Guideline-recommended care processes in acute stroke

Author:
Ouyang, Menglu

GUIDELINE-RECOMMENDED

CARE PROCESSES IN ACUTE

STROKE

Menglu Ouyang

A thesis in fulfilment of the requirements for the degree of

Doctor of Philosophy (Medicine)

The George Institute for Global Health

Faculty of Medicine

University of New South Wales

September 2021

Thesis/Dissertation Sheet

Surname/Family Name	:	**OUYANG**
Given Name/s	:	**MENGLU**
Abbreviation for degree as give in the University calendar	:	**PhD**
Faculty	:	**Medicine**
School	:	**The George Institute**
Thesis Title	:	**Guideline-recommended care processes in acute stroke**

Abstract

Introduction

Although clinical guidelines recommend various care processes to improve outcomes of patients with stroke, evidence to support many of them, such as the management of post-stroke infections and the monitoring of abnormal physiological variables, are scarce. While for those care processes with more evidence, very few studies have quantified their variations across regions and what factors influence their implementation in clinical practice. This thesis aims to determine the utilisation of guideline-recommended care processes for patients with acute stroke, and explore various strategies that may improve their implementation.

Methods

I conducted secondary analyses of a large clinical trial to explore the associations of care processes and clinical outcomes, using data of 11,093 patients with acute stroke from nine countries. These care processes included dysphagia screening, indwelling urinary catheterisation (IUC), and early detection of low blood pressure (BP) and oxygen saturation (SaO_2) levels. To explore variations in the utilisation of care processes, I compared the evidence-based recommendations for stroke unit care across Australia/UK, China, India/Sri Lanka and South America. I also conducted a process evaluation of a 'quality improvement' intervention within an ongoing trial involving the management of patients with acute intracerebral haemorrhage in China, to explore what factors could improve the implementation of systems to improve the quality of care.

Results

Patients who failed a dysphagia screen, had an IUC, had SBP <120mmHg or SaO_2 <93% during the acute phase (up to 7 days after stroke onset) had increased odds of poor outcome. The utilisation of care processes varied across regions, with lower probabilities of reperfusion therapy and allied health care in low- and middle-income countries (LMICs) than high-income countries. Constant training with the clinicians, case reviews, optimisation of workflow within available

2

resources, and having a dedicated team, may facilitate the implementation of evidence-based care.

Conclusions

The utilisations of guideline-recommended care processes are associated with patient outcomes and vary across regions. Timely assessment and appropriate management should be provided to those with dysphagia, IUC, low BP, and low SaO_2 levels, in an effort to improve their recovery after stroke. Future studies are needed to confirm the causality of these associations and to examine opportunities to promote the delivery of evidence-based stroke care, especially in LMICs.

Declaration relating to disposition of project thesis/dissertation

I hereby grant to the University of New South Wales or its agents a non-exclusive licence to archive and to make available (including to members of the public) my thesis or dissertation in whole or in part in the University libraries in all forms of media, now or here after known. I acknowledge that I retain all intellectual property rights which subsist in my thesis or dissertation, such as copyright and patent rights, subject to applicable law. I also retain the right to use all or part of my thesis or dissertation in future works (such as articles or books).

Menglu Ouyang   05/09/2021

…………………………………………   …….…………………...……

              Signature   Date

The University recognises that there may be exceptional circumstances requiring restrictions on copying or conditions on use. Requests for restriction for a period of up to 2 years can be made when submitting the final copies of your thesis to the UNSW Library. Requests for a longer period of restriction may be considered in exceptional circumstances and require the approval of the Dean of Graduate Research.

Table of content

Acknowledgement

I would like to express my sincere gratitude to my supervisor Professor Craig Anderson for giving me the continuous support and valuable guidance of my PhD study and research, for his patience, inspiration, and immense knowledge. I appreciate the time and effort he put aside not only to discuss my doctoral research but all the opportunities I were given to further my research career.

I would like to thank my associate supervisor Laurent Billot and Dr Lili Song, for their wealthy knowledge and great insights to support my PhD study from the very beginning. I also thank Dr Xia Wang and Dr Hueiming Liu, who joined my supervisor committee in my second year, for their close guidance, encouragement, and insightful comments to bring my work to a higher level.

My sincere thanks extend to all my colleagues and friends at The George. I am eternally grateful for their support and friendship. I want to thank Yakubu for sharing his thoughts to improve my work on this thesis. I would like to acknowledge the investigators, coordinators and project staff, for the HeadPoST and INTERACT3 studies, for their outstanding contribution; and all the patients and their families for their time and untiring willingness to participate in these studies.

Furthermore, I wish to send my thanks to all co-authors on the papers who contributed insightful reviews and made it possible for timely submissions and publications in high impact journals.

I thank my loving family for their unwavering support of my desire to pursue a career in clinical research. Especially to my parents and grandparents for their emotional support when I needed it most. Finally, to Shuhao, for your love, patience, encouragement and understanding.

Originality Statement

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at UNSW or any other educational institution, except where due acknowledgement is made in the thesis. Any contribution made to the research by others, with whom I have worked at UNSW or elsewhere, is explicitly acknowledged in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.

Menglu Ouyang

6 September 2021

Copyright and Authenticity Statements

Copyright Statement

I hereby grant the University of New South Wales or its agents a non-exclusive licence to archive and to make available (including to members of the public) my thesis or dissertation in whole or part in the University libraries in all forms of media, now or here after known. I acknowledge that I retain all intellectual property rights which subsist in my thesis or dissertation, such as copyright and patent rights, subject to applicable law. I also retain the right to use all or part of my thesis or dissertation in future works (such as articles or books).

For any substantial portions of copyright material used in this thesis, written permission for use has been obtained, or the copyright material is removed from the final, public version of the thesis.

Authenticity Statement

I certify that the Library deposit digital copy is a direct equivalent of the final officially approved version of my thesis.

Menglu Ouyang

6 September 2021

Inclusion of Publications Statement

UNSW is supportive of candidates publishing their research results during their candidature as detailed in the UNSW Thesis Examination Procedure.

Publications can be used in their thesis in lieu of a Chapter if:
- The student contributed greater than 50% of the content in the publication and is the "primary author", ie. the student was responsible primarily for the planning, execution and preparation of the work for publication
- The student has approval to include the publication in their thesis in lieu of a Chapter from their supervisor and Postgraduate Coordinator.
- The publication is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in the thesis

Please indicate whether this thesis contains published material or not.

☐ *This thesis contains no publications, either published or submitted for publication (if this box is checked, you may delete all the material on page 2)*

☐ *Some of the work described in this thesis has been published and it has been documented in the relevant Chapters with acknowledgement (if this box is checked, you may delete all the material on page 2)*

☒ *This thesis has publications (either published or submitted for publication) incorporated into it in lieu of a chapter and the details are presented below*

CANDIDATE'S DECLARATION		
I declare that: • I have complied with the Thesis Examination Procedure • where I have used a publication in lieu of a Chapter, the listed publication(s) below meet(s) the requirements to be included in the thesis.		
Name **Menglu Ouyang**	**Signature**	**Date (dd/mm/yy)** **26/08/2021**

Postgraduate Coordinator's Declaration (to be filled in where publications are used in lieu of Chapters)		
I declare that: • the information below is accurate • where listed publication(s) have been used in lieu of Chapter(s), their use complies with the Thesis Examination Procedure • the minimum requirements for the format of the thesis have been met.		
PGC's Name **Maree Hackett**	**PGC's Signature**	**Date (dd/mm/yy)** 06/09/2021

For each publication incorporated into the thesis in lieu of a Chapter, provide all of the requested details and signatures required

---

Details of publication #1:
Full title: **Dysphagia screening and risks of pneumonia and adverse outcomes after acute stroke: an international multicentre study**
Authors: **Menglu Ouyang**, Elizabeth Bowden, Hisatomi Arima, Pablo M. Lavados, Laurent Billot, Maree L. Hackett, Verónica V. Olavarría, Paula Muñoz-Venturelli MD PhD, Lili Song, Kris Rogers, Sandy Middleton, Octavio M. Pontes-Neto, Tsong-Hai Lee, Caroline Watkins, Thompson Robinson and Craig S. Anderson
Journal or book name: International Journal of Stroke
Volume/page numbers: 15 (2): 206-215
Date published:21 June 2019

Status	*Published*	**X**	*Accepted and In press*		*In progress (submitted)*	

The Candidate's Contribution to the Work
I co-designed the study, analysed and interpreted the data, wrote the first draft of the manuscript, co-ordinating and incorporating co-authors' edits and preparing and submitted the manuscript, drafted the responses to the editor's and reviewers' comments, and prepared the final draft of the manuscript for publication.

Location of the work in the thesis and/or how the work is incorporated in the thesis:
Chapter 2.1 of my thesis

Primary Supervisor's Declaration
I declare that:
• the information above is accurate
• this has been discussed with the PGC and it is agreed that this publication can be included in this thesis in lieu of a Chapter
• All of the co-authors of the publication have reviewed the above information and have agreed to its veracity by signing a 'Co-Author Authorisation' form.

Supervisor's name **Craig Anderson**	*Supervisor's signature*	*Date (dd/mm/yy)* **01/09/2021**

Details of publication #2:
Full title: **Prognostic significance of early urinary catheterization after acute stroke: secondary analyses of the international HeadPoST trial**
Authors: **Menglu Ouyang,** Laurent Billot, Lili Song, Xia Wang, Christine Roffe, Hisatomi Arima, Pablo M. Lavados, Maree L. Hackett, Verónica V. Olavarría, Paula Muñoz-Venturelli, Sandy Middleton, Octavio M. Pontes-Neto, Tsong-Hai Lee, Caroline L. Watkins, Thompson Robinson, Craig S. Anderson
Journal or book name: International Journal of Stroke
Volume/page numbers: 16 (2): 200-206
Date published: 19 February 2020

Status	*Published*	**X**	*Accepted and In press*		*In progress (submitted)*	

The Candidate's Contribution to the Work
I co-designed the study, analysed and interpreted the data, wrote the first draft of the manuscript, co-ordinating and incorporating co-authors' edits and preparing and submitted

the manuscript, drafted the responses to the editor's and reviewers' comments, and prepared the final draft of the manuscript for publication.

Location of the work in the thesis and/or how the work is incorporated in the thesis:
Chapter 2.2 of my thesis

Primary Supervisor's Declaration

I declare that:
- the information above is accurate
- this has been discussed with the PGC and it is agreed that this publication can be included in this thesis in lieu of a Chapter
- All of the co-authors of the publication have reviewed the above information and have agreed to its veracity by signing a 'Co-Author Authorisation' form.

Supervisor's name	Supervisor's signature	Date (dd/mm/yy)
Craig Anderson		**01/09/2021**

Details of publication #3:

Full title: **Low blood pressure and adverse outcomes in acute stroke: HeadPoST study explanations**

Authors: **Menglu Ouyang**, Paula Muñoz Venturelli, Laurent Billot, Xia Wang, Lili Song, Hisatomi Arima, Pablo M. Lavados, Maree L. Hackett, Verónica V. Olavarría, Alejandro Brunser, Sandy Middleton, Octavio M. Pontes-Neto, Tsong-Hai Lee, Caroline L. Watkins, Thompson Robinson, Craig S. Anderson

Journal or book name: Journal of Hypertension

Volume/page numbers: 39(2): 273-279

Date published: 15 February 2021

Status	Published		Accepted and In press	X	In progress (submitted)	

The Candidate's Contribution to the Work

I co-designed the study, analysed and interpreted the data, wrote the first draft of the manuscript, co-ordinating and incorporating co-authors' edits and preparing and submitted the manuscript, drafted the responses to the editor's and reviewers' comments, and prepared the final draft of the manuscript for publication.

Location of the work in the thesis and/or how the work is incorporated in the thesis:
Chapter 3.1 of my thesis

Primary Supervisor's Declaration

I declare that:
- the information above is accurate
- this has been discussed with the PGC and it is agreed that this publication can be included in this thesis in lieu of a Chapter
- All of the co-authors of the publication have reviewed the above information and have agreed to its veracity by signing a 'Co-Author Authorisation' form.

Supervisor's name	Supervisor's signature	Date (dd/mm/yy)
Craig Anderson		**01/09/2021**

Details of publication #4:

Full title: **Oxygen desaturation and adverse outcomes in acute stroke: secondary analysis of the HeadPoST study**

Authors: **Menglu Ouyang**, Christine Roffe, Laurent Billot, Lili Song, Xia Wang, Paula Muñoz Venturelli, Pablo M. Lavados, Thompson Robinson, Sandy Middleton, Verónica V. Olavarría, Caroline L. Watkins, Tsong-Hai Lee, Alejandro M Brunser, Octavio M. Pontes-

Neto, Maree L. Hackett, Craig S. Anderson
Journal or book name: Clinical Neurology and Neurosurgery
Volume/page numbers: 207: 106796
Date accepted/ published: 3 July 2021

Status	Published	X	Accepted and In press		In progress (submitted)	

The Candidate's Contribution to the Work
I co-designed the study, analysed and interpreted the data, wrote the first draft of the manuscript, co-ordinating and incorporating co-authors' edits and preparing and submitted the manuscript, drafted the responses to the editor's and reviewers' comments, and prepared the final draft of the manuscript for publication.

Location of the work in the thesis and/or how the work is incorporated in the thesis:
Chapter 3.2 of my thesis

Primary Supervisor's Declaration
I declare that:
- the information above is accurate
- this has been discussed with the PGC and it is agreed that this publication can be included in this thesis in lieu of a Chapter
- All of the co-authors of the publication have reviewed the above information and have agreed to its veracity by signing a 'Co-Author Authorisation' form.

Supervisor's name	*Supervisor's signature*	*Date (dd/mm/yy)*
Craig Anderson		**01/09/2021**

Details of publication #5:
Full title: **Quantifying regional variations in components of acute stroke unit (ASU) care in the international HeadPoST study**
Authors: **Menglu Ouyang**, Yao Zhang, Xia Wang, Lili Song, Laurent Billot, Thompson Robinson, Pablo M. Lavados, Hisatomi Arima, Maree L. Hackett, Verónica V. Olavarría, Paula Muñoz-Venturelli, Sandy Middleton, Caroline L. Watkins, Octavio M. Pontes-Neto, Tsong-Hai Lee, Alejandro M. Brunser, Craig S. Anderson
Journal or book name: Journal of Neurological Sciences
Volume/page numbers: 419 (2020): 117187
Date published: 14 October 2020

Status	Published	X	Accepted and In press		In progress (submitted)	

The Candidate's Contribution to the Work
I designed this study, analysed and interpreted the data, wrote the first draft of the manuscript, co-ordinating and incorporating co-authors' edits and preparing and submitted the manuscript, drafted the responses to the editor's and reviewers' comments, and prepared the final draft of the manuscript for publication.

Location of the work in the thesis and/or how the work is incorporated in the thesis:
Chapter 4 of my thesis

Primary Supervisor's Declaration
I declare that:
- the information above is accurate
- this has been discussed with the PGC and it is agreed that this publication can be included in this thesis in lieu of a Chapter
- All of the co-authors of the publication have reviewed the above information and have agreed to its veracity by signing a 'Co-Author Authorisation' form.

Supervisor's name	Supervisor's signature	Date (dd/mm/yy)
Craig Anderson		**01/09/2021**

Details of publication #6:
Full title: **Implementation of a goal-directed care bundle for intracerebral haemorrhage management in China: process evaluation in the INTERACT3 trial**   _Authors:_ **Menglu Ouyang,** Craig S. Anderson, Lili Song, Stephen Jan, Lingli Sun, Guojuan Cheng, Honglin Chu, Xin Hu, Lu Ma, Xiaoying Chen, Chao You, Hueiming Liu   _Journal:_ _Cerebrovascular Diseases_

Status	_Published_		_Accepted and In press_		_In progress (submitted)_	_X_

The Candidate's Contribution to the Work
I co-designed the study, analysed the data, wrote the first draft of the manuscript, co-ordinating and incorporating co-authors' edits and preparing and submitted the manuscript.

Location of the work in the thesis and/or how the work is incorporated in the thesis:
Chapter 5.2 of my thesis

Primary Supervisor's Declaration
I declare that: • the information above is accurate   • this has been discussed with the PGC and it is agreed that this publication can be included in this thesis in lieu of a Chapter   • All of the co-authors of the publication have reviewed the above information and have agreed to its veracity by signing a 'Co-Author Authorisation' form.

Supervisor's name	Supervisor's signature	Date (dd/mm/yy)
Craig Anderson		**01/09/2021**

Abbreviations

AIS	Acute ischaemic stroke
AF	Atrial fibrillation
AHA	American Heart Association
AIC	Aikaike information classification
aOR	Adjusted odds ratio
ASA	American Stroke Association
ASD	Absolute standardised difference
ASU	Acute stroke unit
AU	Australia
AVERT	A Very Early Rehabilitation Trial
BGL	Blood glucose level
BI	Barthel index
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COREQ	Consolidated criteria for reporting qualitative research
CRA	Clinical research associate
CRFs	Case report forms
DALYs	Disability-adjusted life years
DBP	Diastolic blood pressure
DC	Decompressive craniotomy
DCI	Delayed cerebral ischaemia
DM	Diabetes mellitus
DVT	Deep vein thrombosis
ED	Emergency department
EQ-5D	5-Dimension European Quality of life scale
EQ-5D-5L	5-Dimension European Quality of life scale with 5 levels of grading
EQ-VAS	European Quality of life scale and a vertical visual analogue scale
ESO	European Stroke Organisation
EVT	Endovascular treatment

FCS	Fully conditional method
FFP	Fresh frozen plasma
FOOD	Feed or Ordinary Food Collaboration Trial
GCS	Glasgow coma scale
GLM	Generalized linear mixed
HeadPoST	Head Positioning in Acute Stroke Trial
HDL-C	High-density lipoprotein cholesterol
HICs	High-income countries
HOQ	Hospital organisation questionnaire
HRQoL	Health-related quality of life
ICH	Intracerebral haemorrhage
ICP	Intracranial pressure
ICU	Intensive care unit
INCH	International Normalized ratio (INR) normalisation in Coumadin associated intracerebral Haemorrhage trial
INTERACT-2	Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage
INTERACT3	INTEnsive care bundle with blood pressure Reduction in Acute Cerebral haemorrhage Trial
INR	International normalised ratio
IQR	Interquartile range
IUC	Indwelling urinary catheterisation
IVT	Intravenous thrombolysis
LDL-C	Low-dose density lipoprotein cholesterol
LMICs	Low- and middle-income countries
LR	Likelihood ratio
LVO	Large vessel occlusion
MISTE-III	Minimally Invasive Surgery Plus Rt-PA for ICH Evacuation Phase III
MMSE	Mini-mental state examination
MR CLEAN	The Multicenter Randomised Clinical trial of Endovascular treatment for Acute ischaemic stroke in the Netherlands
MoCA	Montreal cognitive assessment
MRC	Medical Research Council
NIHSS	National Institute of Health stroke scale
NOAC	New oral anticoagulant agent

NPT	Normalisation process theory
mRS	modified Rankin scale
OACs	Oral anticoagulant agents
OR	Odds ratio
PCCs	Prothrombin complex concentrates
PE	Process evaluation
PEG	Percutaneous endoscopic gastrostomy
PHQ-9	9 item patient health questionnaire
PI	Principal investigator
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
QASC	Quality in Acute Stroke Care Trial
QoL	Quality of life
RAF	Early Recurrence and Cerebral Bleeding in Patients With Acute Ischaemic Stroke and Atrial Fibrillation
RCT	Randomised controlled trial
RR	Relative risk
rtPA	recombinant tissue plasminogen activator
SAEs	Serious adverse events
SAH	Subarachnoid haemorrhage
SaO_2	Arterial oxygen saturation
SBP	Systolic blood pressure
SD	Standard difference
SES	Socio-economics status
sICH	Symptomatic intracranial haemorrhage
STICH-II	Surgical Trial in Lobar Intracerebral Haemorrhage phase II
Sub-PI	Sub-principal investigator
TIA	Transient ischaemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
UK	United Kingdom
UTI	Urinary tract infection
VERSE	Very Early Rehabilitation for Speech Trial
VKA	Vitamin K anticoagulant
WHO	World Health Organisation

List of Tables

Section 2.2

List of Figures

unit (ASU) admission

Chapter 5

Section 5.1

Publication arising as first authors

1. **Menglu Ouyang**, Elizabeth Bowden, Hisatomi Arima, Pablo M. Lavados, Laurent Billot, Maree L. Hackett, Verónica V. Olavarría, Paula Muñoz-Venturelli, Lili Song, Kris Rogers, Sandy Middleton, Octavio M. Pontes-Neto, Tsong-Hai Lee, Caroline L. Watkins, Thompson Robinson, Craig S. Anderson, for the HeadPoST Investigators. Dysphagia screening and risks of pneumonia and adverse outcomes after acute stroke: An international multicenter study. *International Journal of Stroke*. 2020 Feb; 15(2): 206-215. doi: 10.1177/1747493019858778. Epub 2019 Jun 21. PMID: 31226922.

