.); Faculty of Health and Wellbeing, University of Central Lancashire, Preston, United Kingdom (S.M., C.W., M.L.H.); Departamento de Ciencias Neurológicas, Facultad de Medicina, Universidad de Chile, Santiago, Chile (P.M.L.); Stroke Service, Neurology Division, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil (O.P.-N., T.E.G.S.); Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, Fukuoka, Japan (H.A.); and Department of Cardiovascular Sciences and National Institute for Health Research Leicester Biomedical Research Center, University of Leicester, United Kingdom (T.R.).

Accompanying Tables S1 through S4 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012640

*A complete list of the HEADPOST (Head Positioning in Acute Stroke Trial) Investigators can be found in the Appendix at the end of the article.

Correspondence to: Craig S. Anderson, MD, PhD, The George Institute for Global Health, PO Box M201, Missenden Road, Sydney, NSW 2050, Australia. E-mail: canderson@georgeinstitute.org.au

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Clinical Perspective

What Is New?

- Adherence to evidence-based care was associated with improved outcomes in patients with ischemic stroke who participated in the large pragmatic trial HEADPOST (Head Positioning in Acute Stroke Trial).
- However, there was significant variation in the amount of evidence-based care across regions, and few patients received the entire range (optimal treatment) of such performance indicators.

What Are the Clinical Implications?

- There is considerable opportunity to increase the uptake of evidence-based care in ischemic stroke to improve clinical outcomes from this serious condition.

such a service or only have it organized in a partial manner.[6] Improvements in the delivery of stroke care can translate into better patient outcomes, but most "real-life" quality-of-care evaluations are undertaken in well-resourced hospitals located in high-income countries and without necessarily considering both organizational and patient variables.[7,8] A better understanding of variations in the processes of care in relation to patient outcomes can help prioritize efforts toward improving the implementation of evidence, especially in low- and middle-income countries.[9,10]

In a previous report, we identified large variations in the organization of stroke care (ie, staffing, protocols, and discharge planning) across hospitals in different countries in establishing the network for the international, multicenter HEADPOST (Head Positioning in Acute Stroke Trial).[11] More research is needed on the impact of gaps in evidence-based care in low- and middle-income countries, where access to ASU care, let alone other therapies, is often limited.[12] We aimed to determine the association between the use of recommended evidence-based processes of stroke care and clinical outcomes for patients with AIS who participated in HEADPOST using analyses to account for hospital and patient characteristics.

Methods

The data that support the findings of this study are available through a formal protocol request from researchers to the Research Office of The George Institute Australia via the corresponding author.

Design

HEADPOST was an international, multicenter, cluster-randomized, crossover trial with centralized outcome assessment, the details of which are outlined elsewhere.[13,14] In brief, the trial used a pragmatic design with broad eligibility and assessment criteria, to facilitate the recruitment of 11 093 adult patients with a clinical diagnosis of acute stroke (AIS or intracerebral hemorrhage) to determine the effectiveness of lying flat (0°) compared with sitting up (≥30°) head positioning, applied within the first 24 hours of admission at 114 hospitals in 9 countries, during 2016 to 2017. Patients were eligible for inclusion in the trial if they were aged ≥18 years, presented to the emergency department or an inpatient service at a participating center, and received a clinical diagnosis of acute stroke. Patients were excluded if the local clinician-investigator considered that the assigned head position could not be maintained consistently, if the confirmed diagnosis was a transient ischemic attack, or if the patient declined to participate in the trial. Patients were also excluded if there was a clear indication for, or contraindication to, either of the head positions.[13] Local investigators were required to recruit a prespecified target (cluster) number of consecutive patients into an initial randomized head position that was implemented as a usual standard-of-care policy before the service was crossed over for the other randomized head position to be implemented as a similar standard-of-care policy. The protocol was approved by all regulatory authorities and ethics committees at participating hospitals. A senior executive officer at each hospital acted as a "guardian" (as part of the cluster-randomized trial design) and provided consent at an institutional level for head positioning to be implemented as a "low-risk intervention" to clusters of patients as part of routine care; written informed consent was subsequently obtained from patients (or their approved surrogates) for the collection of medical data and participation in follow-up assessments. The corresponding author has full access to all the data in the study and takes responsibility for their integrity and the data analysis.

To assist the implementation of the intervention at each site, data were gathered on the organization of the hospital and in the wards involved in implementing the randomized interventions. After a baseline assessment that included collecting demographic, medical history, and clinical information on the severity of the neurological deficit, according to the National Institutes of Health Stroke Scale and vital signs, adherence to the allocated head position was monitored in patients over the subsequent 24 hours. Further follow-up data were collected on the management of patients at the time of separation (day 7 or at hospital discharge, transfer, or death, if earlier) and all serious adverse events, including death, until 90 days. Appropriately trained outcome assessors in a central office, who were kept blind to the management of patients, used a script to conduct a telephone assessment of health and physical functioning at 90 days. The key clinical outcome was the degree of disability, according to the modified Rankin

Scale (mRS) score.[15] Main study results showed that disability outcomes after acute stroke did not differ significantly between patients assigned to a lying-flat position for 24 hours and patients assigned to a sitting-up position with the head elevated to at least 30° for 24 hours.[13]

Statistical Analysis

Only patients with AIS were included in these analyses. Comparisons of categorical and continuous variables were assessed with the χ^2 and Wilcoxon Mann-Whitney rank sum tests, respectively. Univariable analyses were used to evaluate associations between patient characteristics and process-of-care indicators with 90-day clinical outcomes. Multilevel logistic regression models were used to examine the associations between processes of care implemented in the first week (by day 7 or at discharge, if earlier) on good outcome (mRS score 0–2). The following processes of care were considered independent variables: (1) use of intravenous recombinant tPA (tissue-type plasminogen activator) or endovascular clot retrieval in patients who presented at the hospital within 4.5 hours of symptom onset; (2) admission to an ASU; use of (3) antihypertensive, (4) antiplatelet, (5) statin, and (6) anticoagulation therapy in those with evidence of atrial fibrillation/flutter (AF); (7) receipt of a dysphagia screen and/or assessment before feeding was commenced; and (8) assessment by a physiotherapist in patients with residual disability (mRS score 3–5 on day 7). A composite variable of early "defect-free" care (including the aforementioned 8 independent processes of care) was constructed to identify the proportion of eligible patients who received all applicable processes of care. A hierarchical mixed logistic regression with fixed period, fixed head position effect, random cluster, and random cluster-period effects, plus the variable for evidence-based care, was used as the base model. Three sequential models were constructed to adjust for other patient- and hospital-level characteristic associations with patient outcomes. Variables were treated as independent variables. Association between defect-free care and excellent outcome (90-day mRS score 0–1) was also evaluated.

Consistency of treatment effect across prespecified subgroups (defined by age, sex, major country/region groupings, baseline National Institutes of Health Stroke Scale score, and pathologic subtype of AIS) was assessed by means of tests for interaction. Sensitivity analyses included the use of multiple imputation because >10% of observations for mRS scores were missing at 90 days[16] and exclusion of those who had died within the first 7 days after admission.