2. **Menglu Ouyang**, Laurent Billot, Lili Song, Xia Wang, Christine Roffe, Hisatomi Arima, Pablo M. Lavados, Maree L. Hackett, Verónica V. Olavarría, Paula Muñoz-Venturelli, Sandy Middleton, Octavio M. Pontes-Neto, Tsong-Hai Lee, Caroline L. Watkins, Thompson Robinson, Craig S. Anderson, for the HeadPoST Investigators. Prognostic significance of early urinary catheterization after acute stroke: Secondary analyses of the international HeadPoST trial. *International Journal of Stroke* 2021 Feb; 16(2): 200-206. doi: 10.1177/1747493020908140. Epub 2020 Feb 19. PMID: 32075569.

3. **Menglu Ouyang**, Yao Zhang, Xia Wang, Lili Song, Laurent Billot, Thompson Robinson, Pablo M. Lavados, Hisatomi Arima, Maree L. Hackett, Verónica V. Olavarría, Paula Muñoz-Venturelli, Sandy Middleton, Caroline L. Watkins, Octavio M. Pontes-Neto, Tsong-Hai Lee, Alejandro M. Brunser, Craig S. Anderson, for the HeadPoST Investigators. Quantifying regional variations in components of acute stroke unit (ASU) care in the international HeadPoST study. *Journal of the Neurological Sciences* 2020 Dec 15; 419: 117187. doi: 10.1016/j.jns.2020.117187. Epub 2020 Oct 14. PMID: 33075592.

4. **Menglu Ouyang**, Paula Muñoz-Venturelli, Laurent Billot, Xia Wang, Lili Song, Hisatomi Arima, Pablo M. Lavados, Maree L. Hackett, Verónica V. Olavarría, Alejandro Brunser, Sandy Middleton, Octavio M. Pontes-Neto, Tsong-Hai Lee, Caroline L. Watkins, Thompson Robinson, Craig S. Anderson, for the HeadPoST Investigators. Low blood pressure and adverse outcomes in acute stroke HeadPoST study explanations. *Journal of Hypertension* 2021 Feb 1; 39(2): 273-279. doi: 10.1097/HJH.0000000000002649. PMID: 32897905.

5. **Menglu Ouyang**, Christine Roffe, Laurent Billot, Lili Song, Xia Wang, Laurent Billot, Paula Muñoz-Venturelli, Pablo M. Lavados, Thompson Robinson, Sandy Middleton, Verónica V. Olavarría, Caroline L. Watkins, Tsong-Hai Lee, Alejandro M. Brunser, Octavio M. Pontes-Neto, Maree L. Hackett, Craig S. Anderson, for the HeadPoST Investigators. Oxyen desaturation and adverse outcomes in acute stroke: secondary analysis of the HeadPoST study. *Clinical Neurology and Neurosurgery* 2021 Aug; 207: 106796. doi: 10.1016/j.clineuro.2021.106796. Epub 2021 Jul 6. PMID: 34246993.

6. **Menglu Ouyang,** Craig S. Anderson, Lili Song, Stephen Jan, Lingli Sun, Guojuan Cheng, Honglin Chu, Xin Hu, Lu Ma, Xiaoying Chen, Chao You, Hueiming Liu. Implementing a goal-directed care bundle after acute intracerebral haemorrhage: process

evaluation for INTERACT3 study in China. *Cerebrovascular Diseases* (forthcoming). Accepted by 3 November 2021.

Other publications undertaken during the course of the thesis

1. Alenjandro M. Brunser, **Menglu Ouyang,** Hisatomi Arima*,* Pablo M. Lavados, Thompson Robinson, Paula Muñoz-Venturelli, Verónica V. Olavarría, Laurent Billot, Maree L. Hackett, Lili Song, Sandy Middleton, Octavio M. Pontes-Neto, Tsong-Hai Lee, Caroline L. Watkins, Craig S. Anderson. No benefit of flat head positioning in early moderate–severe acute ischaemic stroke: a HeadPoST study subgroup analysis. *Stroke and Vascular Neurology* 2020 Dec; 5(4): 406-409. doi: 10.1136/svn-2020-000387. Epub 2020 Jun 25. PMID: 32591406.

2. Lili Song, **Menglu Ouyang**, Lingli Sun, Chen Chen, Craig S. Anderson. Impact of COVID-19 on Patient Behavior to Stroke Symptoms in China. *Cerebrovascular Diseases* 2020; 49(5): 570-571. doi: 10.1159/000511394. Epub 2020 Oct 8. PMID: 33032275.

3. Xia Wang*, **Menglu Ouyang*,** Cheryl Carcel, Chen Chen, Lingli Sun, Jie Yang, Yao Zhang, Guofang Chen, Shoujiang You, Yongjun Cao, Lu Ma, Xin Hu, Yi Sui, Craig S. Anderson, Lili Song, Yongjun Wang, David Wang. Impact of COVID-2019 on stroke services in China: survey from the Chinese Stroke Association. *Stroke & Vascular Neurology* 2020 Dec; 5(4): 323-330. doi:10.1136/svn-2020- 000514. Epub 2020 Sep 28. PMID: 32989012. (*contributed equally)

4. Lili Song, Xia Wang, **Menglu Ouyang**, Lingli Sun, Xiaoying Chen, Hisatomi Arima, Else C. Sandset, Candice Delcourt, Jiguang Wang, Guofang Chen, Thompson Robinson, Richard I. Lindley, John Chalmers, Craig S. Anderson. Associations of an abnormal physiological score with outcomes in acute intracerebral haemorrhage. *Stroke* 2021 Jan; 52(2): 722-725. doi:10.1161/STROKEAHA.120.030435. Epub 2021 Jan 11. PMID: 33423518.

5. Xia Wang, Tom J. Moullaali, **Menglu Ouyang**, Laurent Billot, Else C. Sandset, Lili Song, Candice Delcourt, Maree L. Hackett, Caroline L. Watkins, Thompson G Robinson, Jie Yang, Pablo M. Lavados, Alejandro Brunser, Verónica V. Olavarría, Paula Muñoz-Venturelli, Hisatomi Arima*,* Sandy Middleton, Octavio M. Pontes-Neto, Jeyaraj Durai Pandian, Kris Rogers, Craig S. Anderson. Influence of including patients with premorbid disability in acute stroke trials: the HeadPoST experience. *Cerebrovascular Diseases* 2021 Jan 12:1-10. doi: 10.1159/000512608. Epub ahead of print. PMID: 33434907.

6. Chen Chen, Xia Wang, Xiaoying Chen, **Menglu Ouyang**, Lingli Sun, Hisatomi Arima, Thompson Robinson, Richard I. Lindley, John Chalmers, Gang Li, Lili Song, Craig S. Anderson for the ENCHANTED investigators. Disparities between Asian and non-Asian thrombolyzed acute ischemic stroke patients in the ENCHANTED trial. *Cerebrovascular Diseases* 2021 Jun 21: 1-7. doi: 10.1159/000516487. Epub ahead of print. PMID: 34153968.

7. Ke Peng, Lin Zhou, Xiaoying Liu, **Menglu Ouyang**, Jessica Gong, Yuanyuan Wang, Yu Shi, Jiani Chan, Yichong Li, Mingfan Sun, Yueyun Wang, Wei Lin, Shixin Yuan, Bo Wu, Lei Si. Who is the main caregiver of the mother during the doing-the-month: is there an association with postpartum depression? *BMC Psychiatry* 2021 May 25; 21(1): 270. doi: 10.1186/s12888-021-03203-4. PMID: 34034695.

8. Lili Song, Xin Hu, Lu Ma, Xiaoying Chen, **Menglu Ouyang**, Laurent Billot, Qiang Li, Paula Muñoz-Venturelli, Carlos Abanto, Octavio M. Pontes-Neto, Arauz Antonio, Mohammad Wasay, Asita de Silva, Nguyen Huy Thang, Jeyaraj D. Pandian, Kolawole W. Wahab, Chao You, Craig S. Anderson. *Trials* (forthcoming). Accepted by 8 Oct 2021.

Oral presentations and posters arising from this thesis

Presentations

1. **Menglu Ouyang,** Christine Roffe, Laurent Billot, Lili Song, Xia Wang, Laurent Billot, Paula Muñoz-Venturelli, Pablo M. Lavados, Thompson Robinson, Sandy Middleton, Verónica V. Olavarría, Caroline L. Watkins, Tsong-Hai Lee, Alejandro M. Brunser, Octavio M. Pontes-Neto, Maree L. Hackett, Craig S. Anderson, for the HeadPoST Investigators. Oxygen desaturation and adverse outcomes in acute stroke: secondary analysis of the HeadPoST study. *Stroke Society of Australiasia Virtual Conference 2021*, 14 October 2021.

2. **Menglu Ouyang**, Paula Muñoz Venturelli, Xia Wang, Laurent Billot, Lili Song, Hisatomi Arima, Pablo Lavados, Verónica V Olavarría, Alejandro M. Brunser, Thompson G Robinson, Maree L Hackett, Sandy Middleton, Octavio Pontes-Neto, Tsong-Hai Lee, Caroline Watkins, Craig S. Anderson. Low presenting blood pressure and adverse clinical outcome in acute stroke: secondary analysis of the international HeadPoST trial. *The Joint European Stroke Organisation and World Stroke Organisation Virtual Conference 2020*, 7-9 November 2020.

3. **Menglu Ouyang**, Elizabeth Boaden, Hisatomi Arima, Laurent Billot, Maree L. Hackett, Pablo M. Lavados, Verónica V. Olavarría, Paula Muñoz-Venturelli, Lili Song, Kris Rogers, Sandy Middleton, Octavio M. Pontes-Neto, Tsong-Hai Lee, Caroline Watkins, Thompson Robinson, Craig S. Anderson for the HeadPoST Investigators. Dysphagia screening and risks of pneumonia and adverse outcomes in acute stroke. *European Stroke Organisation Conference*, 22-24 May 2019, Milan, Italy.

4. **Menglu Ouyang**, Laurent Billot, Lili Song, Maree L. Hackett, Paula Muñoz-Venturelli, Pablo M. Lavados, Verónica V. Olavarría, Sandy Middleton, Octavio M. Pontes-Neto, Tsong-Hai Lee, Caroline Watkins, Thompson Robinson, Craig S. Anderson for the HeadPoST Investigators. Urinary catheterisation and clinical catheterisation and clinical outcomes in acute stroke patients: an international multicentre study. *European Stroke Organisation Conference*, 22-24 May 2019, Milan, Italy.

5. **Menglu Ouyang**, Lili Song, Laurent Billot, Maree L. Hackett, Pablo M. Lavados, Verónica V. Olavarría, Paula Muñoz-Venturelli, Sandy Middleton, Octavio M. Pontes-Neto, Tsong-Hai Lee, Caroline Watkins, Thompson Robinson, Craig S. Anderson for the

HeadPoST Investigators. Effect of combined aspirin and clopidogrel versus aspirin alone on functional outcome and recurrence in acute ischemic stroke patients. *European Stroke Organisation Conference*, 22-24 May 2019, Milan, Italy.

Posters:

1. **Menglu Ouyang**, Hueiming Liu, Lili Song, Lingli Sun, Guojuan Cheng, Chunmiao Zhang, Craig S Anderson. Implementation of a complex intervention for intracerebral haemorrhage management: process evaluation of the ongoing INTERACT3 trial. *The Joint European Stroke Organisation and World Stroke Organisation Virtual Conference 2020*, 7-9 November 2020.

2. Lili Song, Lu Ma, Xin Hu, **Menglu Ouyang**, Chunmiao Zhang, Xi Li, Guojuan Cheng, Xia Wang, Laurent Billot, Qiang Li, Chao You, Craig S. Anderson, on behalf of the INTERACT3 Investigators. INTERACT3 update: feasibility of an implementation cluster clinical trial. *European Stroke Organisation Conference*, 22-24 May 2019, Milan, Italy.

Overview

Guidelines recommend certain care processes to improve outcomes for patients with acute stroke. The thesis begins with a background on stroke, covers the definitions of stroke, its epidemiology and prognosis, and outlines various aspects of guideline-recommended stroke management focusing on acute care processes and their relevant implementation (**Chapter 1**). This chapter outlines how this thesis aims to build upon current knowledge of care processes in acute stroke to provide feedback on the impact of clinical guidelines and their use in practice. The specific objectives of my thesis are to:

1. Provide evidence of the impact of two particular care processes - dysphagia screening and urinary catheterisation - on post-stroke infections and other relevant outcomes;

2. Define evidence gaps in the monitoring of physiological parameters - blood pressure (BP) and oxygen saturation (SaO_2);

3. Quantify variations in essential care processes in an acute stroke unit (ASU);

4. Determine the barriers and facilitators of implementing a 'quality improvement' care package for patients with acute intracerebral haemorrhage in routine practice.

Chapter 2 focuses explicitly on important aspects relevant to the prevention and management of two common post-stroke complications include pneumonia and urinary tract infection. The first section (2.1) reports on the utility of dysphagia screening and assessment across study regions, and the associations between these dysphagia evaluations and risk of pneumonia and poor clinical outcome after acute stroke. The second section (2.2) reports on the prognosis in relation to early indwelling urinary catheterisation (IUC) and risk of urinary tract infection (UTI) and death or dependency. Stratified analyses were undertaken to understand the role of UTI on patient outcomes.

In addition to care processes to prevent complications, the monitor and management of abnormal physiological variables are also crucial as part of the key processes of acute stroke care. In **Chapter 3**, the first section (3.1) summarises the characteristics of patients with low presenting BP in the acute phase and describes the relationship between low BP and clinical outcomes. The second section (3.2) reports on the associations of the lowest level of SaO_2 in the first 24 hours after hospital admission and adverse outcomes in patients with acute stroke. The study also identifies an optimal level of SaO_2 related to a favourable outcome.

Besides abnormal parameters monitoring and essential care processes to manage post-stroke infections, stroke unit care is critical to recovery after stroke. It is well acknowledged that access to organised stroke care varies across the world, but limited data exist on quantifying the extent of regional differences in the components of stroke unit care. **Chapter 4** reports upon such variations in guideline-recommended care processes in an acute stroke unit, including comparison within and across four economically defined regions (Australia/UK, China, India/Sri Lanka and South America).

Following determining the variations across the regions upon the care processes that are delivered in the stroke care unit**, Chapter 5** focuses on exploring the strategies for the integration of guideline-recommended care in real-world practice. It outlines the barriers and facilitators of implementing a quality improvement intervention for intracerebral haemorrhage management in China, and suggests the strategies to improve guidelines-recommended stroke care implementation.

Chapter 6 summarises all the data presented in the thesis, discusses the implications of the findings, and provides recommendations for future research. This thesis involves secondary analysis (Chapter 2-4) of the Head Positioning in Acute Stroke Trial (HeadPoST). HeadPoST was an international, multicentre, cluster cross-over, randomised controlled trial involving 11,093 acute stroke patients from nine countries that aimed to determine whether outcomes in acute stroke patients would differ by different types of head positioning (lying flat versus sitting up). It involved collecting clinical and management data as part of routine care during the first few days after admission to the hospital. The large and heterogeneous study population of the HeadPoST study provides a unique opportunity to examine the utility of care processes on the key clinical outcomes in patients with acute stroke. **Chapter 5** is based on the process evaluation incorporated within the third, INTEnsive care bundle with blood pressure Reduction in Acute Cerebral haemorrhage Trial (INTERACT3). INTERACT3 is an ongoing international, multicentre, stepped-wedge, cluster randomised controlled trial that aims to determine the effectiveness of a protocol-directed care bundle for patients with acute intracerebral haemorrhage. This aspect of the trial allows insights to be gained to understand how well the guideline recommendations are implemented into routine practice.

Chapter 1 Introduction

1.1 Synopsis

This Chapter provides an overview of stroke, covering definitions, epidemiology, prognosis, and acute management. The guideline-recommended acute treatment and care processes, which are the main context of this thesis, are outlined. An introduction to the included projects is also provided.

1.2 Stroke

1.2.1 Definitions

In 1689, the term 'stroke' was first introduced by William Cole to describe acute nontraumatic brain injury.[1] Before Cole, the common term used was 'Apoplexy' since 400 BC, which means "loss of consciousness" covering several conditions, including epilepsy.[2] In 1970, the standard definition of stroke was provided by World Health Organisation (WHO) as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin".[3] By applying this definition, brief episodes we called a transient ischaemic attack (TIA), and defined by focal neurological symptoms lasting less than 24 hours, and patients with neurological dysfunction caused by subdural haemorrhage, brain tumours or trauma, are excluded. However, an updated definition of stroke has been developed by experts associated with the American Stroke Association (ASA) for this century that is broader and incorporates clinical and tissue criteria based on neuropathological, modern neuroimaging, and/or where there is clinical evidence.[4] Thus, the term 'stroke' can be broadly used upon the updated definition into the following situations of central nervous system (CNS) infarction, ischaemic stroke, silent CNS infarction, intracerebral haemorrhage (ICH), stroke caused by ICH, silent cerebral haemorrhage, subarachnoid haemorrhage (SAH), stroke caused by SAH, stroke caused by cerebral venous thrombosis, or not otherwise specified stroke.[4]

1.2.2 Types of stroke

Generally, stroke can be classified into two major categories according to the mechanism, that of ischaemic and haemorrhagic stroke.

Ischaemic stroke (infarction) is a lack of blood supply to a vessel due to thrombosis or

embolism, which accounts for 87% of all strokes.[5] There are several subclassifications for ischaemic stroke. The most popular one is that from the Trial of Org 10172 in Acute Stroke Treatment (TOAST), which groups ischaemic stroke into five types according to the aetiology[6]: large artery thrombotic, small artery thrombotic ('lacunar'), cardiogenic embolic, other determined, and undetermined causes of stroke.

Haemorrhagic stroke is caused by a weakened vessel that ruptured with bleeding, mainly within or outside the brain, that of spontaneous ICH or SAH. Spontaneous ICH (as opposed to traumatic haemorrhage) is caused by arteriolar hypertensive disease, which resulting rupture of the small vessels, accounting for 80% of all haemorrhagic strokes.[7, 8] SAH attributes to only 2-7% of all haemorrhagic strokes, and is mainly caused by rupture of an intracranial aneurysm (accounts for 85% of cases) and the rest relates to arteriovenous malformations, intracranial neoplasm, and use of anticoagulants.[7, 9]

1.3 Epidemiology

1.3.1 Global incidence and prevalence

According to the Global Burden of Disease study, there were over 13.7 million new strokes (9.6 million ischemic and 4.1 haemorrhagic strokes) worldwide in 2016.[10] This number is expected to increase with the continued growth and ageing of populations. Although there has been an 11.3% decrease in age-standardised stroke incidence worldwide from 1990 to 2017, the absolute number of stroke cases still increased as a result of population ageing.[11] The number of ischaemic strokes was 7.7 million in 2017, a doubling compared to 1990, but there was a 5% decrease in haemorrhagic events globally.[11] Stroke rates vary by region, with the highest being in Eastern Asia (especially China, with 354 per 100,000 person-years), followed by Eastern Europe (ranging from 200 to 335 per 100,000 person-years),[12] whilst the lowest rates are in Latin America (97 per 100,000 person-years).[12]

The prevalence of stroke was 80.1 million in 2016, being slightly greater in women (41.1 million) than men (39.0 million),[13] with an increase of 3% from 1990-2017, perhaps due to reduced severity and better survival after stroke.[11] The prevalence of ischaemic stroke increased by 2.7%, but haemorrhagic stroke decreased by 1.7%, from 2006 to 2016.[13] The highest age-standardised prevalence figures are Eastern Asia and Eastern Europe.[13] Even though the prevalence of haemorrhagic stroke has decreased overall, the figure remains high with a range of 5.7 to 8.7 million in middle-income countries, where the burden of

hypertension and other risk factors are more significant than in high-income countries.[11, 14] For example, the incidence of ICH in China is 18% higher compared to a predominantly white population.[15]

1.3.2 Risk factors

Stroke shares several risk factors with coronary artery disease, and the risk factors can be categorised as modifiable and non-modifiable. The former include age, sex, genetic variables and ethnicity.[16-18] Stroke is a disease of ageing, and the rates are doubling for each decade after 55 years.[19] Higher rates of stroke are reported in women than men in an older age group because of their longer life expectancy.[20] Racial disparity in stroke is well recognised in studies of African American and Hispanic/Latino people compared to White Americans.[21] Compared to Western Europe, United States and Australia, stroke incidence is particularly high in Asia, where a large majority of the world's population live in low resource developing regions, and disparities remain in the provision of healthcare which continues to challenge effective disease control.[22] Common variants of genetic polymorphisms, such as methylenetetrahydrofolate reductase (MTHFR) C677T and apolipoprotein E (ApoE), are associated with increased risks of ischaemic stroke.[14] The role of family history is complex: in addition to shared genetic factors, there are also shared behavioural and gene-environmental interactions influencing the impact of several modifiable risk factors include high blood pressure (BP) or hypertension, diabetes mellitus (DM), and atrial fibrillation (AF). Other key modifiable risk factors include dyslipidaemia, and unhealthy lifestyles of physical inactivity, smoking, dietary intake and alcohol consumption.[23, 14]

Hypertension

Hypertension is the most critical risk factor, which is attributed to approximately 54% of all strokes.[23] The relationship between BP and risk of stroke is strong, direct and near-continuous, and more significant for haemorrhagic than ischaemic stroke.[14] Hypertension causes alternations in the structure of the cerebrovascular wall, resulting in endothelial damage and atherosclerotic plaques in both small and large arteries, leading to varying degrees of occlusion, rupture and ischaemic injury.[24] Hypertension induces lipohyalinosis (i.e. thickening of vessel walls and reduced luminal diameter) of small arteries, resulting in various abnormalities include small infarcts or 'lacunes', white matter change or leukoaraiosis, and small (micro haemorrhage) and large intracerebral haemorrhage (ICH).[24] The antihypertensive treatment is pivotal for preventing stroke, regardless of age, gender or

ethnicity.[24] With on average of every 1-3 mmHg reduction in systolic blood pressure (SBP), the risk of stroke decreases by 20-30%.[25] Compared to normal BP (<130/85 mmHg), the age- and sex-adjusted risk of stroke increases 1.6 times in untreated hypertension and 3.5 times in patients with poorly controlled SBP.[26] Of the various available antihypertensive drug classes that have been used for first-line treatment, calcium channel blockers and angiotensin receptor blockers have the most substantial evidence for the protection of stroke.[27, 28] Hypertension is the most prevalent risk factor for stroke in Asians.[29] Unlike in many Western countries, both SBP and DBP, and BP variability, are positively correlated with stroke incidence in Asia.[29]

Diabetes Mellitus

DM causes both micro- and macro-vascular complications, including stroke. Elevated blood glucose level (BGL) can induce vascular endothelial dysfunction, increase arterial stiffness, and cause atherosclerotic plaque formation and thickening of basal capillary membranes, leading to stroke.[30] Patients with DM are at a 1.5-3 times greater chance of stroke than those without DM; and those with DM of more than 10 years duration are at 3.2 times greater risk of stroke than others.[31, 32] The hazard ratios (HRs) with DM are 2.27 for ischaemic stroke, 1.56 for haemorrhagic stroke, and 1.84 for unclassified stroke.[33] The risks of ischaemic stroke are higher in young people with DM, especially in the age group of 55-65 years.[34] Women with DM are at a higher relative risk of stroke than men (2.28 versus 1.93),[35] and people with DM are more likely to have risks of comorbidities such as hypertension and hypercholesterolaemia than those without DM.[30]

Atrial Fibrillation

AF is the most common cardiac arrhythmia, which is associated with an increased risk of stroke. Stasis of blood in the atria leads to thrombus and embolization, with the most serious complication being cardioembolic stroke to the brain.[14] The global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries study (INTERSTROKE) has shown that 17.1% for ischaemic strokes can be attributed to AF.[23] AF is the most important cause of ischaemic stroke in people over the age of 75 years.[36] The risk is also modified by sex, where women with AF and no other risk factors appear to have a higher rate of stroke than men (0.7% versus 0.5%).[37] Anticoagulation (i.e. either oral vitamin K inhibitors [warfarin] or new oral anticoagulants [e.g. apixaban]) has been shown can reduce the risk of ischaemic stroke by 65%-85%,[36] despite potential adverse effects of

bleeding in the brain (ICH) or gut.[38] Although aspirin can prevent stroke in those with AF, it is not as potent as anticoagulation and probably works more of co-morbid thrombotic risk from atherosclerosis rather than preventing cardioemboli.[39]

Dyslipidaemia

There is solid evidence that a high level of total cholesterol increases the degree of lipid peroxidation involved in the development of atherosclerosis.[40] There is now substantial evidence that total cholesterol, and particularly low-dose density lipoprotein cholesterol (LDL-C), are risk factors for both coronary artery disease[41] and ischaemic stroke.[42, 43] While a level of high-density lipoprotein cholesterol (HDL-C) ≥0.91 mmol/L has been shown to provide protective effects against ischaemic stroke (i.e. 47% relative risk reduction), this effect appears greater in older than younger people.[41] The use of statin drugs are now well established as providing significant reductions in the risks of ischaemic stroke and cardiovascular deaths by 29% and 22%, respectively.[44]

However, there has been a controversial inverse association between the risk of haemorrhagic stroke and serum cholesterol,[45, 46] with an observational study showing that the relative risk decreased by 31% and 38% with every 1 mmol/L reduction in total cholesterol and LDL-C, respectively.[47] Serum cholesterol of >7.23 mmol/L increased the risk of death from ischaemic stroke, while a level <4.14mmol/L increased the risk of fatal intracranial haemorrhage.[48] A meta-analysis of prospective studies has shown that for every 1 mmol/L increase in HDL-C, the risk for ICH increases by 17%.[47] Low cholesterol may destabilise the endothelium, causing microaneurysms and bleeding.[47]

Diet and nutrition

Diet plays an essential role in the prevention and control of cardiovascular disease, including stroke.[49] A meta-analysis of several randomised controlled trials (RCTs) has shown that Mediterranean diet with lower dietary fat can reduce the risk of stroke by 35%.[50] Folic acid supplementation significantly reduces the risk of stroke by 11%, which may be beneficial to people with elevated BP, low vitamin B_{12} and contraindication of using statins and antiplatelet agents.[51, 52] Diets that are high in sodium/salt, and low in fibre, fruit and vegetables are also associated with an increased risk of stroke.[49] It has been estimated that 35.6% of stroke-related disability-adjusted life years (DALYs) are attributable to diets that are low in fruit (<200 g/day), and 22.6% are related to diets high in sodium (>5 g/day).[53] In 2012, 51.9% of the deaths from stroke in adults (age >25 years) were estimated to be related

to suboptimal dietary habits, including low intake of fruits (22.4%), vegetables (21.9%), whole grains (10.5%), and excess intakes of sodium/salt (10.7%) and sugar beverages (0.7%).[54]

Obesity and physical inactivity

The prevalence of obesity (i.e. body mass index [BMI] ≥30 kg/m^2) has increased from 4% to 34% worldwide over the half-century.[55] Among patients with stroke, an estimated 18-44% and 36% are obese by overall and central measures, respectively.[55] There is firm evidence that obesity is associated with an increased risk of cardiovascular disease,[56] with the risk of ischaemic stroke increasing by 5% for every one-unit increase in BMI.[57] However, both low (<18.5 kg/m^2) and very high (>30kg/m^2) BMI are associated with an increased risk of ICH, by as much as 76%.[58] The relationship between obesity and increased risk of stroke is explained, in part, by an association with hypercholesterolaemia, hypertension and DM.[58] Physical inactivity is associated with many adverse health consequences, including an increased risk of stroke, hypertension and coronary heart disease. Compared to people undertaking any form of regular physical activity, those who are inactive or sedentary (no engagement in leisure-time physical activity or duration of activity <10 minutes) have a 60% increased risk of stroke after the age of 80 years.[59] Very active people had a 27% reduction in the risk of stroke compared to low-active people, and this association holds for both ischaemic and haemorrhagic stroke.[60]

Alcohol

Compared to abstainers, those who consume alcohol ≥60 g per day have a 64% increased risk of total stroke.[61] However, the strength of the relationship varies across stroke subtypes. A J-shape relationship is evident for alcohol intake and ischaemic stroke: light to moderate (<1-2 drinks or <24 g per day) is protective, with a 20-28% relative reduction in risk compared to low intake of alcohol.[61, 62] However, the relationship between alcohol and haemorrhagic stroke increases linearly, which means even a small intake is associated with an increased risk of haemorrhagic stroke.[62, 63] Daily consumption of three or more drinks independently increases the risk of ICH for at least one-fifth.[63] The reduced risk of ischaemic stroke from moderate alcohol intake may be explained by the effects of increasing HDL-C and decreasing platelet aggregation and fibrinolytic activity.[64] Conversely, alcohol can increase BP and coagulation, which contribute to an increased risk of ICH.[64, 65]

Smoking

Smoking has been identified as the leading risk factor for respiratory diseases and cardiovascular disease. Even smoking as little as one cigarette per day is associated with a 35% increased risk of stroke.[66] There was a clear dose-response relationship between pack-years of smoking and risk of stroke, and smoking cessation can rapidly reduce the risk of stroke by as much as 34% compared to those who continue to be regular heavy smokers.[64] The excess risk of stroke nearly returns to the level of non-smokers within 5-15 years of cessation.[68, 69] Moreover, exposure to second-hand smoke is associated with a 30% increased risk of stroke compared to those who are not exposed.[70] Atherosclerosis and arterial damage caused by cigarette smoking contribute to both large- and small-vessel cerebrovascular diseases, with a relative risk ratio (RR) of 2.30, although this is somewhat lower for non-lacunar (RR 1.61) and cardioembolic (RR 1.94) strokes.[71] There is also an increased risk of cerebral aneurysms and damage to small intraparenchymal arteries from cigarette smoking which is associated with both ICH and SAH. Cigarette smoking to levels >15 per day increases the risk of haemorrhagic strokes by 2.29 for females and 1.36 times for males.[72]

In summary, although there are fewer established risk factors for haemorrhagic stroke than ischaemic stroke, the relationship with BP is much higher. DM, AF, smoking and dyslipidaemia, are more potent risk factors for ischaemic stroke. Alcohol consumption is more related to haemorrhagic stroke. Increasing age and sex disparities apply to both types of stroke.[73]

1.4 Prognosis

1.4.1 Death and disability

Stroke is the second leading cause of death and the third leading cause of disability, consequently causing considerable suffering and economic and social burden worldwide.[74,75] The greatest risk of death is in the first few days and weeks after the onset of stroke,[13] where the early case fatality (21 days to 1 month) ranges from 17% to 30%, but is higher for haemorrhagic (25%-35%) than ischemic (12%-23%) stroke.[76] A large prospective US population study indicates cumulative mortality after stroke as 10.5% at 30 days, 21.2% at 1-year, and 40% by 5 years.[77] During the first month, the major causes of death are related to initial stroke (53%), recurrent stroke (2%), and cardiac events (19%).[78] In the long-term (>1 year) after the first-ever stroke, the leading causes of death are cardiovascular disease (67.5%), cancer (11.8%), other diseases (18.3%), and accidents and suicides (2.4%).[78, 79] With improvements in stroke treatment and management over recent decades, age-

standardised deaths from stroke have decreased by 39.2% globally from 1990 to 2016 across all socio-demographic index levels[13] and age groups.[80] From 1990 to 2016, the absolute number of deaths and disability-adjusted life years (DALYs, a metric for 'years of healthy life lost') increased by 28% and 22%, respectively. Stroke is the most common cause of disability in adults, causing more than half of patients to be left with a residual disability, which amounts to over 5 million people affected each year.[81,82] There are more than 116 million DALYs due to stroke annually, and the vast majority (87%) occurs in low- and middle-income countries (LMICs).[10, 83]

1.4.2 Functional recovery

Functional recovery after stroke is influenced by stroke type, size and location of the lesion in the brain as well as underlying neuronal plasticity, external treatment, rehabilitation and motivation.[84] The critical process of recovery from stroke can be conveniently divided into the time points of hyper-acute (0-24 hours), acute (1-7 days), early subacute (7 days to 3 months), late subacute (3-6 months) and chronic (>6 months) phases.[85] During the hyper-acute phase, treatments such as unblock (reperfusion therapy) the clots in blood vessels of the anterior and posterior circulation have the potential to enhance recovery after ischaemic stroke.[85] Most recovery of motor function occurs in the first 12 weeks (recovery ranging from 48% to 91%),[84] while gross cognitive function improves more rapidly, most within 3 weeks.[86] After 6 months, the amount of spontaneous recovery is small, and how much of this relates to internal and external factors that lead to the chronic deficit is uncertain.[85] The first week (hyperacute and acute) to the first month (early subacute) after stroke onset is critical for neural plasticity, which is potential for treatment to influence recovery but has not yet been clearly proven.[87]

1.4.3 Predictors

Baseline characteristics and clinical variables that predict outcome include age, initial severity, pre-morbid levels of function, and pre-existing diseases (i.e. heart failure, ischaemic heart disease, and AF), DM, and previous stroke.[88] An Australian population-based registry reported the highest probability of good outcome after ischemic stroke was in the age group of 18-35 years; this probability declined by ~4.2% per increasing decade but with a steep drop to approximately 10% at 75 years age.[89] Baseline severity of the neurological deficit is often measured by the National Institute of Health Stroke Scale (NIHSS, see Supplementary Appendix 1), an important predictor for functional recovery with good external validation

and calibration.[90] NIHSS is composed of 11 items with a total score range of 0-42, and a score 0 typically indicates a normal function, while a higher score over 15 indicates moderate to severe impairment. For every 1-point increase in the score on the NIHSS, there is a 3-fold increased risk of worsening ambulatory function.[91] Patients with pre-stroke disability (the degree of disability or dependence in daily activities before the occurrence of stroke was evaluated within the first 24 hours of hospital admission using modified Rankin Scale), are more likely to have moderate to severe stroke upon arrival (odds ratio [OR] 3.2, 95% confidence interval [CI] 2.3-4.6), and increased mortality (OR 4.9, 95% CI 3.7-6.5) and dependency on discharge from hospital (OR 3.1, 95% CI 2.3-4.1).[92] Co-morbidities of DM, heart disease and prior stroke are independently associated with poor outcomes after stroke.[93, 94] Hyperglycaemia predicts poor prognosis after stroke (hazard ratio 1.87, 95% CI 1.43-2.45) after adjusting for age, severity, and pathological subtype of stroke.[95] DM independently increases the chance of death or dependency by 23% after acute ischaemic stroke.[96] In a large population-based study, any heart disease (including heart failure) independently predicts future dependency (OR 3.0, 95% CI 1.1-8.0), and AF predicts death (HR 2.4, 95% CI 1.6-3.6) at one year after the first-ever stroke.[97] Three large trials have shown that a history of stroke significant predicts death or dependency at 3 months after acute ischemic stroke (ORs ranging from 1.14 to 1.67, all $p < 0.0001$).[98] In ICH, initial volume and subsequent growth of the haematoma of 24 hours, and initial severity of the neurological deficit on the Glasgow coma scale (GCS) predict adverse outcome.[99] With every 10% increase in baseline haematoma, there are 1% and 18% increasing in the HR for death and dependency by 90 days, respectively.[100] Baseline GCS score is highly correlated with 90-day functional outcome, including the score at Day 5 such that for 1 point increased in GCS, there is a 37% decrease in the odds of death or dependency ($p < 0.001$).[101]