To analyze the association between patients' outcome and hospital characteristics, univariable analyses were performed using hierarchical mixed logistic regression models, as previously described, taking account of the cluster crossover study design. Multivariable analyses included adjustment for patient characteristics that had the potential to influence recovery: age, sex, history of hypertension, stroke, heart disease or diabetes mellitus, premorbid estimated mRS score, baseline National Institutes of Health Stroke Scale score, time from symptom onset to commencement of the intervention, and country. Adjustment variables were selected for potential clinical significance as well as statistical significance on initial univariable analyses. Data are reported with 2-sided *P* values, without adjustment for multiple comparisons, and as odds ratios with 95% CIs. All analyses were undertaken with SAS software, version 9.3 (SAS Institute).

Role of the Funding Source

The study sponsor was not involved in the study design or collection, analysis, and interpretation of data; and had no role in the writing of this report or in the decision to submit the manuscript for publication.

Results

There were 9485 patients with AIS included in analyses (Figure 1). Table 1 shows that patients with AIS who received defect-free stroke care had more risk factors, lower levels of premorbid disability, and greater baseline neurological impairment, compared with those who did not receive defect-free stroke care. Defect-free care was more frequent in hospitals in Australia and the United Kingdom, in those with lower numbers of stroke admissions per annum, in nonacademic hospitals, and in those where specific protocols for stroke care were in place and where multidisciplinary teams were involved in usual care.

Table 2 shows the results of multilevel modeling: use of antiplatelets, use of statins, dysphagia screen, and physiotherapy assessment were associated with better clinical outcome. The use of standard reperfusion treatment (recombinant tPA or endovascular clot retrieval within the first 4.5 hours of symptoms onset) was also associated with better disability-free survival after adjusting for patient and hospital characteristics. Early implementation of all stroke care eligible processes of care was associated with greater likelihood of good clinical outcome (odds ratio, 1.40; 95% CI, 1.18–1.65). When the outcome considered was mRS score 0 to 1, the association between early implementation of defect-free care and greater likelihood of excellent outcome (mRS score 0–1) remained significant (odds ratio, 1.22; 95% CI, 1.04–1.43). These results were further confirmed in sensitivity analyses with multiple imputations for missing primary outcome data (Table S1) by excluding patients with

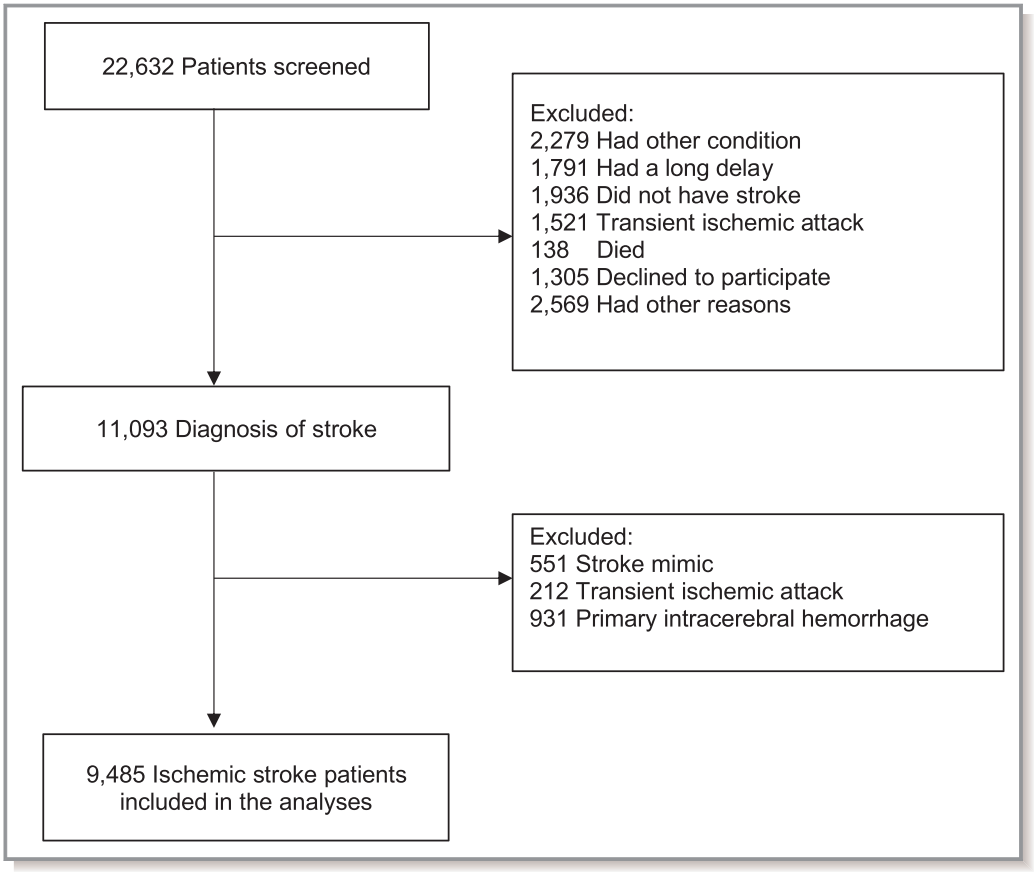

Figure 1. Patient flow diagram.

early death (Table 2), and after excluding patients who received reperfusion therapy and anticoagulation for AF (Table 2). In terms of survival at 90 days, multilevel modeling showed that use of all processes of care was associated with better survival (odds ratio, 2.23; 95% CI, 1.62–3.09) (Table S2).

Overall, use of the AIS processes of care was low (1445/9485, 15.2%) and varied widely across regions, being highest in Australia/United Kingdom (1001/3850, 26.0%) and India/Sri Lanka (151/658, 22.9%), intermediate in South America (122/691, 15.2%), and lowest in China (171/4178, 4.1%) ($P<0.001$) (Table S3). Those components with the greatest regional differences were ASU admission, use of antihypertensive therapy, anticoagulation for AF, and physiotherapy assessment. There was consistency in the beneficial associations across patient subgroups (Figures 2 and 3), but no hospital characteristic was independently predictive of clinical outcome (Table S4).

Discussion

These secondary analyses of a large international clinical trial have 2 major findings. First, data show that the implementation of guideline-recommended AIS processes of care is associated with clear beneficial clinical outcome, including a dramatic halving in the risk of death within 90 days, even after accounting for a range of confounding variables. Second, overall use of defect-free stroke care was low, and there was considerable regional variation, especially across several components, including the use of ASU care. Although the organization of services is important for delivering efficient and effective stroke care, we were unable to identify a specific hospital characteristic that was independently associated with clinical outcome; patient-level characteristics were the main driver of clinical outcome.