Approximately half of all in-hospital deaths are caused by serious medical or neurological complications, including recurrent stroke and increased intracranial pressure after ischaemic stroke.[102] Brain oedema significantly increases the odds of in-hospital death (OR 18.93, 95% CI 14.65-24.46)[103] and recurrent stroke increases the odds of death or dependency by 10.45 (95% CI 1.03-38.93).[104] Other post-stroke complications include pneumonia, urinary tract infections, and urinary incontinence, are also strong predictors of poor functional recovery across all types of stroke and age groups.[104, 105] An observational study indicates that post-stroke pneumonia is associated with a doubled risk of poor outcome, while infections other than in the urinary tract have increased the risk by 59%.[104] Moreover, patients with urinary

incontinence have a significantly increased risk of an unfavourable outcome after ischaemic (OR 13.9, 95% CI 5.4-35.5) and haemorrhagic (OR 25.0; 95% CI 3.9-160.5) stroke.[105] Post-stroke fatigue has been reported to be an independent predictor of living in an institution (OR 2.71, 95% CI 1.94-3.77) and to result in greater dependency in daily activities (OR 5.00, 3.72-6.72), in comparison to those without fatigue.[106] Moreover, post-stroke fatigue in young stroke patients (age 18-50 yrs) has been reported to be associated with poor functional outcome (OR 4.0, 95% CI 1.6-9.6), even after almost a decade of follow-up.[107] Chronic pain syndrome after stroke is associated with greater dependence (OR 2.16, 95% CI 1.82-2.56) and an increased risk of recurrent stroke compared to those without pain (8.5% vs. 7.3%, p=0.07),[108] but no significant association has been found between the absence of pain complication in the first 90 days and worse functional outcome.[104] Mortality at 1.5 yrs of follow-up is higher in patients with stroke-related aphasia compared to those non-aphasic patients (36% vs. 16%).[109] Aphasia at baseline and persisting over 90 days is associated with poor functional recovery after stroke.[110] Other complications after stroke, such as visual impairment, may be permanent and be associated with reduced quality of life, poor rehabilitation outcomes, and loss of daily living activities.[111] Cognitive impairment at 6 months has been reported to be a predictor of a lower level of independence (coefficient -3.605, 95% -5.705 to -1.505), worse quality of life (coefficient -0.595, 95% -0.943 to -0.248) and increased likelihood of depression (OR 4.60, 95% 1.22-1.74) at 5-year follow up.[112]

Low socioeconomic status is also an important predictor of stroke mortality; that is, people with the lowest education and income, or defined by a composite of low socioeconomic variables, have a significant increase in death from stroke.[113] Socio-economics status (SES) also involves caregiver support, marital status, and disease awareness, which are essential for survival and recovery from stroke.[94] Patients with low SES are also more likely to have greater co-morbidities and less access to rehabilitation, which contributes to poor functional recovery from inadequate or delayed therapy, and aids and adaptions to the living environment.[114] Race-ethnicity also explains some of the variations in outcomes after acute stroke. For example, Caucasians had significantly higher mortality (p=0.0003) and worse quality of life (p=0.003) compared to Asians, although functional recovery is similar between these groups at 3-months (p=0.14).[115]

1.4.4 Outcome evaluation

There are three commonly used and validated outcome assessment scales in stroke: the

NIHSS, modified Rankin Scale (mRS, see Supplementary Appendix 2), and Barthel Index (BI, see Supplementary Appendix 3), with each suited to different aspects of measuring physical function,[116] whilst the health-related quality of life (HRQoL) is typically measured with the 5-Dimension European Quality of life scale (EQ-5D, see Supplementary Appendix 4) which taps into the patient's own (or their caregiver's) perception of their recovery.

National Institute of Health Stroke Scale

The NIHSS is an 11-item scale that can provide an ordinal, non-linear measure of neurological impairments, with the total score ranging from 0 (no deficit) to 42 (maximum deficit). A score of ≥21 is typically used to indicate 'severe stroke'.[117] The scale incorporates assessments of language, motor function, sensory loss, consciousness, visual fields, extraocular movements, coordination, neglect, and speech.[117] It is the gold standard for rating stroke severity among participants of clinical stroke trials.[118] Compared to mRS and BI, NIHSS provides a more sensitive measure of neurological impairment. Therefore, when using NIHSS as a measure of early recovery, it requires a smaller sample size to detect therapeutic effects.[116] To this end, the NIHSS is a valid surrogate endpoint of recovery in the first week after the onset of symptoms in trials of acute ischaemic stroke, particularly Phase II(b) studies where extra time and costs are required to administer the mRS at 3 months.[119] However, caution is advised in using the NIHSS scale as it is not a measure of disability biased towards lesions of the left hemisphere and has only moderate inter- and intra-rate reliability.[118]

modified Rankin Scale

The mRS is a valid and reliable tool to assess disability after stroke and the most popular primary endpoint to explore the efficacy of acute treatments in ischaemic stroke.[120] It is a 7-level scale that covers the entire range of function from no symptoms (score 0), no significant disability (1), slightly disability (2), moderate disability (3), moderately-severe disability (4), severe disability (5) and death (score of 6), which can be easily grasped and understood by clinicians and patients.[121] The broad categories of the mRS provide a global measure of physical activities covering walking, dressing, and grooming albeit emphasising motor function and so extent covering higher level, instrumental activities of living such as the preparation of meals, shopping and handling money, where assistance may also be required for everyday activities.[121, 122] However, the limited range of scoring of the mRS makes it less responsive to change than other scales, and there can be inconsistency and interobserver

variability.[116] Thus, a simplified mRS has been developed with structured questions that require 'yes/no' answers has been shown to improve its consistency of use.[116] The assessment can be conducted face-to-face or by telephone, either directly with a patient or an appropriate surrogate who takes care of the patients.

Barthel Index

The BI is adapted from the Maryland Disability Index, and is more commonly used to assess functioning in a rehabilitation setting as well as in acute stroke trials.[116] The BI evaluates 10 aspects of function in activities of daily living (ADL): feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfers, mobility and stairs; scores range from 0 to 100, with a higher score indicating greater independence.[123] A cut-off score of >80 is often used to indicate an independent function that is suitable to return home, while a score <40 indicates extreme dependency.[124] However, as BI does not include a measure of mortality, it is more suitable to measure inpatient rehabilitation of stroke survivors.[116]

5-Dimension European Quality of life scale

Quality of life (QoL) is the overall and meaningful quality of an individual's life.[125] HRQoL focuses on the measure of an individual's wellbeing and functioning in relation to health.[126] The EQ-5D, as a simple generic measure of HRQoL, is commonly used among patients with stroke. It comprises two main elements: descriptive assessments across five dimensions and a vertical visual analogue scale (EQ-VAS).[127] This instrument makes index values and health profiles with the five dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and the EQ-VAS allows patients to rate the quality of their health on a vertical thermometer scale, from 0 (worst imaginable health state) to 100 (best imaginable health state).[128] The EQ-5D can be completed by patients or a surrogate such as family/caregivers. More recently, the EQ-5D has evolved into 5 levels of grading (EQ-5D-5L) for the five dimensions as a more sensitive measure on the functioning over time.[129] Due to HRQoL being subjective, it may be influenced by personal and socio-cultural expectations, which has led to debate over the degree of bias being introduced by proxy assessments, particularly for people with cognitive impairment, fatigue, stress or communication difficulties.[116, 130]

1.4.5 Medical complications

Medical complications occur with wide-ranging frequency (40% to 96%) after stroke onset, and are often associated with poor outcome.[131] Common complications include neurological

deterioration, infections (e.g. pneumonia and urinary tract infection [UTI]), cardiac arrhythmias, deep vein thrombosis, pulmonary embolus, falls, pressure sores, pain, and psychological disorders (depression and anxiety).[131] Most complications occur within the first few weeks after stroke, particularly those directly related to the injured brain and the complications of disability, while the risk of falls and mood disorders persist through rehabilitation and recovery at home.[131]

Neurological complications

Recurrent stroke is a frequent complication after stroke.[132] The pooled cumulative risk of stroke recurrence ranges from 3% within one month, 10% by one year, and up to 25% at 5 years.[133] After the first-ever ischaemic stroke, 91% of the recurrent strokes are ischaemic, while after ICH, 56% of the recurrent strokes are haemorrhagic and 41% ischaemic.[134] A meta-analysis of 34 studies, including both ischaemic stroke and TIA, concluded the annual risk of recurrent stroke is 4.3%.[135] After ICH, the annual rate of recurrence is 2%.[136] Age, stroke severity, baseline BP, family history of stroke, DM, smoking, peripheral artery disease, and hypercoagulable status are common risk factors for recurrent stroke.[137]

Brain oedema from the evolving complications of cerebral ischaemia occurs in approximately 8% of the patients in the first week after ischaemic stroke.[138] Cerebral oedema is more common after haemorrhagic stroke: 12% after SAH, resulting in about one-third of patients dying or left with a severe disability;[139] For ICH, it is approximately 17% within 24 hours after onset, increasing by 3% and 1% at 48 hours and 72 hours, respectively.[140] Cerebral oedema is characterised by the movement of accumulated intracellular water across the blood-brain barrier into the interstitial space caused by high BP in the acute phase, and is often leading to compartmental shift and potential for cerebral herniation.[141, 142] Other less frequent neurological related complications include haemorrhagic transformation (2%), carotid stenosis (2%), brain herniation (2%), seizures (1%) and delirium (1%).[143]

Infections

Infections are common after stroke, occurring in up to two-thirds of patients.[132] Timely assessment and prevention management are critical for survival and functional recovery after acute stroke.[132]

Pneumonia is the most frequent post-stroke infection, which is in some way linked to aspiration.[7, 144, 145] Older age (>65 years), severe stroke, speech impairment, cognitive impairment, dysphagia, and the use of mechanical ventilation, are predictors of pneumonia.[146]

The frequency of pneumonia varies across clinical settings, ranging from 9.5% to 56.6% in intensive care units to 3.9% to 12.0% in general medical wards.[147, 148] The frequency of pneumonia also varies by stroke subtype, being higher in ICH (16.8%) than ischaemic stroke (11.5%).[149] Pneumonia is also associated with other complications, including gastrointestinal bleeding, decubitus ulcers, deep vein thrombosis, epileptic seizures, UTI, AF and recurrent stroke.[149]

UTI occurs in up to one-quarter of the patients in the first few weeks after the stroke onset.[150] Patients are vulnerable due to immunosuppression, bladder dysfunction, and catheter use. Risk factors include stroke severity, indwelling urinary catheterisation, depressed conscious level, and DM.[150, 151,147] UTIs are associated with worse recovery, poor neurological outcome and increased costs from a prolonged stay in hospital and inflammatory responses.[150] A recent review, however, suggests that post-stroke UTI is not independently associated with death and disability.[152] Further studies are needed to better define the relationships between UTIs and outcomes after stroke.

Cardiac complications

Since stroke and heart disease share common risk factors, it is not surprising that serious cardiac adverse events are common in patients with stroke.[145] The Virtual International Stroke Trials Archive suggests one-fifth of patients experience at least one serious cardiac adverse event after ischaemic stroke.[153] Acute myocardial infarction/angina occurs in approximately 6% of patients after stroke,[154] with other events include AF, and ventricular tachycardia and ectopic beats; these increase the risk of systemic embolism, further strokes and sudden death.[145] Congestive heart failure occurs in 2%-11% of patients and obviously increases the likelihood of reduced long-term survival.[145, 153] Cardiac events account for 2%-6% of deaths after ischaemic stroke, mainly in relation to heart failure, DM, renal failure, and severity of the illness.[153]

Other common complications

Deep vein thrombolysis (DVT) can develop early after stroke, particularly in patients with limb paralysis,[145] and is predicted by older age, neurological severity and dehydration.[145] The overall frequency of DVT is reported as 2%-4%, but can be up to 50% in patients with hemiparesis who have not used thromboembolism prophylaxis.[155] DVT can cause local pain and swelling, and it is the leading risk factor of pulmonary embolisms that can be fatal in the first few weeks after the onset of stroke.[143] Pulmonary embolism occurs in approximately

1% of patients with stroke and now is less frequent with the broader use of heparin.[145] Falls are another complication, occurring in up to 22% of patients after stroke, which can result in hip fractures, and consequently increased risks of death and disability, especially in older patients with age-associated osteoporosis.[145] Pain syndromes can occur in relation to a limb or shoulder, more often on the affected hemiparetic side.[145] Depression can occur in one-third of patients after stroke,[156] and this impedes rehabilitation, adherence to medication and other therapy, and therefore reduces chances of an optimum recovery.[145]

1.5 Acute stroke management

1.5.1 Clinical guidelines for stroke management

Clinical practice guidelines are systematically developed recommendations based on currently available evidence that guide clinicians in their provision of care for patients.[157] Guidelines are considered to address the gap between research and practice, and therefore, reduce variability in clinical practice.[158] Clinical guidelines in stroke management provide up-to-date comprehensive recommendations, covering pre-hospital care, emergency management, diagnostics, stroke unit service, acute treatments, primary/secondary prevention, management of complications, and rehabilitation.[159] Each guideline has its hierarchical system to classify the evidence to assist the clinician's decision-making and judgement. One of the most widely cited guidelines are those of the American Heart Association (AHA) / American Stroke Association (ASA), where their recommendations are classified into three classes: I - treatment/procedure should be performed; II - reasonable/considered to perform; III - no benefit/harm. These are based upon evidence levels classified as A (multiple populations evaluated), B (limited populations evaluated) and C (very limited populations evaluated).[160, 161] Similar classifications of evidence level are applied by the European Stroke Organisation (ESO)[148] and Australian Stroke Foundation.[162] The recommendations at Level C or low level of evidence indicate limited data and the need for continued research.

1.5.2 Stroke Unit Care

An acute stroke unit (ASU), defined as an organised stroke care or a stroke-specific dedicated team, can provide quality of care to improve patient's recovery through the provision of multidisciplinary care for diagnosis, emergency treatments, prevention of complications, rehabilitation, and secondary prevention.[163] The dedicated multidisciplinary team consists of

doctors, nurses, physiotherapists, occupational therapists, speech and language therapists, clinical psychologists, dieticians and social workers.[164] A Cochrane review has shown that ASU care can significantly reduce the odds of death (OR 0.81, 95% CI 0.69-0.94) and death or disability (OR 0.79, 95% CI 0.68-0.90) at one year.[165] The benefits of the organised ASU are consistent across subgroups defined by patient age, sex, stroke severity and stroke type, as compared to alternative services (i.e. general wards).[166] Thus, guidelines recommend all patients with acute stroke be treated in an ASU immediately upon hospital admission.[159, 162, 166, 167] The organisational care provided in the ASU generally includes, but not limited to, reperfusion therapy for acute ischaemic stroke, early use of antiplatelet agents for ischaemic stroke, anticoagulants for patients with AF, antihypertensive for secondary prevention, dysphagia screening, formal dysphagia assessment (see by a speech pathologist) if screening fails, feeding to assist in those with dysphagia, early mobilisation, an assessment of rehabilitation needs (see by a physiologist / occupational therapist), and an assessment of any mood disorder (see by a psychologist).[168-170]

Even though the benefits of ASU are well recognised, variations exist in the use of various components of care, as highlighted in a wide range of studies. For example, European registries have shown significant variations in care processes across populations, and where there is greater organisational capability, there are better levels of patient survival.[171, 172] Despite some contextual factors, such as health policy, knowledge, beliefs, skills, and costs related to these variations in the quality of care, day and time of admission also influence the delivery and performance of standardised care from reduced or changed staffing in evenings and weekends.[173-175] However, there are conflicting results as to the influence of setting, organisation or process of care on a patient's recovery.[176] The variations in the utility of care processes across regions and their impact on stroke outcomes require further research.

1.5.3 Treatment of acute ischaemic stroke

Reperfusion therapy

The primary therapeutic goal in acute ischaemic stroke is the rapid dissolution of a clot that blocking a blood vessel to restore blood flow into an ischaemic area of the brain to improve the chances of recovery after stroke.[177] There is now strong evidence that intravenous thrombolysis (IVT), mainly the use of recombinant tissue plasminogen activator (rtPA, or alteplase), is effective for patients with acute ischaemic stroke.[178] A meta-analysis of randomised trials has shown administration of alteplase within 6 hours of the onset of

symptoms significantly reduces the chance of death or disability (defined as mRS 3-6) by 26% (p=0.0006), with the greatest effect observed within 3 hours (risk reduction of 32%, p=0.002).[179] Another individual participant data meta-analysis has shown that IV alteplase significantly increased the odds of an excellent outcome (mRS 0-1) when given <3 hours (OR 1.75, 95% CI 1.35-2.27) but not after 4.5 hours (OR 1.15, 95% CI 0.95-1.40).[180] However, this treatment is complicated by an increased risk of symptomatic intracranial haemorrhage (sICH) and fatal intracranial haemorrhage (OR 3.75 and 1.69, respectively).[179] Since the time window is a principal criterion for selecting reperfusion therapy, current guidelines recommend use within 4.5 hours of the onset of stroke symptoms (or last known to be well).[160] A rapid assessment of patients with suspected stroke is required for timely reperfusion treatment.

IV alteplase is less effective in patients with acute ischaemic stroke due to large vessel occlusion (LVO) of the anterior circulation.[178] Endovascular treatment (EVT) has emerged over the last several years as an effective treatment for these patients, where guidelines now recommend the therapy within 6 hours from the onset of symptoms.[181] A meta-analysis of RCTs has shown EVT can significantly reduce disability compared to standard care (generally IVT alone) where there is a lesion related to the proximal anterior circulation, even up to 12 hours after the onset of symptoms (common OR 2.49, 95% CI 1.76-3.53).[182] Compared to IVT, EVT is associated with a higher probability of recanalization (>80% versus 46%).[183] The multicentre randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands study (MR CLEAN) has shown a good achievement of functional outcome occurred in 13.5% of participants despite a slight increase in sICH.[184] The benefits of EVT have been extended to patients who are unable to receive IVT and in those presenting at longer times, provided there is viable ischaemic brain tissue evident on advanced brain imaging demonstration of a perfusion mismatch.[185]

However, the risk of sICH is a major concern of reperfusion therapy. Thus, guidelines recommend the close observation and monitoring of patients for at least 24 hours to allow for early detection and management, in the event of any neurological deterioration. This includes checking for any alteration in homeostasis (i.e. heart rate, BP, oxygen saturation) and biochemistry parameters (e.g. hyperglycaemia), or any other adverse event.[160,186] Although reperfusion therapies, both IVT and EVT, have been shown to reduce mortality and morbidity after stroke, only a minority of patients meet the criteria for them since the therapies require well-organised systems of care and are high-resource (e.g. costly). Among

high-income countries with ASU, IVT occurs in about 14.5%-34.5% of cases, while EVT is even low (5% being eligible).[82] Further research is required to enhance access and quality of care for these highly effective interventions.

Antithrombotic treatment

Antithrombotic therapy, including administration of anticoagulants and/or antiplatelets, is recommended for secondary prevention to reduce the risk of recurrent stroke and other serious vascular events.[187] Aspirin, commonly at a dose of 160-300mg, is recommended in patients with ischaemic stroke and commenced within 24-48 hours after onset; in patients who receive IV rtPA, antiplatelet therapy is delayed until 24 hours later to avoid increasing the risk of ICH.[160] The Antithrombotic Trialists' Collaboration analysed 10 trials to show that aspirin after an ischaemic stroke or TIA significantly reduced the risk of serious vascular events by 17% (p=0.001), major coronary events by 21% (p=0.01), nonfatal myocardial infarction by 36% (p=0.003), and any stroke by 17% (p=0.01).[188] However, the treatment led to a slight absolute increase in the risk of haemorrhagic stroke (RR 1.90, 95% CI 1.06-3.44) and gastrointestinal bleeding (RR 2.69, 95% CI 1.25-5.76).[188]

The use of anticoagulation early after the onset of AIS is not recommended due to concerns about the potential risk of ICH.[160] A Cochrane review indicates there is no evidence to support the initiation of anticoagulant therapy within the first 14 days of the onset of AIS (outcome of death or dependency, OR 1.05, 95% CI 0.98-1.12).[189] Although early use of anticoagulants can reduce the risk of recurrent ischaemic stroke by 24% (95% CI 12%-35%), this is offset due to a significant increase of sICH (OR 2.55, 95% CI 1.95-3.33) and extracranial haemorrhage (OR 2.99, 95% CI 2.4-3.99).[89] For patients with AIS and AF, non-vitamin K antagonist oral anticoagulants are now the preferred treatment over warfarin for secondary prevention of recurrent stroke and/or thromboembolism.[190] The Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation (RAF) study showed that initiating anticoagulation in such patients within 4-14 days from stroke onset significantly reduced recurrent stroke and major bleeding events (sICH or extracranial bleeding) by 47%.[191]

Antihypertensive therapy

Elevated BP (i.e. >140/90 mmHg) occurs in approximately 75% of the AIS patients within 24 hours of the onset of symptoms and is associated with increased odds of death and dependency.[192] As such, clinical guidelines recommend early treatment of hypertension to

reduce BP by about 15% in the first 24 hours of AIS, particularly in patients with severe comorbidities such as acute coronary heart disease, heart failure, aortic dissection, and post-thrombolysis sICH.[160] However, a meta-analysis suggests that early BP lowering within 3 days of AIS does not significantly reduce the odds of death or dependency at 3 months (RR 1.04, 95% CI 0.96-1.13).[193] Another review of RCTs indicates that BP lowering within the first 48 hours does not significantly reduce the odds of either early or long-term death and dependency (RR 1.04, 95% CI 0.94-1.19 and RR 1.00, 95% CI 0.95-1.05, respectively).[194] The controversy may be related to the complexity of AIS, where a rapid reduction in BP could reduce perfusion of the ischaemic penumbra and collateral flow within the ischaemic region of the brain.[195] However, a cohort study indicates that using an angiotensin receptor blocker at the time of hospital discharge is associated with a lower risk of death at one year of follow-up than no such treatment (9.4% versus 26.9%).[196] Several RCTs have shown that intensive antihypertensive therapy is effective for secondary prevention of stroke.[197] The pivotal perindopril protection against recurrent stroke study (PROGRESS) showed that active treatment of hypertension reduced the risks of recurrent stroke by 26% over several years of follow-up.[198] A meta-analysis of 10 RCTs has also shown that antihypertensive agents can reduce the risks of recurrent stroke and cardiovascular events by 29% and 31% in patients with prior stroke or TIA, respectively.[199]

1.5.4 Treatment of intracerebral haemorrhage

Blood pressure lowering

Acute hypertension (>160/100 mmHg) occurs in up to 90% of the patients with ICH, and it predicts haematoma expansion, death and disability.[200] Thus, BP lowering seems appropriate to be included within a package of management strategies to stabilise abnormal cardiorespiratory parameters and neurological complications associated with ICH. There is solid evidence that the expansion of the haematoma and peri-haematoma oedema contribute to secondary brain damage and worsen outcomes from ICH.[201] Large haematomas, whatever their location, can result in rapid neurological deterioration and death from increased intracranial pressure (ICP) or direct compression of the brainstem.[202] Thus, BP control could reduce haematoma growth and neurological deterioration. This rationale was tested in the main phase of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage (INTERACT2) study, where patients who received early intensive BP lowering to a target SBP <140mmHg had significantly better functional recovery and health-related quality of life

compared to those received standard care.[203] There were no increases in death or serious adverse events (SAEs).[203] Guidelines, therefore, recommend SBP control to <140 mmHg in all patients with ICH and SBP between 150-220mmHg without a contraindication to treatment.[161] In patients with SBP >220mmHg, the treatment is considered reasonable with continuous IV infusion and frequent BP monitoring, but more evidence is required to support a firm recommendation.[161]

Haemostatic therapy

Underlying haemostatic abnormalities are another important cause of ICH. Patients undertaking oral anticoagulant agents (OACs) comprise 12%-20% of ICH in high-income countries where AF is now standard, and the use of warfarin and NOACs is increasing in older people.[204, 205] However, the benefit of these agents is offset due to risks of haemorrhage: warfarin intake increases an annual risk of ICH by 0.3-3.7% in patients with the international normalized ratio (INR) is at the therapeutic range of 2-4.5,[206] and also increases a greater risk of death (OR 2.2; 95% CI 1.3-3.8).[207] In the event of ICH, haemostatic therapy is essential in minimising haematoma expansion and improving the chances of a good outcome. A cohort study has shown that reversal of INR levels to <1.3 is associated with lower rates of haematoma enlargement (19.8%) compared to no treatment (41.5%).[208] Therefore, guidelines recommend that ICH patients with an elevated INR on vitamin K antagonists (VKAs) should receive fresh frozen plasma (FFP) or prothrombin complex concentrates (PCCs) alongside vitamin K to rapidly correct INR.[161] The INR normalisation in Coumadin associated intracerebral haemorrhage trial (INCH) has shown that PCC can rapidly normalise and reduce haematoma expansion without any increase in thrombotic complications, as compared to FFP.[209] For patients taking a NOAC (e.g. dabigatran, rivaroxaban and apixaban), there is no requirement for laboratory monitoring, but PCC can still be considered to correct haemostasis and coagulopathy.[161]

Surgical treatment

The main surgical approaches to treat ICH include craniotomy or minimally invasive procedures and decompressive craniotomy (DC), which aim to evacuate and reduce the haematoma, respectively. However, despite much effort over several decades, the results in RCTs comparing surgery to conservative medical management have not shown a clear benefit for surgery.[161] On the one hand, surgery to evacuate the haematoma can reduce ICP and prevent herniation of the brain, but on the other hand, this involves cutting through the

healthy brain in sick patients who often have other comorbidities and are at high risk of complications.[161] The US-led Minimally Invasive Surgery Plus Rt-PA for ICH Evacuation Phase III (MISTE-III) trial has shown that patients who receive minimally invasive surgery and use of thrombolysis to evacuate the haematoma had only marginally, non-significant, improved functional outcome compared to standard medical care (45% versus 41%, p=0.33), but there was no difference in adverse events including symptomatic bleeding and cerebral bacterial infections (2% and 1%, respectively).[210] Similar neutral findings were obtained in an earlier international study, the Surgical Trial in Lobar Intracerebral Haemorrhage phase II (STICH-II) trial, where poor outcomes were similar for early DC versus delayed or conservative treatment (59% versus 62%, p=0.37).[211] A systematic review suggests DC might be safe and improves outcomes for a targeted group of patients with impaired consciousness (GCS scores 10-13) and large haematoma volume.[212]

1.5.5 Treatment of subarachnoid haemorrhage

The management of SAH has some similarities to ICH, where involves strict BP control and surgical interventions to secure the bleeding aneurysm (bleeding source) and prevent rebleeding and complications. Rebleeding is the most severe complication of SAH, which occurs in 7%-26% of patients.[213] Rebleeding may be prevented by reducing acute hypertension and repairing the aneurysm as soon as possible.[9] BP control can decrease transmural pressure in the aneurysm and thus reduce rebleeding. However, there is also, albeit limited, evidence indicating that control of SBP <140 mmHg is associated with an increased risk of rebleeding compared to SBP >140mmHg (14.2% versus 5.9%).[214] Thus, studies suggest that hypertension after SAH is a compensatory phenomenon and should not be treated.[215] A prospective randomised study has shown that administrating antifibrinolytic agents within 72 hours after SAH reduced the incidence of rebleeding from 10.8% to 2.4%.[216] Surgical clipping and endovascular coiling of aneurysms are now established treatment choices, according to availability, affordability and location of the aneurysm.[217] There does not appear to be any significant differences between the approaches according to endpoints of in-hospital mortality (OR 1.04; 95% CI 0.70-1.54), discharge to rehabilitation (OR 1.07; 95% CI 0.72-1.58) or readmission at 30 days (OR 1.44; 95% CI 0.70-1.87).[218] Delayed cerebral ischaemia (DCI) and vasospasm that are indirectly related to the aneurysm occur in 60% of the SAH patients between day 4-10, and are associated with worse outcome.[219] Triple H therapy, that is the use of hypertension, hypervolaemia and haemodilution, appears able to improve cerebral blood flow and oxygen delivery in DCI.[219] The calcium channel blocker,

nimodipine, which is recommended as a standard treatment to prevent DCI, is associated with a significantly lower risk of death or dependence (RR 0.67, 95% CI 0.55-0.81).[220]

1.5.6 Acute care processes

Stroke care processes are defined as quality indicators that relate to patient outcomes.[221] Clinical guidelines recommended a variety of acute care processes, such as dysphagia screening, dysphagia assessment, subsequent feeding restrictions, appropriate urinary catheterisation, monitoring of physiological parameters, assessment and treatment. Much of this work is undertaken by nurses, together with allied health care professionals and other members of a multidisciplinary stroke team, as part of general active and supportive in-hospital management of patients with acute stroke.

Screening and assessment for dysphagia

Dysphagia occurs in ~50% of patients in the acute phase of stroke and consequently increases the risk of aspiration pneumonia from ineffective swallowing of food and/or fluids.[222, 223] Evidence shows that early detection of dysphagia can reduce the risk of pulmonary complications, dehydration and malnutrition, as well as decrease the length of hospital stay and health care costs.[224] Patients with dysphagia are 3-4 times more likely to develop pneumonia.[225, 226] Dysphagia screening is a simple, invasive procedure (e.g. 3-oz water swallow test) that enables early identification of vulnerable individuals with aspiration risk, while dysphagia assessment is a more formal, comprehensive approach that uses a valid instrument assessment (e.g. video-fluoroscopic swallowing study) by specialists to detect swallow dysfunction in these patients.[227] An observational study has shown that early identification of dysphagia is associated with a reduced likelihood of pneumonia (3.8% versus 11.6%) and reduced length of hospital stay (8 versus 9 days).[228] Current guidelines recommend dysphagia screening should be performed in the first 24 hours after stroke; and that those patients who fail in screening should be referred to a speech pathologist to perform a further specialist assessment.[162] The results of an assessment should then inform subsequent management, which may entail remaining 'nil by mouth' or having a modified consistency of food and/or fluids, and reassessments performed at regular intervals. However, the evidence to support the implementation of dysphagia screening and subsequent assessment is only graded as a Level C recommendation in guidelines.[160] Even though a range of simple and systematic approaches exist for the evaluation of dysphagia, more research is required to underpin their incorporation in clinical practice.[226]

Assisted feeding for dysphagia

For patients who failed a swallow assessment, their nutrition should be maintained by way of a nasogastric feeding tube and transition to oral intake after improvement in swallow function.[229] A feeding tube is not essential in all dysphagia patients, but short-term use is preferable in those with severe dysphagia where the likelihood of improvement will take a longer time.[229] Guidelines recommend the initial use of a nasogastric tube should occur within the first week of the stroke, and the percutaneous endoscopic gastrostomy (PEG) tube can be placed more permanently in those with persistent swallow dysfunction at 2-3 weeks.[160] The large, multicentre, international, Feed or Ordinary Food Collaboration Trial (FOOD) has shown that a supplemental diet was associated with a reduced risk of death by 0.7%, and an early tube feeding (<7 days after admission) decreased the absolute risk of death by 5.8%.[230] A Cochrane review on feeding strategies for dysphagia treatment after stroke suggests there is no difference between PEG and nasogastric feeding, in terms of death or dependency, but a PEG significantly reduces the likelihood of a treatment failure (OR 0.09, 95% CI 0.01-0.51), gastrointestinal bleeding (OR 0.25, 95% CI 0.09-0.69) and high intake of food (OR 22.00, 95% CI 16.15-27.85).[231] However, a large stroke registry identified that the use of direct enteral tubes (e.g. PEG) was associated with higher levels of disability at the time of hospital discharge (89.6% versus 78.4%), aspiration pneumonia (14.4% versus 5.1%) and other complications, as well as mortality at 2 years (41.1 versus 35.9%), in comparison to temporary use of nasogastric tubes alone.[232] This might be related to severe patients being more likely to have persistent dysphagia and thus prone to the need for PEG tubes, but are also that they are more likely to have a poor outcome. Moreover, patients with assisted feedings were more likely to have swallowing difficulties, impaired consciousness or older age, compared to patients without assisted feeding who often lack these characteristics.[164, 233] Swallow treatment combined swallowing exercises and modified diets that are prescribed by speech pathologists, has a positive effect in reducing the risk of pneumonia after stroke, but there is limited evidence of their benefit in the rehabilitation stage of stroke.[234]

Indwelling urinary catheter (IUC)

The insertion of IUC is often used in patients with incontinence issues to drain and collect urine. In some circumstances, such as urine retention, incontinence, surgery or measuring fluid balance in the intensive care unit, the use of IUC is particularly necessary. Studies suggest that IUC is used in 25% of patients after acute stroke, mostly (86%) in the first few

days of admission.[235] However, IUC is a well-recognised cause of UTIs, particularly in older patients.[236] In the general medical population, the risks of UTI increase by 3% to 10% per day, and approach 100% after 30 days.[150] Compared to patients without urinary incontinence or IUC, patients who are urinary incontinent and with IUC have approximately 2 times the greater odds of death.[237] Current guidelines recommend against the routine use of an IUC, and that any need for catheterisation should be removed as soon as possible in stable patients.[160] However, evidence for this recommendation is again only at Level C, with limited data about the impact on long-term outcomes, especially in a diverse range of patients from different regions.

Monitoring of abnormal physiological parameters

BP, body temperature, BGL and arterial oxygen saturation (SaO_2), are often altered from impaired autoregulation in those with severe or specifically localised types of stroke.[238] BP and temperature generally increase in the acute phase of stroke and normalise within 1-2 days as part of a hypertensive response;[239] while BGL and SaO_2 may persist with a more variable pattern.[238] Left untreated, some of these abnormal physiological parameters can have serious consequences. Thus, frequent monitoring and responses are essential to inform timely and appropriate clinical management.[240] Table 1 summarises the recommendations of various national guidelines (American, European, Australian, UK) regarding the management of physiological parameters in acute stroke. In general, they recommend tolerating higher BP but treating excessive elevation use of BP lowering with caution; and treatment of fever, hyperglycaemia, hypoglycaemia and hypoxia. However, the evidence underlying these recommendations, particularly around treatment thresholds and targets, are very limited; and guidelines lack harmonisation over abnormal ranges in action over management that should be taken.[162]

Table 1. National guideline recommendations for physiological parameters management

Physiological variable	AHA/ASA Guidelines[160, 161]	ESO[241-243]	Australia Stroke Foundation[162]	UK NICE Guideline[244]
BP	AIS: Patients with elevated BP and are otherwise eligible for IV alteplase is recommended to target SBP <185 mmHg and DBP <110 mmHg before IV fibrinolytic therapy is initiated (Level B); Hypotension and hypovolaemia should be corrected to maintain systemic perfusion levels necessary to support organ function (Level C). ICH: Patients with SBP 150-220mmHg and without contraindication, acute lowering to SBP <140 mmHg is recommended (Level A); For those with SBP >220 mmHg, reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring	AIS: BP <220/110mmHg not treated with intravenous thrombolysis/mechanical thrombectomy is recommended routine lowering BP lowering at least in first 24 hours unless specific comorbid conditions (Moderate Level); Patients undergoing treatment with intravenous thrombolysis to maintain SBP <185/110 mmHg for 24 hours after alteplase infusion; and lowering SBP to 130–140mmHg during the first 72 hours (Moderate Level). ICH: In patients with hyperacute (<6 hours), suggests lowering SBP <140mmHg (and to keep it above 110 mmHg) is recommended (Moderate Level).	AIS: Patients eligible for intravenous thrombolysis should have BP reduced <185/110 mmHg before treatment and in the first 24 hours after treatment; patients with BP >220/120 mmHg should have BP cautiously reduced (e.g. by no more than 20%) over the first 24 hours. (Consensus-based) ICH: In patients with ICH, BP may be acutely reduced to a target SBP of ~140 mmHg (Weak)	AIS: Antihypertensive is recommended only if there is a hypertensive emergency with serious concomitant medical issues; BP reduction to ≤185/110 mmHg should be considered in people who are candidates for intravenous thrombolysis. ICH: Rapid BP lowering to target SBP 130-140 mmHg within 1 hour and maintain for at least 7 days is recommended in people within 6 hours stroke onset and have a SBP of 150-220 mmHg; for those beyond 6 hours of onset or have a SBP ≥220 mmHg, recommend to a target of 130-140 mmHg within 1 hour and maintain for at least 7 days.

	(Level C).			
Temperature	AIS: Sources of hyperthermia (temperature >38°C) should be identified and treated, and antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke (Level C). ICH: Treatment of fever after ICH may be reasonable (Level C).	AIS: Do not recommend induction of hypothermia (Very low Level). ICH: No specific advice.	All stroke patients should have their temperature monitored at least four times a day for 72 hours (Strong); Stroke patients with fever ≥37.5 ºC may be treated with paracetamol as an antipyretic therapy (Weak).	AIS: Not recommend therapeutic hypothermia. ICH: No specific advice
Blood Glucose Level (BGL)	AIS: Hypoglycaemia (BGL<60 mg/dL) should be treated (Level C); persistent in-hospital hyperglycaemia during the first 24 hours is reasonable to treat to achieve BGL in a range of 140-180 mg/dL and to closely monitor to prevent hypoglycaemia (Level C). ICH: Glucose should be monitored, and both hyperglycaemia and hypoglycaemia should be avoided (Level C)	AIS: Suggest against routine use of IV insulin to achieve a tight glycaemic control (Low Level). ICH: Suggest against routine use of IV insulin to achieve a tight glycaemic control (Very low Level).	All stroke patients should have BGL monitored for the first 72 hours and appropriate glycaemic therapy instituted to treat hyperglycaemia (BGL ≥10 mmol/L), regardless of their diabetic status (Strong); an intensive approach to the maintenance of tight glycaemic control (between 4.0–7.5 mmol/L) is not recommended (Strong).	Maintain BGL concentration of 4-11 mmol/L in people with acute stroke; no specific advice for AIS or ICH, respectively.