Various stroke quality assessment and improvement programs exist around the world. In the United States, for example, the Centers for Disease Control and Prevention monitors adherence to 10 quality-of-care measures in hospitals across 7 states through the Paul Coverdell National Acute Stroke Registry, where patients who received the best quality of care have been shown to have an increased chance of long-term survival.[8] Quality of care and process improvement have also been presented in numerous publications from the American Heart Association's Get With The Guidelines program.[17] Similar initiatives have been developed in Australia and the United Kingdom,[7,18,19] but there are few available in

Table 1. Characteristics of Ischemic Stroke Patients and Hospitals, Stratified by Receipt of "Defect-Free" Evidence-Based Care

Variable	Defect-Free Care			
	Total (N=9485)	Yes (N=1445)	No (N=8040)	*P* Value*
Patients				
Age, y	69 (59–79)	72 (63–81)	68 (59–78)	0.999
Men	5759 (60.7)	826 (57.2)	4933 (61.4)	0.914
Hypertension	6141 (64.9)	1154 (80.0)	4987 (62.2)	<0.001
Prior stroke	2258 (23.9)	280 (19.4)	1978 (24.7)	0.826
Coronary artery disease	1339 (14.2)	250 (17.4)	1089 (13.6)	0.002
Atrial fibrillation	1059 (11.2)	106 (7.4)	953 (11.9)	<0.001
Heart failure	358 (3.8)	57 (4.0)	301 (3.8)	0.184
Diabetes mellitus	2354 (24.9)	451 (31.3)	1903 (23.7)	<0.001
Tobacco use	1924 (20.5)	241 (16.8)	1683 (21.2)	0.917
Aspirin or other antiplatelet use	5182 (54.7)	677 (46.9)	4505 (56.1)	<0.001
Anticoagulant use	824 (8.7)	86 (6.0)	738 (9.2)	<0.001
Premorbid function on the mRS				
0 (No symptoms)	5800 (61.3)	968 (67.1)	4832 (60.2)	0.012
1 (No significant disability)	1691 (17.9)	214 (14.8)	1477 (18.4)	. . .
2 (Slight disability)	998 (10.5)	125 (8.7)	873 (10.9)	. . .
3 (Moderate disability)	598 (6.3)	93 (6.4)	505 (6.3)	. . .
4 (Moderate/severe disability)	306 (3.2)	32 (2.2)	274 (3.4)	. . .
5 (Severe disability)	76 (0.8)	11 (0.8)	65 (0.8)	. . .
Admission NIHSS score	4 (2–8)	4 (2–8)	4 (2–8)	<0.001
Symptom onset to intervention, h	14 (5–37)	16 (7–33)	14 (5–39)	<0.001
Initial head position lying flat	4532 (47.8)	685 (47.4)	3847 (47.8)	0.770
Region of recruitment				
Australia/United Kingdom	3850 (40.6)	1001 (69.3)	2849 (35.4)	<0.001
China, including Taiwan	4178 (44.0)	171 (11.8)	4007 (49.8)	. . .
India and Sri Lanka	658 (6.9)	151 (10.4)	507 (6.3)	. . .
South America	799 (8.4)	122 (8.4)	677 (8.4)	. . .
Hospitals				
No. of stroke patients annually				
<500	2252 (24.1)	442 (30.6)	1810 (22.9)	0.010
500–1000	3642 (39.0)	673 (46.6)	2969 (37.6)	. . .
>1000	3446 (36.9)	330 (22.8)	3116 (39.5)	. . .
Academic teaching hospital	8094 (86.5)	1112 (77.0)	6982 (88.3)	0.007
Pathway for stroke care	8491 (90.8)	1416 (98.0)	7075 (89.5)	<0.001
Protocols for fever/blood glucose/swallow	7043 (75.3)	1088 (75.3)	5955 (75.3)	0.899
ED protocols	8847 (94.6)	1309 (90.6)	7538 (95.3)	0.256
Multidisciplinary teams	5561 (59.5)	1170 (81.0)	4391 (55.5)	<0.001
Endovascular clot retrieval	5305 (57.4)	685 (48.8)	4620 (58.9)	0.042

Data are given as number (percentage) or median (interquartile range). ED indicates emergency department; mRS modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale. **P* values from unadjusted hierarchical mixed logistic regression model, with link function being logit with fixed period, fixed head position effect, random cluster, and random cluster-period effects.

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Table 2. Evidence-Based AIS Processes of Care and Good Outcome, in Various Models

	Good Outcome	Total	Unadjusted		Model 1		Model 2		Model 3	
Variable	(N=5112)	(N=8383)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Reperfusion therapy (n=3093)	591 (34.2)	1051 (34.0)	1.06 (0.91–1.25)	0.454	0.87 (0.73–1.04)	0.129	1.39 (1.13–1.71)	0.002	1.40 (1.14–1.73)	0.001
ASU admission	2633 (51.5)	4723 (56.3)	0.77 (0.65–0.91)	0.003	1.01 (0.82–1.25)	0.932	1.01 (0.81–1.25)	0.940	1.05 (0.84–1.32)	0.669
Antihypertensive therapy	2771 (54.2)	4725 (56.4)	0.89 (0.81–0.98)	0.023	1.06 (0.96–1.18)	0.255	1.08 (0.95–1.24)	0.221	1.09 (0.95–1.24)	0.208
Antiplatelet therapy	4975 (97.3)	8063 (96.2)	1.98 (1.56–2.50)	<0.001	1.91 (1.49–2.47)	<0.001	1.50 (1.12–2.00)	0.007	1.52 (1.13–2.03)	0.006
Statin therapy	4390 (85.9)	6960 (83.0)	1.64 (1.45–1.87)	<0.001	1.47 (1.28–1.69)	<0.001	1.27 (1.09–1.48)	0.003	1.26 (1.08–1.47)	0.004
Anticoagulation in AF (n=1203)*	259 (49.7)	574 (47.7)	1.14 (0.89–1.45)	0.293	. . .		. . .		. . .	. . .
Swallow assessment	3916 (76.6)	6279 (74.9)	1.47 (1.30–1.67)	<0.001	1.38 (1.20–1.58)	<0.001	1.26 (1.09–1.46)	0.002	1.26 (1.08–1.47)	0.003
Physiotherapy in disabled patients (n=3073)	645 (72.5)	2194 (71.4)	1.20 (0.96–1.50)	0.102	1.53 (1.17–1.99)	0.002	1.50 (1.14–1.97)	0.004	1.47 (1.11–1.95)	0.008
"Defect-free" stroke care	770 (15.1)	1229 (14.7)	1.45 (1.26–1.67)	<0.001	1.48 (1.27–1.71)	<0.001	1.40 (1.19–1.65)	<0.001	1.40 (1.18–1.65)	<0.001
Defect-free stroke care (without reperfusion/anticoagulation)	1146 (22.4)	1941 (23.2)	1.21 (1.07–1.37)	0.002	1.36 (1.19–1.56)	<0.001	1.28 (1.10–1.49)	0.002	1.28 (1.10–1.49)	0.002
Defect-free stroke care (only survivors >7 d) (n=8265)	770 (15.1)	1224 (14.8)	1.39 (1.21–1.60)	<0.001	1.42 (1.22–1.65)	<0.001	1.38 (1.17–1.63)	<0.001	1.38 (1.16–1.63)	<0.001

Analyses used multilevel logistic regression models with fixed period, fixed head position effect, random cluster, and random cluster-period effects. Model 1: adjusted for country, prestroke modified Rankin Scale score, age, and sex. Model 2: further adjustment for baseline National Institutes of Health Stroke Scale score; history of stroke, heart disease, diabetes mellitus, and hypertension; and time from stroke onset to intervention. Model 3: further adjustment for number of patients with stroke admitted annually, availability of a multidisciplinary team, hospital status (academic or not), use of pathway or service organization for stroke care, and availability of endovascular treatment. Good outcome indicates modified Rankin Scale score 0 to 2. AF indicates atrial fibrillation; AIS, acute ischemic stroke; ASU, acute stroke unit; OR, odds ratio.