Oxygen saturation (SaO$_2$)	AIS: Supplemental oxygen should be provided to maintain SaO$_2$>94% (Level C); Supplemental oxygen is not recommended in nonhypoxic patients (Level B). ICH: No specific advice	No specific advice.	AIS: patients who have SaO$_2$ >92% on room air, the routine use of supplemental oxygen is not recommended; hyperbaric oxygen therapy is not recommended (Weak). ICH: No specific advice	Give supplemental oxygen to people with SaO$_2$ <95%. The routine use of supplemental oxygen is not recommended in people with acute stroke who are not hypoxic. No specific advice for AIS or ICH, respectively.

AIS denotes acute ischaemic stroke, ICH intracerebral haemorrhage, AHA American Heart Association, ASA American Stroke Association, ESO European Stroke Organisation, UK United Kingdom, NICE National Institute for Health and Care Excellence

Hypotension: Low BP is relatively less common in acute stroke, ranging from 18% to 25% in 48 hours after onset,[245] and is related to sepsis, cardiac arrhythmias, heart failure, ischaemia, hypovolaemia, and aortic dissection.[246] Current guidelines focus on the management of the more common situation of elevated BP in AIS and ICH, without addressing approaches to low BP.[160, 161] Evidence on the consequences and threshold of low BP are conflicting. Some studies have shown that low BP has prognostic significance,[247-249] and others have not.[250] Additionally, there are arguments over reversal causality in that low BP is simply a marker of an underlying severe premorbid condition.[251] More research is needed to define an optimal range of BP for better recovery in acute stroke.

Oxygen desaturation: Hypoxia (defined as a lower-than-normal SaO_2 range of 95-98%),[252] is common after acute stroke and is related to aspiration pneumonia, pulmonary embolism, sleep apnoea and respiratory muscle impairment, especially in patients with respiratory comorbidities (dyspnoea, chronic obstructive airways disease, asthma or heart failure).[253] Decreases in SaO_2 can lead to neurological damage and poor outcomes.[254] AHA/ASA guidelines recommend the use of supplemental oxygen to maintain SaO_2 >94%, and to avoid supplemental oxygen in nonhypoxic patients.[160] It remains unclear whether SaO_2 has independent prognostic significance or is simply a marker of severe stroke.[255] Moreover, the appropriate level of SaO_2 for treatment is not standardised across guidelines. Further research on this topic is needed to guide clinical practice recommendations.

Allied health care

Guideline-recommended stroke care incorporates allied healthcare professionals as part of the expert multidisciplinary team.[159, 160, 162] Rehabilitation includes input from physiotherapy, occupational therapy, and speech-language therapy, and is now accepted as being critical for giving patients the best opportunity to recover function (e.g. walking) and daily activities (e.g. dressing, showering, communication) and to assist them in returning to work, leisure activities and roles in society.[256] Psychological screening and assessment of cognitive function and mood in the acute phase is recommended to identify any significant cognitive impairment and depression.

Early rehabilitation: Guidelines recommend rehabilitation should be commenced within 24-48 hours of admission, including an assessment by a physiotherapist within the multidisciplinary team of the ASU.[256] A cohort study indicates that 78% of patients with stroke receive physical and occupational therapy in the acute care, but only 41% receive such

input early after hospital discharge.[257] Very early mobilisation as part of rehabilitation within the first 24 hours after stroke onset, is considered important in reducing complications, such as infections.[132] A cohort study found that mobilisation within the first day after admission was associated with a 57% reduction in the risk of pneumonia and a 44% lower risk of UTIs.[168] A meta-analysis indicates that early mobilisation is associated with an average increase of 0.66 scores of BI and shorter hospital stay (-2.0 days), but not significantly improved functional outcome (mRS 0-2).[258] Findings are consistent with the large, international, A Very Early Rehabilitation Trial (AVERT), which has shown that mobilisation <24 hours of admission was associated with a significant reduction of 27% in the odds of favourable functional outcome compared to usual care, which is against the common concepts of early mobilisation.[259, 260] There are concerns that early upright mobilisation might compromise reperfusion of the ischaemic penumbra in patients treated with thrombolysis and cause elevation of BP in those with ICH, which potentially increases the risk of bleeding. However, a national wide cohort study reported a higher proportion of functional independence with early rehabilitation compared to standard care (41.2% versus 36.6%), without any increase in sICH.[261] Guidelines recommend early speech rehabilitation should be available in stroke services as part of multidisciplinary care. Aphasia occurs in 35-40% of the patients after acute stroke and is associated with poor recovery.[262] From a large national-wide registry study, aphasia is associated with higher in-hospital mortality compared to those free of aphasia (11% versus 4%) and poor functional outcomes at 2-years of follow up (61% versus 48%).[263] A single centre study reported improved functional communication in patients with aphasia who received early speech rehabilitation compared to those who received usual care (11.3 score improvement, p=0.004).[264] However, the Australian multicentre Very Early Rehabilitation for Speech Trial (VERSE) showed no difference in communication recovery, quality of life, depression or adverse events, between intensive aphasia therapy (commences <15 days after admission) and usual care group at 12 or 26 weeks.[265] While another clinical trial conducted in Germany has shown significant improvement in verbal communication by 10% in patients with chronic post-stroke aphasia after they received intensive speech and language therapy for ≥3 weeks (mean difference 2.61 points, 95% CI 1.49-3.72).[266]

Cognition screening: Some degree of cognitive impairment occurs in up to 70% of patients immediately after stroke.[267] An observational study has shown that cognitive screening based upon the popular Mini-Mental State Examination (MMSE) and Montreal Cognitive

Assessment (MoCA) at baseline can predict functional outcomes at 3-6 months.[268] Although guidelines suggest that all survivors of stroke should undergo a screen for cognitive or perceptual deficits by an expert (e.g. neuropsychologist, occupational therapist) using validated and reliable screening tools prior to discharge from hospital,[256] there is very limited research about various methodological considerations (sensitivity, specificity and accuracy) and implementation barriers in clinical practice.[269] There are also strong arguments against the use of cognitive screening due to lack of empirical evidence on clinical efficacy, potential increases in anxiety, and unnecessary costs that outweigh any potential benefits.[270]

Depression screening: Depression is common after stroke, occurring in about one-third of patients,[271] and is related to disability and mortality.[270] Post-stroke depression significantly increases 1.5 times the risk of death compared to non-depressed patients.[272] Guidelines recommend routine screening for post-stroke depression, but the optimal time point for screening and the best management approaches are uncertain.[160] Early post-stroke depression often remains underdiagnosed and untreated due to the lack of a gold standard for assessment. The diagnosis is also complex in the context of other impairments such as aphasia, cognitive impairment, and fatigue.[272] A meta-analysis on screening for post-stroke depression indicates a simple tool such as the patient health questionnaire-9 (PHQ-9) has high sensitivity and specificity, which could improve outcomes by providing an accurate diagnosis and ensuring timely and effective treatment.[273] However, there are cautions that early depression/anxiety screening may not be feasible or accurate, even in medically stable patients.[274]

1.5.7 Stroke care in low- and middle-income countries

Stroke guidelines in low- and middle-income countries

A systematic review of the stroke guidelines in 28 LMICs indicates issues regarding lack of standards for guideline development, breadth of the target audience, coverage of the components of stroke services, and adaption to relevant socio-economic context. This study also shows that guidelines in LMICs have less demonstrated transparency than those from high-income countries (HICs).[275] Though HICs guidelines recommendations (e.g. AHA guidelines) were used in 22% of the guidelines in LMICs and the Level A/Class I recommendations were homogenous among LMICs, while patient views and preferences were less considered in the guidelines of LMICs compared to those in HICs.[276] Moreover, the stroke surveillance, rehabilitation, speech therapy, nursing care and cognition assessment post

stroke, are not well addressed in most of the guidelines in LMICs.[275]

Acute care barriers in low- and middle-income countries

The emerging issues of acute care for stroke in LMICs are in relation to limited health systems. Compared to HICs, stroke units are less common in low-income countries (91% vs. 18%) and relevant aspects of acute stroke treatment are seldom offered in LMICs (26% vs. 60%).[277] In India, stroke units are relatively sparse and mainly provided by the private sector.[278] In other LMIC settings, such as in Africa, stroke units do not exist, and patients have to be admitted to generic wards for multidisciplinary team care that is formed by non-specialised health providers where allied health professionals such as speech therapists, are often absent.[279] In addition, inadequate facilities also provide structural barriers to providing effective stroke care processes. Although there is evidence that thrombolysis treatment is cost-effective, even in LMICs, very few patients are able to receive this important treatment in these countries.[280] In India, for example, it has been reported that delays in brain imaging prior to administration of thrombolysis exclude large numbers of otherwise eligible patients who are outside the treatment time window.[281] Rehabilitation represents a key part of stroke care, but many interventions are in limited supply in most LMICs.[280] For example, access to early rehabilitation after stroke (within 24-48 hours) is low in LMICs, mainly due to insufficient numbers of different rehabilitation professionals.[280, 282] Stroke survivors in LMICs are less able to access rehabilitation specialists after their discharge to home after receiving their acute care in hospital.[283] Lack of infrastructure, financial support, clinical guidelines and national policies to support and provide stroke rehabilitation is widespread in LMICs.[283]

1.6 Implementation of guideline recommendations

Guideline implementation challenges

Although the identification of evidence gaps in the management of stroke is a priority for enhancing the process for updating the best practice recommendations and thereby the quality of care, there is considerable non-adherence to guidelines that lead to unnecessary diagnostics and suboptimal or inadequate treatment.[284] It has been reported that most of the guideline recommendations are not adequately applied, with 30-40% of patients receiving treatment that is not based upon high-quality scientific evidence and 20-25% receiving treatments that are unneeded or potentially harmful.[284] Translating guidelines into clinical practice are challenging, sometimes taking an average of 17 years for less than 20% of the published

evidence to translate into practice.[285] Despite this issue, implementation strategies are rarely reported within the conduct of clinical trials that reveal effectiveness and efficacy, especially for the uptake of research into practice across different contexts and populations. Implementation strategies should be based on current knowledge about potentially effective interventions to assess barriers and facilitators for better adoption of clinical guidelines.[286] However, knowledge on appropriate implementing guidelines remains scarce, with no implementation strategy being identified that is effective across all circumstances.[284] Thus, it is necessary to embed studies of implementation strategies within clinical research, to help accelerate the translation findings into practice, as well as to understand whether clinical interventions are ready for implementation and scale-up.[287]

Implementation barriers

Despite the range of evidence supporting various recommendations in stroke management, the uptake of guideline recommendations is compromised by multiple barriers across organisational and health professional levels.[288] A review of this topic suggests poor institutional support, limited skills or incompetence in the use of particular therapies, low awareness, lack of familiarity or knowledge of the effectiveness of a particular evidence-based therapy, and inadequate support among health professionals and patients are all barriers that affect the delivery of evidence-based practice care in high-income countries (HIC).[288] However, very few studies are being conducted in LMICs or regions where resources are often limited. A summary of the services that are required for optimal acute stroke care at each stage, and their relevant barriers to implement in LMICs is shown in Supplemental Table S2. The delivery of acute stroke care in LMICs is reported to be affected by factors that include financial constraints, inadequate facilities and various socio-cultural practices.[289] Considering the rising burden of stroke in LMICs, it is crucial that key barriers are well defined in order to explain the low uptake of evidence-based care in LMICs. The implementation of guideline recommendations in LMICs may be impeded by factors such as insufficient health care providers, limited access to health care services, ineffective health policies, and shortage of infrastructure.[290] Implementation research will be the key to studying and improving all forms of stroke care delivery, with detailed implementation study designs able to inform and accelerate activities for sustainability.[283] Since such an endeavour to explore the barriers or facilitators is unique to stroke specialists, doctors, nurses and allied health staffs, all various stakeholders' perspectives in stroke care need to be involved when considering strategies to promote the integration of guideline recommendations into routine

practice. Each LMIC may need to analyse its health system capacity and identify factors that impede the implementation of stroke guidelines. This is key to developing guidelines that are relevant to the country context, and therefore, more likely to be effective.[278]

1.7 The Head Positioning in Acute Stroke trial (HeadPoST)

This thesis involved secondary analysis of the Head Positioning in Acute Stroke Trial (HeadPoST) data. The large-scale size of this study, which involved the recruitment of patients with a minimum selection bias across different LMICs and HICs, provides a unique opportunity to undertake cross-regional comparisons of different aspects of acute stroke care. Herein, I outline the design, statistical analysis, and main results of this large trial.

Trial overview

HeadPoST was an international, multicentre, cluster-randomised, crossover, open-label, blinded outcome assessed trial which aimed to determine the effectiveness and safety of a simple nursing intervention of different head positions in acute stroke. This trial was conducted at 114 hospitals in nine countries, including Australia, Brazil, Chile, China (include Taiwan), India, Colombia, Sri Lanka, and the United Kingdom (UK), between March 2015 and November 2016. All hospitals participated in both the lying flat (0°) and sitting up ($\geq 30^{\circ}$) head position treatment, then crossed over to the opposite intervention until the target number of patients was reached. Patients with age ≥ 18 years, who presented to a participating centre with a clinical diagnosis of acute stroke, were eligible for the trial. Patients with any contraindication to either of the assigned head positions, had a confirmed TIA, or where the investigator considered head position could not be maintained were excluded. The assigned head position was initiated in patients as soon as possible at the time of their admission, and it was to be strictly maintained for the next 24 hours. Patients assessed with dysphagia had a restricted oral intake or received assisted feeding actions in the assigned head position. A guardian consent process was used to implement the randomised intervention as a policy of usual service delivery to a pre-defined patient cluster; patients provided consent for the use of their medical record data and centralised telephone follow-up. The primary outcome was the degree of disability at 90 days, analysed as an ordinal outcome on mRS. Secondary outcomes included death or dependency (mRS 3-6) at 90 days, death within 90 days, length of hospital stay, NIHSS or death at 7 days as well as any SAE, including pneumonia. HeadPoST is registered at ClinicalTrials.gov (NCT02162017). The detailed HeadPoST study protocol has been published.[291]

Data collection

Demographic, stroke details, vital signs/laboratory test results, medical history, medications at the time of admission, and swallowing tests include dysphagia screening, assessment and feeding restrictions/actions, were collected at baseline (data availability is shown in Appendix 5-6). A 24-hour bedside diary was used to record interruption time and reason of assigned head position, vital signs, and lowest SaO_2. Hospitalisation data were collected on Day 7/before discharge, including final diagnosis, acute care and medications administration. Trained staff who were blind to the randomised intervention contacted patients by telephone for the 90-day assessment. SAEs were reported by site investigators during the hospital stay to the end of follow-up.

Statistical analysis

The full statistical analysis plan of HeadPoST study was published in 2017.[292] The analysis used an intention-to-treat approach. The primary analysis of the intervention effect was evaluated with an ordinal, logistic regression, hierarchical, mixed model, with adjustment for fixed intervention effect (lying flat versus sitting up), fixed crossover period effect, random cluster effect and effect of the interaction between cluster and crossover period. This primary model was defined as the 'unadjusted'. Sensitivity analysis adjusted the following variables: region (grouped by Australia/UK, China include Taiwan, India/Sri Lanka, South America [Chile/Brazil/Colombia]), pre-stroke mRS, age and sex, baseline NIHSS, previous history of heart disease, stroke or DM. Multiple imputations using a fully conditional specification[267] was applied as a sensitivity analysis if >10% of mRS observations were missing (methodology is described in Appendix 7).

Main results

A total of 11,093 acute stroke patients were assigned to randomised head position (5292 in lying flat and 5798 in sitting up). The mean age of patients was 68 years (with 23% >80 years), 40% were female, and 85% were diagnosed with AIS. The median NIHSS score was 4 (interquartile range [IQR] 2-8). The median time from stroke onset to commencement of head position was 14.0 (IQR 5.0-35.0) hours. Patients randomised to the lying flat group were more likely to prematurely cease the position within 24 hours after initiation compared to the sitting up group (13.0% versus 4.2%). There was no significant difference between the two groups in the primary outcome of a shift on the mRS at 90 days (OR 1.01, 95% CI 0.92-1.10). Results from sensitivity analysis with prespecified adjustments and multiple

imputations for missing outcomes were consistent with the primary analysis. There was no significant difference between lying flat and sitting up on death or dependency at 90 days (38.9% versus 39.7%; OR 0.94, 95% CI 0.85-1.05) and death within 90 days after stroke (7.3% versus 7.4%; OR 0.98, 95% CI 0.85-1.14). No significant difference was evident for other outcomes and prespecified subgroup analyses. No significant difference in the rate of any SAE (14.3% versus 13.5%; OR 1.05, 95% CI 0.91-1.20) or pneumonia (3.1% versus 3.4%; OR 0.86, 95% CI 0.68-1.08) within 90 days. More detailed findings can be found in the main publication for HeadPoST study.[294]

1.8 The INTEnsive care bundle with blood pressure Reducation in Acute Cerebral haemorrhage Trial (INTERACT3)

Trial overview

The third phase, INTEnsive care bundle with blood pressure Reduction in Acute Cerebral haemorrhage Trial (INTERACT3), is an ongoing pragmatic, international, multicentre, stepped-wedge, clustered RCT that aims to determine the effectiveness of a multifaceted care package in the early management of patients with ICH. This trial has been conducted since December 2017 and is now recruiting patients from 110 hospitals in nine LIMICs, including Brazil, China, India, Mexico, Nigeria, Pakistan, Peru, Sri Lanka, and Vietnam, and one HIC, Chile. Adult patients (≥18 years) who present to the hospital within 6 hours of ICH with a confirmed ICH by clinical history and CT brain imaging are eligible. Patients with definite evidence that the ICH is secondary to a structural abnormality in the brain, who have had recent thrombolysis/thrombectomy, or have a high likelihood of non-adherence to the study treatment/follow-up regime, are excluded. A mixed consent process is used, where a cluster/guardian consent or appropriate approval is obtained to implement the randomised care bundle followed by individual consent for the data collection and centralised follow-up. The stepped-wedge cluster design allows all participating hospitals to commence in a usual care (control) phase, before progressively transferring over to the care bundle (intervention) phase at pre-determined stages according to the randomisation assignment. The timeline for each phase depends on when the pre-determined target recruitment number of eligible ICH patients (vary from 1 to 50 patients according to service configuration and patient volumes) or the 3-month time limit is reached. INTERACT3 is registered at ClinicalTrials.gov (NCT03209258) and Chinese Trial Registry identifier (ChiCTR-IOC-17011787).