*Result models not shown because of failure to converge caused by low numbers.

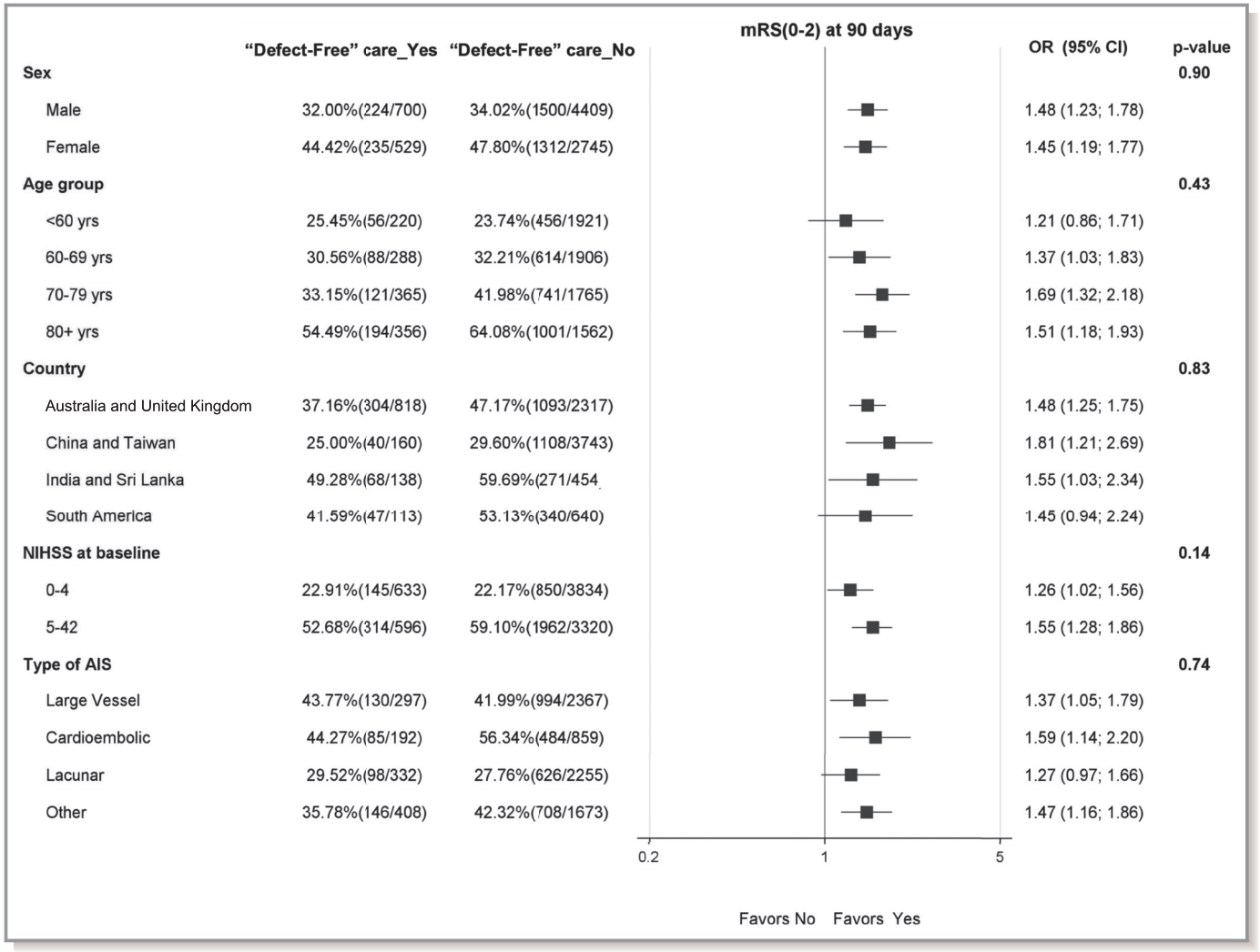

Figure 2. "Defect-free" stroke care and good outcome (modified Rankin Scale [mRS] scores 0–2) at 90 days, by subgroups. AIS indicates acute ischemic stroke; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

developing countries.[20] In keeping with our findings of the cumulative benefit on outcomes from multiple processes of care, data from the Australian Stroke Clinical Registry have shown that patients who received 3 processes of care (stroke unit care, discharged on antihypertensive agents, and discharged with a care plan) had a 70% reduced hazard of death at 180 days.[18]

Within the various processes of care analyzed, reperfusion treatment and ASU care showed the greatest variations across the participating countries in our study, despite being recognized as those with the largest benefit. As a time-critical treatment, use of intravenous thrombolysis is often restricted by local barriers, such as system networks and patient awareness of disease, resulting in early emergency consultation. For example, fewer patients receive recombinant tPA when arriving within 4 hours of symptom onset (39%),[21] compared with those arriving within 2 hours (88%).[22] Another consideration to be made is about stroke care performance and admission volume because our findings are opposed to the usual assumption that practice improves processes of care. This might have been related to overwhelming clinical volumes in larger hospitals, mostly from the Asian region.

We recognize that the definitions and timing of defect-free stroke care treatments may vary,[21,22] as is the case for anticoagulation in those with AF and the initiation of antihypertensive treatment after AIS. Although current guidelines recommend initiation of anticoagulation within 2 weeks of a cardioembolic stroke, except for patients with large infarcts or other risk factors for hemorrhage,[23] timing for treatment initiation after the onset of AIS presents high variability in practice. On the other hand, there is global consensus on the use of blood pressure–lowering treatment in patient candidates for acute reperfusion therapy and in patients not receiving reperfusion therapy but with severe