Intervention and outcome

The intervention of a goal-directed care bundle involves early intensive BP lowering (to achieve a target of SBP <140mmHg within 1 hour of initiation), glucose control (target BGL of 6.1-7.8 mmol/L for non-diabetic and 7.8-10.0 mmol/L for diabetic patients), treatment of pyrexia (target of <37.5 °C within 1 hour of initiation) and reversal of previous use of anticoagulation (target of INR <1.5 within 1 hour of treatment). The intervention involves the target goals being maintained for the next 7 days in the hospital, or to hospital discharge if earlier. The control group receives usual care or previous routine protocols before transferring over to the intervention phase. The primary outcome is functional recovery according to an ordinal analysis of the mRS at 6 months, measured by trained staff that blind to the randomised allocation. The secondary outcomes include death or neurological deterioration according to the change in NIHSS at 7 days, unfavourable outcome (mRS 3-6), death, disability (mRS 3-5), HRQoL using the EQ5D, duration of hospital stay, measured at 6 months. The safety outcomes of all-cause and cause-specific SAEs, are recorded according to standard definitions for the duration of follow-up.

The intention of introducing this care bundle is to promote the implementation of guidelines or recommendations, narrow the evidence-practice gap, and translate care and research into practice in LIMCs to improve outcomes in ICH. Regular intervention implementation quality reports, remote communications and on-site monitoring are conducted to improve the adherence of the intervention implementation. A process evaluation, designed to gain insights into the barriers and facilitators to change systems of care and adherence to the protocol, is undertaken through formative stakeholder engagement by survey, focus group and interviews, during the study.

1.9 Conclusions

Acute stroke continues to have a poor prognosis, where timely management offers the chance of improving recovery and outcomes for those affected. Clinical guidelines recommend reperfusion therapy, antithrombotic treatment, antihypertensive therapy, screening and restricted feeding for dysphagia, appropriate IUC, vital signs monitoring and allied health care to improve clinical outcomes in patients with acute stroke. However, evidence to support dysphagia screening and IUC are at low to moderate quality, requires further studies to fill the gaps for clinical guideline development. In addition, insufficient data exists on thresholds for various abnormal physiological parameters, such as low presenting BP and SaO_2 levels, to support early detection and management to improve patient outcomes. Challenges of

implementing evidence-based care in clinical practice remain in settings with limited resources, especially in LMICs. Studies are required to determine the variations in the utility of guideline-recommended stroke care across regions and explore the strategies to improve stroke care implementation.

The large, international, HeadPoST database provides a unique opportunity to examine the utility of various care processes on outcomes in acute stroke patients and further support (or otherwise) for guideline development. The broad inclusion of participants from nine countries across different economic levels in HeadPoST enables the comparison of variations in the components of ASU care across regions.

The process evaluation undertaken within INTERACT3 allows better understandings of the barriers and facilitators of implementing a novel care bundle for ICH management in China, which might provide insightful strategies to improve guideline uptake and delivery in LMICs with similar issues.

Chapter References

1.	Cole W. *A physico-medical essay, concerning the late frequency of apoplexies. Together with a general method of their prevention and cure. In a letter to a physician*. London: London : Printed for Dan. Browne, ..., and Sam. Smith ... 1693.

2.	Adams F. The genuine works of hippocrates. Translated from the greek, with a preliminary discourse and annotations. New York: William wood & company. 1891. *Buffalo Medical and Surgical Journal*. 1891;XXXI:315

3.	WHO MONICA Project Investigators. The world health organization MONICA project (monitoring trends and determinants in cardiovascular disease). *Journal of Clinical Epidemiology*. 1988;41:105-114

4.	Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:2064-2089

5.	Donkor ES. Stroke in the 21st century: A snapshot of the burden, epidemiology, and quality of life. *Stroke research and treatment*. 2018;2018:3238165-3238165

6.	Adams HP, Adams Jr HP, Bendixen BH, Bendixen BH, Kappelle LJ, Biller J, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial. *Stroke (1970)*. 1993;24:35-41

7.	Caplan LR. *Caplan's stroke: A clinical approach*. Philadelphia: Philadelphia : Elsevier/Saunders; 2009.

8.	Daroff RB. *Neurology in clinical practice*. London: Elsevier Health Sciences; 2012.

9.	Maher M, Schweizer TA, Macdonald RL. Treatment of spontaneous subarachnoid haemorrhage: Guidelines and gaps. *Stroke*. 2020;51:1326-1332

10.	M Patrice Lindsay BN, Ralph L. Sacco, Michael Brainin, Werner Hacke, Sheila Martins, Jeyaraj Pandian, Valery Feigin. World stroke organisation(WSO): Global stroke face sheet 2019-2020;2021

11.	Avan A, Digaleh H, Di Napoli M, Stranges S, Behrouz R, Shojaeianbabaei G, et al. Socioeconomic status and stroke incidence, prevalence, mortality, and worldwide burden: An ecological analysis from the global burden of disease study 2017. *BMC Med*. 2019;17:191-191

12.	Gorelick PB. The global burden of stroke: Persistent and disabling. *Lancet Neurol*. 2019;18:417-418

13. Johnson CO, Nguyen M, Roth GA, Alam T, Abd-Allah F, Adeoye AM, et al. Global, regional, and national burden of stroke, 1990–2016: A systematic analysis for the global burden of disease study 2016. *Lancet Neurol*. 2019;18:439-458

14. Boehme AK, Esenwa C, Elkind MSV. Stroke risk factors, genetics, and prevention. *Circ Res*. 2017;120:472-495

15. Khan N, McAlister, FA., Pilote, L., Palepu, A., Quan, H., Hill, MD., Fang, J., Kapral, MK. Temporal trends in stroke incidence in South Asian, Chinese and White population: A population-based analysis. *PLoS ONE*. 2017;12:e0175556

16. Lee S-H. *Stroke revisited: Pathophysiology of stroke: From bench to bedside*. Springer; 2020.

17. Tsai C-F, Thomas B, Sudlow CLM. Epidemiology of stroke and its subtypes in Chinese vs White populations: A systematic review. *Neurology*. 2013;81:264-272

18. Bruno A, Carter S, Qualls C, Nolte KB. Incidence of spontaneous intracerebral hemorrhage among Hispanics and non-Hispanic whites in new Mexico. *Neurology*. 1996;47:405-408

19. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. Heart disease and stroke statistics--2008 update: A report from the American Heart Association statistics committee and stroke statistics subcommittee. *Circulation*. 2008;117:e25-146

20. Appelros P, Stegmayr B, Terent A. Sex differences in stroke epidemiology: A systematic review. *Stroke*. 2009;40:1082-1090

21. Cruz-Flores S, Rabinstein A, Peterson E, Rosamond W, Trimble B, Valderrama AL, et al. Racial-ethnic disparities in stroke care: The American experience: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42:2091-2116

22. Venketasubramanian N, Yoon BW, Pandian J, Navarro JC. Stroke epidemiology in South, East, and South-east Asia: A review. *Journal of stroke*. 2017;19:286-294

23. O'Donnell MJD, Xavier DP, Liu LP, Zhang HP, Chin SL, Rao-Melacini PM, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the interstroke study): A case-control study. *Lancet*. 2010;376:112-123

24. Yu J-G, Zhou R-R, Cai G-J. From hypertension to stroke: Mechanisms and potential prevention strategies: Hypertension and stroke prevention. *CNS neuroscience & therapeutics*. 2011;17:577-584

25. Staessen JA WJ, Thijs L. Cardiovascular protection and blood pressure reduction: A meta-analysis. *Lancet*. 2001;350:1305-1315

26. Cairu LI, EngstrÖM G, Hedblad B, Berglund G, Janzon L. Blood pressure control and risk of stroke: A population-based prospective cohort study. *Stroke*. 2005;36:725-730

27. Papadopoulos DP, Papademetriou V. Aggressive blood pressure control and stroke prevention: Role of calcium channel blockers. *J Hypertens*. 2008;26:844-852

28. Wang J-G. A combined role of calcium channel blockers and angiotensin receptor blockers in stroke prevention. *Vasc Health Risk Manag*. 2009;5:593-605

29. Turana Y TJ, Chia YC, Nathaniel M, Wang JG, Sukonthasarn A, Chen CH, Minh HV, Buranakitjaroen P, Shin J, Siddique S, Nailes JM, Park S, Teo BW, Sison J, Ann Soenarta A, Hoshide S, Tay JC, Prasad Sogunuru G, Zhang Y, Verma N, Wang TD, Kario K; HOPE Asia Network. . Hypertension and stroke in Asia: A comprehensive review from HOPE Asia. *J Clin Hypertens (Greenwich)*. 2020;23:513-521

30. Chen R OB, Feng W. Diabetes and stroke: Epidemiology, pathophysiology, pharmaceuticals and outcomes. *The American Journal of the Medical Sciences*. 2016;351:380-386

31. Banerjee C, Moon YP, Paik MC, Rundek T, Mora-Mclaughlin C, Vieira JR, et al. Duration of diabetes and risk of ischemic stroke: The Northern Manhattan Study. *Stroke*. 2012;43:1212-1217

32. Diabetes India. Diabetes & metabolic syndrome: Clinical research & reviews. *Diabetes and metabolic syndrome*. 2007

33. Emerging Risk Factors Collaboration SN, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010;375:2215-2222

34. Khoury JC, Kleindorfer D, Alwell K, Moomaw CJ, Woo D, Adeoye O, et al. Diabetes mellitus: A risk factor for ischemic stroke in a large biracial population. *Stroke*. 2013;44:1500-1504

35. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men. *Circulation (New York, N.Y.)*. 2014;129

36. Hart RG. Atrial fibrillation and stroke prevention. *N Engl J Med*. 2003;349:1015-1016

37.   Friberg L, Benson L, Rosenqvist M, Lip GYH. Assessment of female sex as a risk factor in atrial fibrillation in Sweden: Nationwide retrospective cohort study. *BMJ*. 2012;344:14-e3522

38.   Yaghi S, Kamel H. Stratifying stroke risk in atrial fibrillation: Beyond clinical risk scores. *Stroke*. 2017;48:2665-2670

39.   The SPAF III Writing Committee for the Stroke Prevention in Atrial Fibrillation Investigators. Patients with nonvalvular atrial fibrillation at low risk of stroke during treatment with aspirin: Stroke prevention in atrial fibrillation III Study. *JAMA: the journal of the American Medical Association*. 1998;279:1273-1277

40.   Cheng P, Pan J, Xia J, Huang W, Bai S, Zhu X, et al. Dietary cholesterol intake and stroke risk: A meta-analysis. *Oncotarget*. 2018;9:25698-25707

41.   Sacco RL, Benson RT, Kargman DE, Boden-Albala B, Tuck C, Lin IF, et al. High-density lipoprotein cholesterol and ischemic stroke in the elderly: The northern manhattan stroke study. *JAMA*. 2001;285:2729-2735

42.   Soyama Y, Miura K, Morikawa Y, Nishijo M, Nakanishi Y, Naruse Y, et al. High-density lipoprotein cholesterol and risk of stroke in Japanese men and women: The Oyabe study. *Stroke*. 2003;34:863-868

43.   Wannamethee SG, Shaper AG, Ebrahim S. Hdl-cholesterol, total cholesterol, and the risk of stroke in middle-aged British men. *Stroke*. 2000;31:1882-1888

44.   Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality: An overview of randomized trials. *JAMA*. 1997;278:313-321

45.   Iso H, Jacobs DR, Jr., Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *N Engl J Med*. 1989;320:904-910

46.   Zhang X, Patel A, Horibe H, Wu Z, Barzi F, Rodgers A, et al. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. *Int J Epidemiol*. 2003;32:563-572

47.   Wang X, Dong Y, Qi X, Huang C, Hou L. Cholesterol levels and risk of hemorrhagic stroke: A systematic review and meta-analysis. *Stroke*. 2013;44:1833-1839

48.   Piechowski-Jóźwiak B, Bogousslavsky J. Cholesterol as a risk factor for stroke: The fugitive? *Stroke*. 2004;35:1523-1524

49.   Mehdi F, Mohsen A, Zahra M, Reza G, Fariborz K, Gholamreza A. Stroke and nutrition: A review of studies. *International journal of preventive medicine*. 2013;4:S165-S179

50.   Liyanage T, Ninomiya T, Wang A, Neal B, Jun M, Wong MG, et al. Effects of the Mediterranean diet on cardiovascular outcomes-a systematic review and meta-analysis. *PLoS One*. 2016;11:e0159252-e0159252

51.   Zhao M, Wu G, Li Y, Wang X, Hou FF, Xu X, et al. Meta-analysis of folic acid efficacy trials in stroke prevention: Insight into effect modifiers. *Neurology*. 2017;88:1830-1838

52.   Park J-H, Saposnik G, Ovbiagele B, Markovic D, Towfighi A. Effect of b-vitamins on stroke risk among individuals with vascular disease who are not on antiplatelets: A meta-analysis. *Int J Stroke*. 2016;11:206-211

53.   Feigin VL RG, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, Mensah G, Norrving B, Shiue I, Ng M, Estep K, Cercy K, Murray CJL, Forouzanfar MH. Global burden of stroke and risk factors in 188 countries, during 1990–2013: A systematic analysis for the global burden of disease study 2013. *Lancet Neurology*. 2016;15:913-924

54.   Micha R, Peñalvo JL, Cudhea F, Imamura F, Rehm CD, Mozaffarian D. Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the united states. *JAMA*. 2017;317:912-924

55.   Kernan WN, Inzucchi SE, Sawan C, Macko RF, Furie KL. Obesity: A stubbornly obvious target for stroke prevention. *Stroke*. 2013;44:278-286

56.   Rexrode KM. A prospective study of body mass index, weight change, and risk of stroke in women. *JAMA: the journal of the American Medical Association*. 1997;277:1539-1545

57.   Kurth T. Body mass index and the risk of stroke in men. (archives of internal medicine). *JAMA: the journal of the American Medical Association*. 2003;289:1757

58.   Biffi A, Cortellini L, Rosand J, Nearnberg CM, Ayres AM, Schwab K, et al. Body mass index and etiology of intracerebral hemorrhage. *Stroke*. 2011;42:2526-2530

59.   Willey JZ, Moon YP, Sacco RL, Greenlee H, Diaz KM, Wright CB, et al. Physical inactivity is a strong risk factor for stroke in the oldest old: Findings from a multi-ethnic population (the Northern Manhattan study). *Int J Stroke*. 2017;12:197-200

60. Lee CD, Folsom AR, Blair SN. Physical activity and stroke risk: A meta-analysis. *Stroke*. 2003;34:2475-2481

61. Reynolds K, Lewis B, Nolen JDL, Kinney GL, Sathya B, He J. Alcohol consumption and risk of stroke: A meta-analysis. *JAMA*. 2003;289:579-588

62. Gill JS, Gill SK, Zezulka AV, Shipley MJ, Beevers DG. Stroke and alcohol consumption. *N Engl J Med*. 1986;315:1041-1046

63. Hillbom M, Saloheimo P, Juvela S. Alcohol consumption, blood pressure, and the risk of stroke. *Curr Hypertens Rep*. 2011;13:208-213

64. Zakhari S. Alcohol and the cardiovascular system: Molecular mechanisms for beneficial and harmful action. *Alcohol Health Res World*. 1997;21:21-29

65. Gill JS, Shipley MJ, Tsementzis SA, Hornby RS, Gill SK, Hitchcock ER, et al. Alcohol consumption—a risk factor for hemorrhagic and non-hemorrhagic stroke. *Am J Med*. 1991;90:489-497

66. Hackshaw A MJ, Boniface S et al. Low cigarette consumption and risk of coronary heart disease and stroke: Meta-analysis of 141 cohort studies in 55 study reports. *BMJ*. 2018;361:k1611-k1611

67. Bhat VM, Cole JW, Sorkin JD, Wozniak MA, Malarcher AM, Giles WH, et al. Dose-response relationship between cigarette smoking and risk of ischemic stroke in young women. *Stroke*. 2008;39:2439-2443

68. Fagerstrom K. The epidemiology of smoking: health consequences and benefits of cessation. *Drugs*. 2002;62:1-9

69. Song Y-M, Cho H-J. Risk of stroke and myocardial infarction after reduction or cessation of cigarette smoking: A cohort study in Korean men. *Stroke*. 2008;39:2432-2438

70. Malek AM, Cushman M, Lackland DT, Howard G, McClure LA. Secondhand smoke exposure and stroke: The reasons for geographic and racial differences in stroke (regards) study. *Am J Prev Med*. 2015;49:e89-e97

71. Ohira T, Shahar E, Chambless LE, Rosamond WD, Mosley TH, Folsom AR. Risk factors for ischemic stroke subtypes: The atherosclerosis risk in communities study. *Stroke*. 2006;37:2493-2498

72. Neaton JD, Wentworth DN, Cutler J, Stamler J, Kuller L. Risk factors for death from different types of stroke. *Annals of epidemiology*. 1993;3:493-499

73.   Andersen KK, Olsen TS, Dehlendorff C, Kammersgaard LP. Hemorrhagic and ischemic strokes compared: Stroke severity, mortality, and risk factors. *Stroke*. 2009;40:2068-2072

74.   Walter Johnson OO, Mayowa Owolabi, Sonal Sachdev. Stroke: A global response is needed. *Bulletin of the World Health Organization*. 2016;94:634-634A

75.   Norrving B. *Oxford textbook of stroke and cerebrovascular disease*. Oxford: Oxford University Press, Incorporated; 2014.