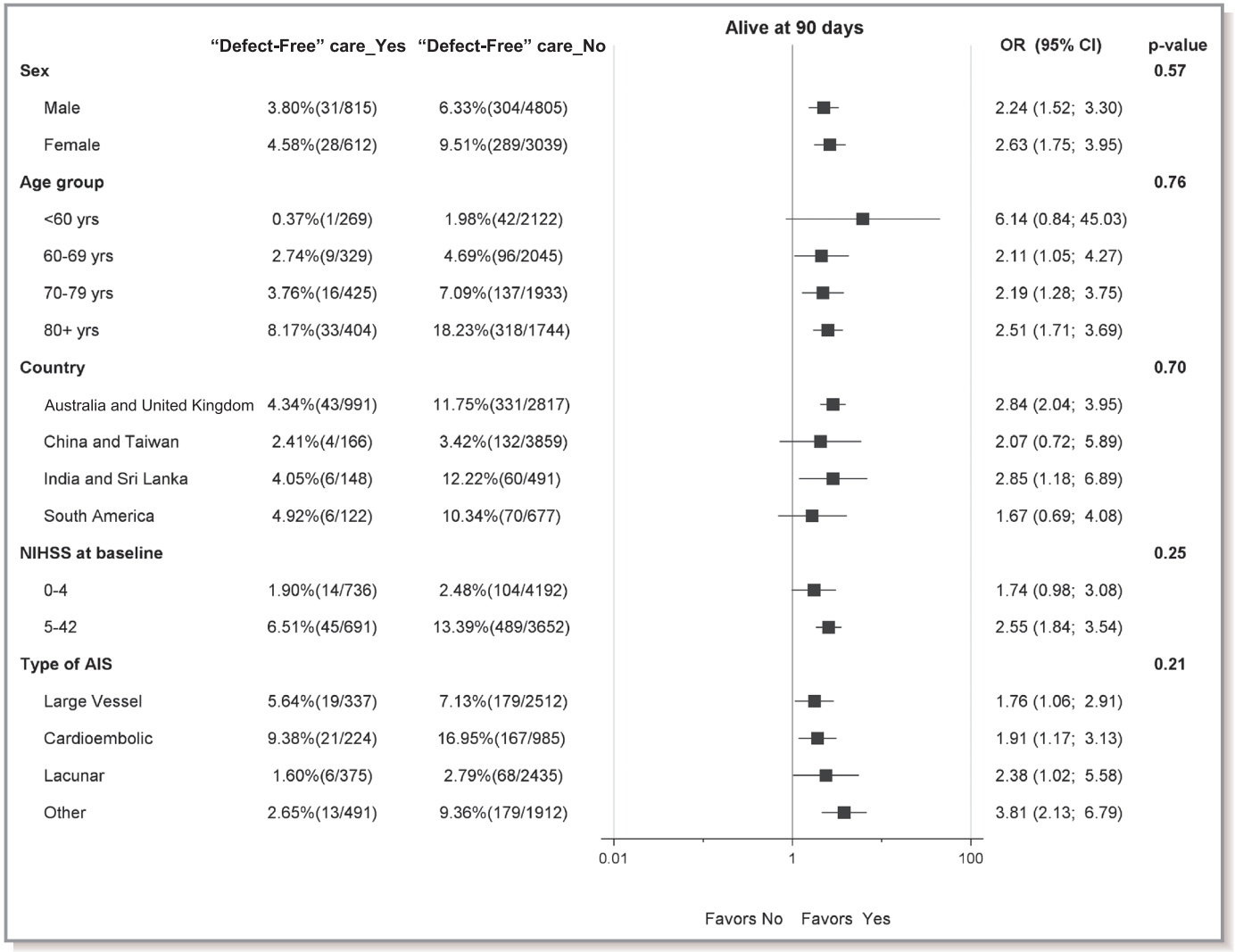

Figure 3. Impact in 90-day mortality of "defect-free" stroke care in different prespecified subgroups. AIS indicates acute ischemic stroke; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

hypertension.[24] Early commencement of antihypertensive therapy in patients with milder hypertension is subjected to more debate, although it appears to be safe and reasonable to improve long-term blood pressure control, unless contraindicated. Although we have shown that the initiation of anticoagulation and blood pressure lowering within 7 days was related to higher survival after AIS, there is the potential for this to reflect indication bias, whereby the treating clinician could have commenced the treatment earlier in those considered at low risk of complications and clinically stable.

Even after excluding the use of thrombolysis and thrombectomy, which can be more complex and dependent on specific time frames, and anticoagulation for AF, where early initiation is debatable, we have shown that defect-free treatment was only applied in approximately one fifth of patients from this international cohort, revealing an alarming gap in guideline-directed treatment. Direct comparison with other studies is limited by use of different criteria; however, an audit of UK hospitals revealed 46% of patients with AIS received good quality treatment in the first 72 hours.[19] The latter considered different quality criteria, including brain scan; early evaluation by stroke consultant or associate specialist, nurse, and therapists; swallow evaluation; admission to stroke unit; antiplatelet use; and fluid/nutrition. When individual processes of care are compared, results are similar to our findings on swallow assessment, ASU, and antiplatelets use.[19] In a recent report from INTERSTROKE (a case-control study of the global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries), use of thrombolysis, antiplatelets, and statins was lower in comparison to our results, and higher for blood pressure lowering.[12] Moreover, the authors showed that patients enrolled from hospitals in low- and

middle-income countries had poorer access to investigations, treatments, and services compared with those enrolled from hospitals in high-income countries. In line with our results, these patients had worse clinical outcomes, which could only be partly explained by the inclusion of patients with more severe stroke. These findings highlight the importance of widespread implementation of stroke processes of care, particularly across low-resource areas, where they are still scarce.

As stroke is a national priority in China, the central government has initiated a program of quality improvement strategies that include screening for high-risk individuals in the community, process-of-care performance measures, and organizational development to improve stroke care.[25] Multifaceted initiatives have been shown to improve adherence to performance measures in Chinese hospitals, but were not able to show significant change in the defect-free stroke care.[26] Accordingly, our data reemphasize the importance of quality improvement initiatives in China.

To our knowledge, this is the first study to assess the impact of using multiple evidence-based stroke care processes on clinical outcomes in a large multinational cohort of patients. HEADPOST was a clinical trial with broad inclusion criteria, allowing the participation of a wide range of patients; and the analyses herein presented were strengthened by the use of multilevel modeling to account for patient- and hospital-level variables. Inevitably, though, these secondary analyses of nonrandomized processes of care are limited by the potential for chance associations and residual confounding, as well as broad assumption of patient eligibility for different process of care. Interactions between different stroke care interventions were not explored, leading to possible risk of confounding by indication. Because the main study had 10% of missing primary outcome data in mRS score, the decision to use imputation for missing mRS scores is also to be acknowledged as a limitation of the study.

In summary, in this study, we have shown, among eligible patients with AIS, that those who received evidence-based processes of care had better outcomes, but the overall uptake of the suite of therapies was low across a multinational population. Strategies to facilitate implementation of evidence-based stroke care are needed, particularly in low-resource regions.

Appendix

HEADPOST (Head Positioning in Acute Stroke Trial) Study Group and Trial Investigators

Steering Committee: Gillian Mead (Chair), Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, United Kingdom; Maree Hackett (Principal Investigator), Craig S. Anderson (Co–Principal Investigator), and Laurent Billot, The George Institute for Global Health, Sydney, Australia; Pablo M. Lavados and Verónica V. Olavarría, Servicio de Neurología, Departamento de Neurología and Psiquiatría, Clínica Alemana de Santiago, Universidad del Desarrollo, Santiago, Chile; Sandy Middleton, St Vincent's Health Australia (Sydney) and Australian Catholic University, Sydney, Australia; Caroline L. Watkins, School of Health, Stroke Practice Research Unit, Lancashire Clinical Trials Unit, University of Central Lancashire, Preston, United Kingdom, and Australian Catholic University, Sydney, Australia; Thompson G. Robinson, Department of Cardiovascular Sciences, University of Leicester, British Heart Foundation Cardiovascular Research Centre, Leicester, United Kingdom; Hisatomi Arima (Co–Principal Investigator), Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, Fukuoka, Japan; H. Asita De Silva, Department of Pharmacology, Faculty of Medicine, University of Kelaniya, Colombo, Sri Lanka; Jeyaraj D. Pandian, Department of Neurology, Christian Medical College and Hospital, Ludhiana, India; Ruey-Tay Lin, Department of Neurology, Kaohsiung Medical University and Hospital, Kaohsiung, Taiwan; Tsong-Hai Lee, Department of Neurology, Linkou Chang Gung Memorial Hospital, Taipei, Taiwan; Liying Cui and Bin Peng, Peking Union Medical College Hospital, Beijing, China; and Octavio M. Pontes-Neto, Ribeirao Preto School of Medicine University of São Paulo, Ribeirão Preto, Brazil.

Advisory Committee: Stephane Heritier, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia; Richard Lindley and Stephen Jan, The George Institute for Global Health, Sydney, Australia; Elizabeth Boaden, College of Health and Wellbeing, School of Health Sciences, University of Central Lancashire, Preston, United Kingdom; and Alejandro Brunser, Departamento de Neurología y Psiquiatría, Clínica Alemana de Santiago, Universidad del Desarrollo, Santiago, Chile.

Data Safety Monitoring Board: Robert Herbert (Chair), Neuroscience Research Australia, University of New South Wales, Sydney, Australia; Christopher P. L. H. Chen, Department of Pharmacology, National University of Singapore, Singapore; and Anne Forster, Bradford Institute for Health Research, Bradford Royal Infirmary, Leeds, United Kingdom.

Statisticians: Laurent Billot, Mark Woodward, Kris Rogers, and Anish Scaria, The George Institute for Global Health, Sydney, Australia.

International Coordinating Center, The George Institute for Global Health, Sydney, Australia: *Project Management:* Joyce Y. Lim (Project Manager), Natalie Espinosa, Lucy McEvoy, Lee Blackburn, Sarah S. Richtering, Shoujiang You, Simon Ladwig, Gabrielle P. Merritt, and Bryce Thomsen; *Centralized Follow-Up:* Kerry Jenson, Penelope Gordon, Dennis Ryan Nguyen, Wei Wei Quan, Tessa Pei-Yi Lo, Jonathan Lim, and Selena Goh;

Data Management: Elizaveta Ivanova, Leibo Liu, Mirza Ahmad Baig, Ravider Singh, Paul Donnelly, and Manuela Armenis; *Contracts and Quality Assurance:* Marna Van Zyl, Helen Monaghan, Phillipa Smith, and Parisa Glass.

Regional Coordinating Centers: *China (The George Institute China Incorporating George Clinical):* Fanli Zhou, Yun Shen, Li Lei, Di Li, Ting Zhang; *Centralized Follow-Up:* Lili Song, Xiaoyan Zhang, Yun Peng, Lingling Feng, Zhiping Ye, and Philip Gregory. *India (Christian Medical College-Ludhiana):* Jeyaraj D. Pandain, and Deepti Arora. *South America (Clinica Alemana de Santiago, Universidad del Desarrollo):* Pablo M. Lavados, Paula Munoz-Venturelli, Francisca Gonzalez, Bernardita Portales, Octavio Pontes-Neto, Taiza Santos-Pontelli, Brunna Rimoli, and Monica Braga; *Centralized Follow-Up:* Lorena Hoffmeister, Carolina Vidal, Dafna Benadof, Rodrigo J. Rivas, Laura Carvallo, Pamela Carvallo, Rubia Miranda, and Brunna Pileggi. *Sri Lanka (RemediumOne Pvt Ltd):* H. Asita de Silva, Shalomi Weerawardena, Thanushanthan Jeevarajah, Devaki Dharmawardena, Dumindi Ranasinghe, and Matheesha Dharshana; *Centralized Follow-Up:* M. M. M. Shafras, Nilesh Nandadeva, and Savithri Nawarathna. *Taiwan (Kaohsiung Medical University Chung-Ho Memorial Hospital):* Ruey-Tay Lin, Tsong-Hai Lee, Jiu-Haw Yin, Shoou-Jeng Yeh, and Ruei-Jen Ma. *United Kingdom (Lancashire Clinical Trials Unit, University of Central Lancashire):* Caroline L. Watkins, Gemma Whiteley, Denise Forshaw, Catherine Elizabeth Lightbody, Joanna Cox, Jane Fitzgerald, John F. Heney, Helen Byfield, Simone Finley, and Hayley E. Tyrer; *Centralized Follow-Up:* Carole Bruce and Alison Gibbon.

Principal Investigators and Coordinators (according to country and center, with numbers of patients in parentheses): Australia (7 hospitals and 602 patients): *Calvary Public Hospital Bruce (179):* Brett Jones, Emma Siracusa, Koushik Gowda, Shahla Cowans, Briana Forman, Sherin Jacob, Kristine Caprecho, Roshan Khatri, Po Yi Wan, Maria Lopez, Sifiso Vanika, Wilhelmina Bleeker, and Marinka Ireland; *Royal North Shore Hospital (121):* Sheila Jala, Susan Day, Eric Ha, Martin Krause, Melissa Passer, and Sarah Giaccari; *Royal Prince Alfred Hospital (133):* Nadia Burkolter, Michael Braithwaite, and Kylie Tastula; *Concord Repatriation General Hospital (95): Fiona Stanley Hospital (39):* Darshan Ghia, Tapuwa Musuka, Anthony Alvaro, Gillian Edmonds, and Nicole O'Loughin, Rebecca Phair, and Joanne Kaoutal; *Sir Charles Gairdner Hospital (20):* David J. Blacker and Belinda L Saint; *Port Macquarie Base Hospital (15):* Kim Parrey, Michelle Coad, Matthew Kinchington, Nishantha Senanayake, Johanna Alaban, and Irma Kuehne. *Brazil (4 hospitals and 264 patients)*: *Hospital das Clinicas da Faculdade de Medicina de Ribeirao Preto, Universidade de Sao Paulo (147):* Taiza Santos-Pontelli, Monica Braga, Brunna Rimoli, Millene Camilo, and Milena Libardi; *Clinicas de Porta Alegre (52):* Sheila Martins, Batista Carlos, Magda Martins, Leonardo Carbonera, Andrea Almeida, and Martin Kelin; *Hospital Governador Celso Ramos (33):* Gladys Martins, Carla Pauli, Mariana Lunardi, Luciane Silveira, Olga Chagas, and Daily Souza; *Hospital de Faculdade de Medicina de Botucatu, UNESP (São Paulo State University) (32):* Rodrigo Bazan, Gabriel Braga, Priscila Ribeiro, Gustavo Luvizutto, Marcia Polin, and Fernanda Winckler. *China (39 hospitals and 4479 patients)*: *Yangquan Coalmine Group General Hospital (155):* Jinfeng Liu, Zhenjiang Wang, Huibing Wang, Suying Lin, and Jing Dong; *Nanjing First Hospital, Nanjing Medical University (150):* Junshan Zhou, Suping Qin, and Hui Zhan; *Dunhua City Hospital (144):* Yongquan Xue, Dong Tian, Dan Yang, Yan Yin, and He Li; *85 Hospital of People's Liberation Army (142):* Changming Geng, Jieyi Liu, Xiaolin Jiang, and Yujun Wu; *Third People's Hospital of Dalian (142):* Wei Sun; *Zhucheng Traditional Chinese Medicine Hospital (141):* Bingqi Yu, Yanmei Guan, Qin Wang, Bo Wei, Huirong Wang, and Yan Wang; *Hospital of Hebei Medical University (141):* Liwen Tai and Wenchao Zhang; *Affiliated Hospital of Chifeng University (141)*: Weili Zhao, Xueying Wang, Guoli Li, Zhiming Ni, Fudong Guo, Lan Cen, Jun Lu, Zheng Chen, Guoming Yin, Yingchun Wang, Jiping Zheng, Zhimin Zhou, and Hongquan Wang; *The Third Hospital of Wafangdian (140):* Renlin Zou, Bin Xue, Airu Li, Jing Guo, Ying Guo, and Xingguo Jiang; *Beijing Pinggu Hospital (140):* Xiuge Tan and Chunpeng Zhang; *The First Affiliated Hospital of Wenzhou Medical University (140):* Bei Shao and Xiaoting Niu; *The Second Affiliated Hospital of Soochow University (140):* Chunfeng Liu, Dongqin Chen, Ping Liang, Xia Zhang, Chunqing Zhang, Wenjie Gong, Zhichao Huang, Huihui Liu, Shoujiang You, Junying Huang, and Rongfang Shi; *Qilu Hospital of Shandong University (140):* Cuilan Wang and Ying Liu; *Yutian County Hospital (138):* Jinchao Wang, Guojun Wu, and Zhihong Gao; *The Yongjia County People's Hospital (138):* Qunli Lin, Cong Xu, Huile Zheng, Xinghai Ye, and Xiaoqiong Jin; *The Third Hospital of Hebei Medical University (133):* Junyan Liu, Xiaoyun Cao, Yan Zhang, Jinyang Wang, Yuzhu Xu, and Yan Li; *Xuanwu Hospital Capital Medical University (132):* Xin Ma and Qi Kong; *Affiliated Hospital of Jining Medical University (131):* Yanlei Hao, Baojun Qiao, and Hui Yan; *The Third People's Hospital of Huizhou (126):* Zhiyong Huang, Baoqiang Chang, Jinjin Yan, Pinjun Liao, and Wei Zhang; *The People's Hospital of Nanpi County (124):* Ling Liu, Tingting Zhu, Xuehui Liu, and Yongping Li; *The Second Cangzhou Central Hospital (121):* Ruifang Dong; *Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (121):* Miao Chen, Xiaoli Ge, Hairong Wang, Lihua Dai, and Jiafu Liu; *Baogang Hospital (120):* Shixia Wang, Jihui Du, and Aixiu Song; *Hospital Central South University (120):* Yunhai Li, Jie Feng, and Cheng Yu; *The First Affiliated Hospital of Harbin Medical University (117):* Honglin Feng, Xiaojia Sun, Ruihong Sun, Weisong Liu, and Jianfeng Liu; *People's Hospital of Hejian City (117): Tong Ren Hospital Shanghai Jiao Tong University School (117):* Xuesheng Lu and Enzhuo Chen;

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Gunatilake, Pamuditha M. W. Madanayake, Shiran A. Paranavitane, Bimsara Senanayake, Vaidhehi Vishwanathan, Maathury Sivapalan, Ruwangi U. 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SUPPLEMENTAL MATERIAL

Table S1. Distribution of the evidence-based interventions and model analysis results for ischemic stroke treatment based on mRS at 3 months including multiple imputation.

				Unadjusted		Model 3+MI	
Evidence-based interventions	mRS 0-2 (N=5112)	mRS 3-6 (N=3271)	Total (N=8383)	OR (95%CI)	P value	OR (95%CI)	P value
Reperfusion therapy (n=3093)	591 (34.2%)	460 (33.7%)	1051 (34.0%)	1.06 (0.91,1.25)	0.454	1.37 (1.13,1.67)	0.002
ASU admission	2633 (51.5%)	2090 (63.9%)	4723 (56.3%)	0.77 (0.65,0.91)	0.003	1.10 (0.88,1.38)	0.396
Antihypertensives	2771 (54.2%)	1954 (59.7%)	4725 (56.4%)	0.89 (0.81,0.98)	0.023	1.08 (0.95,1.23)	0.237
Antiplatelet therapy	4975 (97.3%)	3088 (94.4%)	8063 (96.2%)	1.98 (1.56,2.50)	<0.001	1.49 (1.12,1.99)	0.006
Statin therapy	4390 (85.9%)	2570 (78.6%)	6960 (83.0%)	1.64 (1.45,1.87)	<0.001	1.22 (1.05,1.42)	0.010
Anticoagulation in AF (n=1203)	259 (49.7%)	315 (46.2%)	574 (47.7%)	1.14 (0.89,1.45)	0.293		
Swallow assessment	3916 (76.6%)	2363 (72.2%)	6279 (74.9%)	1.47 (1.30,1.67)	<0.001	1.26 (1.08,1.46)	0.002
Physiotherapy in disabled patients (n=3073)	645 (72.5%)	1549 (71.0%)	2194 (71.4%)	1.20 (0.96,1.50)	0.102	1.41 (1.06,1.88)	0.018
Optimal stroke care	770 (15.1%)	459 (14.0%)	1229 (14.7%)	1.45 (1.26,1.67)	<0.001	1.36 (1.15,1.61)	<0.001
Optimal stroke care (without reperfusion/anticoagulation)	1146 (22.4%)	795 (24.3%)	1941 (23.2%)	1.21 (1.07,1.37)	0.002	1.25 (1.08,1.45)	0.004

mRS: modified Rankin scale, MI: multiple imputation, ASU: acute stroke unit, AF: atrial fibrillation

Table S2. Distribution of the evidence-based interventions and model analysis results for ischemic stroke treatment based on mortality at 3 months.

Evidence-based interventions	Alive (N=8619)	Dead (N=652)	Total (N=9271)	Unadjusted		Model 1		Model 2		Model 3	
				OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Reperfusion therapy (n=3509)	1110 (34.9%)	98 (29.7%)	1208 (34.4%)	1.27 (0.98,1.64)	0.069	1.05 (0.80,1.39)	0.711	1.69 (1.24,2.31)	<0.001	1.72 (1.26,2.35)	<0.001
ASU admission	4985 (57.8%)	469 (71.9%)	5454 (58.8%)	0.70 (0.53,0.93)	0.013	1.40 (0.98,2.00)	0.062	1.58 (1.11,2.25)	0.011	1.69 (1.17,2.43)	0.005
Antihypertensive therapy	4891 (56.7%)	376 (57.7%)	5267 (56.8%)	1.15 (0.97,1.36)	0.111	1.42 (1.18,1.70)	<0.001	1.38 (1.10,1.72)	0.004	1.38 (1.11,1.72)	0.004
Antiplatelet therapy	8342 (96.8%)	586 (89.9%)	8928 (96.3%)	3.06 (2.27,4.12)	<0.001	3.13 (2.29,4.29)	<0.001	1.99 (1.37,2.88)	<0.001	1.98 (1.37,2.87)	<0.001
Statin therapy	7255 (84.2%)	410 (62.9%)	7665 (82.7%)	3.17 (2.64,3.81)	<0.001	2.72 (2.24,3.30)	<0.001	2.11 (1.70,2.62)	<0.001	2.12 (1.70,2.64)	<0.001
Anticoagulation in AF (n=1354) †	560 (49.5%)	92 (41.3%)	652 (48.2%)	1.35 (1.00,1.83)	0.053	-		-	<0.001	-	<0.001
Swallow assessment	6582 (76.4%)	403 (61.8%)	6985 (75.3%)	2.39 (1.96,2.90)	<0.001	2.25 (1.84,2.74)	<0.001	1.92 (1.54,2.39)	<0.001	1.94 (1.55,2.42)	<0.001
Physiotherapy in disabled patients (n=3443)	2145 (74.2%)	391 (70.7%)	2536 (73.7%)	1.52 (1.18,1.95)	0.001	2.67 (1.98,3.60)	<0.001	2.29 (1.67,3.13)	<0.001	2.22 (1.60,3.07)	<0.001
Optimal stroke care	1368 (15.9%)	59 (9.0%)	1427 (15.4%)	2.43 (1.83,3.23)	<0.001	2.45 (1.83,3.27)	<0.001	2.16 (1.57,2.97)	<0.001	2.23 (1.62,3.09)	<0.001
Optimal stroke care (without reperfusion/ anticoagulation)	2137 (24.8%)	132 (20.2%)	2269 (24.5%)	1.83 (1.47,2.26)	<0.001	2.10 (1.68,2.62)	<0.001	1.88 (1.47,2.41)	<0.001	1.94 (1.51,2.49)	<0.001
Optimal stroke care (only survivors >7 days) (n=9153)	1368 (15.9%)	54 (10.1%)	1422 (15.5%)	2.09 (1.55,2.82)	<0.001	2.13 (1.57,2.89)	<0.001	1.92 (1.38,2.67)	<0.001	1.95 (1.40,2.73)	<0.001

ASU: acute stroke unit, AF: atrial fibrillation

Un-adjusted: hierarchical mixed logistic regression model, the link function is logit with fixed period, fixed head position effect, random cluster, and random cluster-period effects.

Model 1: Adjusted for country, prestroke mRS score, age and sex.

Model 2: Further adjusted for baseline NIHSS score, and previous history of stroke, heart disease, or diabetes, history of hypertension, and time from stroke onset to intervention.

Model 3: Further adjusted for # of stroke patients admitted annually, multi-discipline team available, academic hospital, local special pathway or service organization for stroke care, endovascular therapies available for stroke patients.

†Results not shown because the models did not converge based on low numbers.

Table S3. Evidence-based interventions for ischemic stroke treatment and optimal treatment stratified by region.

Evidence-based interventions	Australia and UK (N=3850)	China and Taiwan (N=4178)	India and Sri Lanka (N=658)	South America (N=799)	Total (N=9485)	P value
Reperfusion therapy	810 (37.7%)	215 (25.3%)	56 (29.9%)	142 (37.6%)	1223 (34.3%)	<0.001
ASU admission	3785 (98.3%)	855 (20.5%)	560 (85.1%)	336 (42.1%)	5536 (58.4%)	<0.001
Antihypertensives therapy	2661 (69.1%)	1788 (42.8%)	383 (58.2%)	533 (66.7%)	5365 (56.6%)	<0.001
Antiplatelet therapy	3681 (95.6%)	4041 (96.7%)	632 (96.0%)	777 (97.2%)	9131 (96.3%)	0.026
Statin therapy	2908 (75.5%)	3621 (86.7%)	561 (85.3%)	750 (93.9%)	7840 (82.7%)	<0.001
Anticoagulation in AF	457 (46.9%)	102 (37.4%)	28 (77.8%)	78 (84.8%)	665 (48.4%)	<0.001
Swallow assessment	3226 (83.8%)	2865 (68.6%)	438 (66.6%)	607 (76.0%)	7136 (75.2%)	<0.001
Physiotherapy in disabled patients	1718 (94.9%)	346 (34.1%)	207 (63.1%)	314 (83.5%)	2585 (73.3%)	<0.001
Optimal stroke care	1001 (26.0%)	171 (4.1%)	151 (22.9%)	122 (15.3%)	1445 (15.2%)	<0.001

ASU: acute stroke unit, AF: atrial fibrillation
P value from logistic regression model

Table S4. Patient outcome by hospital characteristics: uni and multivariable logistic regression adjusted for patient characteristics.

	Univariable analysis					Multivariable analysis				
Hospital characteristics	mRS 0-2 (N=5112)	mRS 3-6 (N=3271)	Total (N=8383)	OR (95%CI)	P value	mRS 0-2 (N=4931) †	mRS 3-6 (N=3068) †	Total (N=7999) †	OR (95%CI)	P value
Number of stroke patients admitted annually										
<500	1133 (22.6%)	887 (27.5%)	2020 (24.5%)			1100 (22.7%)	836 (27.6%)	1936 (24.6%)		
[500,1000]	1792 (35.7%)	1343 (41.6%)	3135 (38.0%)	1.10 (0.84,1.44)		1718 (35.5%)	1269 (42.0%)	2987 (38.0%)	0.96 (0.74,1.24)	
>1000	2092 (41.7%)	995 (30.9%)	3087 (37.5%)	1.87 (1.41,2.47)	<0.001	2019 (41.7%)	920 (30.4%)	2939 (37.4%)	1.12 (0.84,1.50)	0.421
Academic hospital	4461 (88.9%)	2737 (84.6%)	7198 (87.2%)	1.36 (0.98,1.88)	0.067	4321 (89.3%)	2563 (84.6%)	6884 (87.5%)	1.02 (0.77,1.36)	0.882
Local special pathway or service organisation for stroke care	4459 (88.8%)	2990 (92.5%)	7449 (90.2%)	0.76 (0.51,1.13)	0.176	4290 (88.7%)	2795 (92.2%)	7085 (90.0%)	1.19 (0.85,1.65)	0.316
Local protocols for fever/blood glucose/swallow dysfunction	3828 (76.3%)	2355 (72.8%)	6183 (74.9%)	1.22 (0.93,1.61))	0.149	3697 (76.4%)	2201 (72.6%)	5898 (74.9%)	1.04 (0.84,1.29)	0.703
Organized ED clinical pathway/checklist/protocols for evaluation	4790 (95.4%)	3029 (93.7%)	7819 (94.7%)	1.46 (0.89,2.38)	0.130	4621 (95.5%)	2853 (94.1%)	7474 (95.0%)	1.20 (0.78,1.83)	0.404
Availability of a local multidisciplinary team	2675 (53.3%)	2114 (65.4%)	4789 (58.0%)	0.60 (0.48,0.76)	<0.001	2571 (53.1%)	1980 (65.3%)	4551 (57.8%)	0.80 (0.62,1.05)	0.106
Endovascular therapies available for stroke patients	2955 (59.3%)	1774 (55.5%)	4729 (57.8%)	1.22 (0.95,1.55)	0.112	2869 (59.7%)	1671 (55.7%)	4540 (58.2%)	1.22 (0.95,1.55)	0.270

†: Only patients with all non-missing covariates
mRS: modified Rankin Scale, ED: emergency department
Univariable analysis: hierarchical mixed logistic regression model, the link function is logit, with fixed period, fixed head position effect, random cluster, and random cluster-period effects.
Multivariable analysis: Adjusted for age, sex, previous history of stroke, heart disease, or diabetes, history of hypertension, prestroke mRS score, baseline NIHSS score, time from stroke onset to intervention and country.