76.   Feigin VLMD, Lawes CMMF, Bennett DAP, Barker-Collo SLP, Parag VM. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: A systematic review. *Lancet Neurol*. 2009;8:355-369

77.   Koton S, Schneider ALC, Rosamond WD, Shahar E, Sang Y, Gottesman RF, et al. Stroke incidence and mortality trends in US communities, 1987 to 2011. *JAMA*. 2014;312:259-268

78.   Hartmann A, Rundek T, Mast H, Paik MC, Boden-Albala B, Mohr JP, et al. Mortality and causes of death after first ischemic stroke: The Northern Manhattan stroke study. *Neurology*. 2001;57:2000-2005

79.   BrØNnum-Hansen H, Davidsen M, Thorvaldsen P. Long-term survival and causes of death after stroke. *Stroke*. 2001;32:2131-2136

80.   Seminog O SP, Wright L, Rayner M, Goldacre MJ. Determinants of the decline in mortality from acute stroke in England: Linked national database study of 795 869 adults. *BMJ*. 2019;366:l4934-l4934

81.   Kapoor A, Lanctôt KL, Bayley M, Kiss A, Herrmann N, Murray BJ, et al. "Good outcome" isn't good enough: Cognitive impairment, depressive symptoms, and social restrictions in physically recovered stroke patients. *Stroke*. 2017;48:1688-1690

82.   Grefkes C, Fink GR. Recovery from stroke: Current concepts and future perspectives. *Neurol Res Pract*. 2020;2:17-17

83.   Lanas F, Seron P. Facing the stroke burden worldwide. *Lancet Glob Health*. 2021;9:e235-e236

84.   Lee KB, Lim SH, Kim KH, Kim KJ, Kim YR, Chang WN, et al. Six-month functional recovery of stroke patients: A multi-time-point study. *Int J Rehabil Res*. 2015;38:173-180

85.   Bernhardt J, Hayward KS, Kwakkel G, Ward NS, Wolf SL, Borschmann K, et al. Agreed definitions and a shared vision for new standards in stroke recovery research:

The stroke recovery and rehabilitation roundtable taskforce. *Int J Stroke*. 2017;12:444-450

86. Branco JP OS, Sargento-Freitas J, Laíns J, Pinheiro J. Assessing functional recovery in the first six months after acute ischemic stroke: A prospective, observational study. *Eur J Phys Rehabil Med*. 2019;55:1-7

87. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF. Getting neurorehabilitation right: What can be learned from animal models? *Neurorehabil Neural Repair*. 2012;26:923-931

88. Gattringer T, Posekany A, Niederkorn K, Knoflach M, Poltrum B, Mutzenbach S, et al. Predicting early mortality of acute ischemic stroke: Score-based approach. *Stroke (1970)*. 2019;50:349-356

89. Knoflach M, Matosevic B, Seyfang L, Kiechl S, Willeit J, RÜCker M, et al. Functional recovery after ischemic stroke—a matter of age: Data from the Austrian stroke unit registry. *Neurology*. 2012;78:279-285

90. Abdul-Rahim AH, Fulton RL, Sucharew H, Kleindorfer D, Khatri P, Broderick JP, et al. National institutes of health stroke scale item profiles as predictor of patient outcome: External validation on independent trial data. *Stroke*. 2015;46:395-400

91. Jain A, Houten DV, Sheikh L. Retrospective study on national institutes of health stroke scale as a predictor of patient recovery after stroke. *J Cardiovasc Nurs*. 2016;31:69-72

92. Han TS, Fry CH, Gulli G, Affley B, Robin J, Irvin-Sellers M, et al. Prestroke disability predicts adverse poststroke outcome: A registry-based prospective cohort study of acute stroke. *Stroke*. 2020;51:594-600

93. Bushnell CD, Lee J, Duncan PW, Newby LK, Goldstein LB. Impact of comorbidities on ischemic stroke outcomes in women. *Stroke*. 2008;39:2138-2140

94. Alawieh A, Zhao J, Feng W. Factors affecting post-stroke motor recovery: Implications on neurotherapy after brain injury. *Behav Brain Res*. 2018;340:94-101

95. Weir CJ, Murray GD, Dyker AG, Lees KR. Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long term follow up study. *BMJ*. 1997;314:1303-1346

96. Jia Q, Zhao X, Wang C, Wang Y, Yan Y, Li H, et al. Diabetes and poor outcomes within 6 months after acute ischemic stroke: The china national stroke registry. *Stroke*. 2011;42:2758-2762

97.   Appelros P, Nydevik I, Viitanen M. Poor outcome after first-ever stroke: Predictors for death, dependency, and recurrent stroke within the first year. *Stroke*. 2003;34:122-126

98.   de Ridder IR, Dijkland SA, Scheele M, den Hertog HM, Dirks M, Westendorp WF, et al. Development and validation of the dutch stroke score for predicting disability and functional outcome after ischemic stroke: A tool to support efficient discharge planning. *Eur Stroke J*. 2018;3:165-173

99.   Chang GY. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology*. 2007;68:471-472

100.   Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology*. 2006;66:1175-1181

101.   Maas MB, Francis BA, Sangha RS, Lizza BD, Liotta EM, Naidech AM. Refining prognosis for intracerebral hemorrhage by early reassessment. *Cerebrovasc Dis*. 2017;43:110-116

102.   Heuschmann PU, Kolominsky-Rabas PL, Misselwitz B, Hermanek P, Leffmann C, Janzen RWC, et al. Predictors of in-hospital mortality and attributable risks of death after ischemic stroke: The german stroke registers study group. *Arch Intern Med*. 2004;164:1761-1768

103.   Bustamante A, Giralt D, García-Berrocoso T, Rubiera M, Álvarez-Sabín J, Molina C, et al. The impact of post-stroke complications on in-hospital mortality depends on stroke severity. *Eur Stroke J*. 2017;2:54-63

104.   Rohweder G, Ellekjær H, Salvesen Ø, Naalsund E, Indredavik B. Functional outcome after common poststroke complications occurring in the first 90 days. *Stroke*. 2015;46:65-70

105.   Turhan N, Atalay A, Atabek HK. Impact of stroke etiology, lesion location and ageing on post-stroke urinary incontinence as a predictor of functional recovery. *Int J Rehabil Res*. 2006;29:335-338

106.   Glader EL, Stegmayr B, Asplund K. Poststroke fatigue: A 2-year follow-up study of stroke patients in Sweden. *Stroke*. 2002;33:1327-1333

107.   Maaijwee NAMM, Arntz RM, Rutten-Jacobs LCA, Schaapsmeerders P, Schoonderwaldt HC, van Dijk EJ, et al. Post-stroke fatigue and its association with

poor functional outcome after stroke in young adults. *J Neurol Neurosurg Psychiatry*. 2015;86:1120-1126

108. O'Donnell MJ, Diener H-C, Sacco RL, Panju AA, Vinisko R, Yusuf S. Chronic pain syndromes after ischemic stroke: PROFESS trial. *Stroke*. 2013;44:1238-1243

109. Laska AC, Hellblom, A., Murray, V., Kahan, T., Von Arbin, M. Aphasia in acute stroke and relation to outcome. *Journal of Internal Medicine*. 2001;249:413-422

110. Ali M, Lyden P, Brady M. Aphasia and dysarthria in acute stroke: Recovery and functional outcome. *Int J Stroke*. 2015;10:400-406

111. Falkenberg HK, Mathisen TS, Ormstad H, Eilertsen G. "Invisible" visual impairments. A qualitative study of stroke survivors` experience of vision symptoms, health services and impact of visual impairments. *BMC Health Services Research*. 2020;20:302

112. Rohde D, Gaynor E, Large M, Mellon L, Hall P, Brewer L, et al. The impact of cognitive impairment on poststroke outcomes: A 5-year follow-up. *J Geriatr Psychiatry Neurol*. 2019;32:275-281

113. Wang S, Zhai H, Wei L, Shen B, Wang J. Socioeconomic status predicts the risk of stroke death: A systematic review and meta-analysis. *Preventive medicine reports*. 2020;19:101124-101124

114. Cooke EV, Mares K, Clark A, Tallis RC, Pomeroy VM. The effects of increased dose of exercise-based therapies to enhance motor recovery after stroke: A systematic review and meta-analysis. *BMC Med*. 2010;8:60-60

115. Krishnan K, Beishon L, Berge E, Christensen H, Dineen RA, Ozturk S, et al. Relationship between race and outcome in Asian, Black, and Caucasian patients with spontaneous intracerebral hemorrhage: Data from the virtual international stroke trials archive and efficacy of nitric oxide in stroke trial. *Int J Stroke*. 2018;13:362-373

116. Harrison JK, McArthur KS, Quinn TJ. Assessment scales in stroke: Clinimetric and clinical considerations. *Clin Interv Aging*. 2013;8:201-211

117. National Institute of Health. National Institute of neurological disorders and stroke. Stroke scale. https://www.stroke.nih.gov/documents/NIH_Stroke_Scale_508C.pdf.

118. Lyden P. Using the national institutes of health stroke scale: A cautionary tale. *Stroke*. 2017;48:513-519

119. Chalos V, van der Ende NAM, Lingsma HF, Mulder MJHL, Venema E, Dijkland SA, et al. National institutes of health stroke scale: An alternative primary outcome measure for trials of acute treatment for ischemic stroke. *Stroke*. 2020;51:282-290

120. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin Scale: Implications for stroke clinical trials a literature review and synthesis. *Stroke*. 2007;38:1091-1096

121. Bonita R, Beaglehole R. Recovery of motor function after stroke. *Stroke (1970)*. 1988;19:1497-1500

122. de Haan R, Limburg M, Bossuyt P, van der Meulen J, Aaronson N. The clinical meaning of rankin 'handicap' grades after stroke. *Stroke*. 1995;26:2027-2030

123. Wade DT, Collin C. The Barthel ADL Index: A standard measure of physical disability? *Int Disabil Stud*. 1988;10:64-67

124. Sinoff G, Ore L. The Barthel Activities of Daily Living Index: Self-reporting versus actual performance in the old-old (≥ 75 years). *J Am Geriatr Soc*. 1997;45:832-836

125. Christensen MC, Mayer S, Ferran J-M. Quality of life after intracerebral hemorrhage results of the factor seven for acute hemorrhagic stroke (fast) trial. *Stroke*. 2009;40:1677-1682

126. Karimi M BJ. Health, health-related quality of life, and quality of life: What is the difference? *Pharmacoeconomics*. 2016;34:645-649

127. Pickard AS, Johnson JA, Feeny DH, Shuaib A, Carriere KC, Nasser AM. Agreement between patient and proxy assessments of health-related quality of life after stroke using the eq-5d and health utilities index. *Stroke*. 2004;35:607-612

128. Nord E. Euroqol©: Health-related quality of life measurement. Valuations of health states by the general public in Norway. *Health Policy*. 1991;18:25-36

129. Herdman M, Gudex C, Lloyd A, Janssen B, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of eq-5d (eq-5d-5l). *Qual Life Res*. 2011;20:1727-1736

130. Sneeuw KC, Aaronson NK, de Haan RJ, Limburg M. Assessing quality of life after stroke. The value and limitations of proxy ratings. *Stroke*. 1997;28:1541-1549

131. Langhorne P, Stott DJ, Robertson L, MacDonald J, Jones L, McAlpine C, et al. Medical complications after stroke: A multicenter study. *Stroke*. 2000;31:1223-1229

132. Bhalla A. *Management of post-stroke complications*. Cham: Springer International Publishing : Imprint: Springer; 2015.

133. Mohan KM, Wolfe CDA, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: A systematic review and meta-analysis. *Stroke*. 2011;42:1489-1494

134. Chen Y, Yang L, Bian Z, Pan D, Zhang Y, Qin H, et al. Mortality and recurrent vascular events after first incident stroke: A 9-year community-based study of 0·5 million Chinese adults. *Lancet Glob Health*. 2020;8:e580-e590

135. Boulanger M, Béjot Y, Rothwell PM, Touzé E. Long-term risk of myocardial infarction compared to recurrent stroke after transient ischemic attack and ischemic stroke: Systematic review and meta-analysis. *J Am Heart Assoc*. 2018;7:n/a

136. Vermeer SE, Algra A, Franke CL, Koudstaal PJ, Rinkel GJE. Long-term prognosis after recovery from primary intracerebral hemorrhage. *Neurology*. 2002;59:205-209

137. Zhuo Y, Wu J, Qu Y, Yu H, Huang X, Zee B, et al. Clinical risk factors associated with recurrence of ischemic stroke within two years: A cohort study. *Medicine (Baltimore)*. 2020;99:e20830-e20830

138. Balami JSM, Chen R-LP, Grunwald IQP, Buchan AMP. Neurological complications of acute ischaemic stroke. *Lancet Neurol*. 2011;10:357-371

139. Claassen J, Ricardo Carhuapoma J, Kreiter KT, Du EY, Connolly ES, Mayer SA. Global cerebral edema after subarachnoid hemorrhage: Frequency, predictors, and impact on outcome. *Stroke*. 2002;33:1225-1232

140. Majidi S, Qureshi MH, Foster LD, Ewida A, Sianati B, Qureshi AI. Abstract 52: Global cerebral edema in patients with primary intracerebral hemorrhage: Results from brain edema at cerebral hemorrhage (BEACH) study. *Stroke (1970)*. 2018;49

141. Krieger DW, Demchuk AM, Kasner SE, Jauss M, Hantson L. Early clinical and radiological predictors of fatal brain swelling in ischemic stroke. *Stroke*. 1999;30:287-292

142. Coca A. High blood pressure and brain oedema in acute stroke: The relevance of ambulatory blood pressure monitoring during the first 24 h after stroke onset. *J Hypertens*. 2003;21:2023-2025

143. Johnston KC, Li JY, Lyden PD, Hanson SK, Feasby TE, Adams RJ, et al. Medical and neurological complications of ischemic stroke : Experience from the ranttas trial. *Stroke (1970)*. 1998;29:447-453

144. Al-Khaled M, Matthis C, Binder A, Mudter J, Schattschneider J, Pulkowski U, et al. Dysphagia in patients with acute ischemic stroke: Early dysphagia screening may

reduce stroke-related pneumonia and improve stroke outcomes. *Cerebrovascular Diseases*. 2016;42:81-89

145.   Kumar S, Selim M, Caplan L. Medical complications after stroke. *The Lancet Neurology*. 2010;9:105-118

146.   Sellars C, Bowie L, Bagg J, Sweeney MP, Miller H, Tilston J, et al. Risk factors for chest infection in acute stroke : A prospective cohort study. *Stroke*. 2007;38:2284-2291

147.   John G, Bardini C, Mégevand P, Combescure C, Dällenbach P. Urinary incontinence as a predictor of death after new-onset stroke: A meta-analysis. *European Journal of Neurology*. 2016;23:1548-1555

148.   Hannawi Y, Hannawi B, Rao CPV, Suarez JI, Bershad EM. Stroke-associated pneumonia: Major advances and obstacles. *Cerebrovascular Diseases*. 2013;35:430-443

149.   Ji R, Wang D, Shen H, Pan Y, Liu G, Wang P, et al. Interrelationship among common medical complications after acute stroke: Pneumonia plays an important role. *Stroke*. 2013;44:3436-3444

150.   Poisson NS, Johnston CS, Josephson AS. Urinary tract infections complicating stroke: Mechanisms, consequences, and possible solutions. *Stroke*. 2010;41:e180-e184

151.   Westendorp W, Nederkoorn P, Vermeij J-D, Dijkgraaf M, de Beek Dv. Post-stroke infection: A systematic review and meta-analysis. *BMC Neurology*. 2011;11:110

152.   Smith C, Almallouhi E, Feng W. Urinary tract infection after stroke: A narrative review. *J Neurol Sci*. 2019;403:146-152

153.   Prosser J, Macgregor L, Lees KR, Diener H-C, Hacke W, Davis S. Predictors of early cardiac morbidity and mortality after ischemic stroke. *Stroke*. 2007;38:2295-2302

154.   Jensen JKMD, Atar DMDD, Mickley HMDD. Mechanism of troponin elevations in patients with acute ischemic stroke. *Am J Cardiol*. 2007;99:867-870

155.   Brandstater ME, Roth EJ, Siebens HC. Venous thromboembolism in stroke - literature-review and implications for clinical-practice. *Arch Phys Med Rehabil*. 1992;73:S379-S391

156.   Hackett ML, Yapa C, Parag V, Anderson CS. Frequency of depression after stroke : A systematic review of observational studies. *Stroke*. 2005;36:1330-1340

157.   Andersen R. Reviews and notes: Guidelines for clinical practice: from development to use. *Annals of internal medicine*. 1994;120:252

158. Gundersen L. The effect of clinical practice guidelines on variations in care. *Ann. Intern. Med*. 2000;133:317–318

159. The European Stroke Organisation Executive Committee, the ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis*. 2008;25:457-507

160. Powers JW, Rabinstein AA, Ackerson MT, Adeoye CO, Bambakidis MN, Becker CK, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50:e344-e418

161. Hemphill CJ, Greenberg MS, Anderson SC, Becker RK, Bendok LB, Cushman NM, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46:2032-2060

162. Stroke Foundation. Clinical guidelines for stroke management. 2019. https://informme.org.au/en/Guidelines/Clinical-Guidelines-for-Stroke-Management

163. Stroke Unit Trialists Committee. Organised inpatient (stroke unit) care for stroke. *Cochrane Database of Systematic Reviews*. 2013

164. Party ISW. National clinical guideline for stroke. 2016

165. Collaboration SUT. Organised inpatient (stroke unit) care for stroke (Cochrane review). *The Cochrane Library*. 2013

166. Powers JW, Rabinstein AA, Ackerson MT, Adeoye CO, Bambakidis MN, Becker CK, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49:e46-e99

167. Government of India. Guidelines for prevention and management of stroke. 2019. https://main.mohfw.gov.in/sites/default/files/Guidelines%20for%20Prevention%20an d%20Managment%20of%20Stroke.pdf

168. Ingeman A, Andersen G, Hundborg HH, Svendsen ML, Johnsen SP. Processes of care and medical complications in patients with stroke. *Stroke*. 2011;42:167-172

169. Hall RE, Khan F, Bayley MT, Asllani E, Lindsay P, Hill MD, et al. Benchmarks for acute stroke care delivery. *International journal for quality in health care: journal of the International Society for Quality in Health Care*. 2013;25:710

170. Wiedmann S, Norrving B, Heuschmann PU, Nowe T, Abilleira S, Asplund K, et al. Variations in quality indicators of acute stroke care in 6 European countries: The European implementation score (EIS) collaboration. *Stroke*. 2012;43:458-463

171. Ayis SA, Coker B, Bhalla A, Wellwood I, Rudd AG, Di Carlo A, et al. *Variations in acute stroke care and the impact of organised care on survival from a European perspective: The European registers of stroke (eros) investigators*. Journal of Neurology, Neurosurgery & Psychiatry; 2013.

172. Muñoz Venturelli P, Robinson T, Lavados PM, Olavarría VV, Arima H, Billot L, et al. Regional variation in acute stroke care organisation. *Journal of the neurological sciences*. 2016;371:126

173. Melnychuk M, Morris S, Black G, Ramsay AIG, Eng J, Rudd A, et al. Variation in quality of acute stroke care by day and time of admission: Prospective cohort study of weekday and weekend centralised hyperacute stroke unit care and non-centralised services. *BMJ Open*. 2019;9:e025366-e025366

174. Black GB, Ramsay AIG, Baim-Lance A, Eng J, Melnychuk M, Xanthopoulou P, et al. What does it take to provide clinical interventions with temporal consistency? A qualitative study of London hyperacute stroke units. *BMJ Open*. 2019;9:e025367-e025367

175. Bray BDD, Cloud GCF, James MAF, Hemingway HP, Paley LBA, Stewart KF, et al. Weekly variation in health-care quality by day and time of admission: A nationwide, registry-based, prospective cohort study of acute stroke care. *Lancet*. 2016;388:170-177

176. Candelise LP, Gattinoni MP, Bersano AMD, Micieli GMD, Sterzi RMD, Morabito AP. Stroke-unit care for acute stroke patients: An observational follow-up study. *Lancet*. 2007;369:299-305

177. Balami JS, Hadley G, Sutherland BA, Karbalai H, Buchan AM. The exact science of stroke thrombolysis and the quiet art of patient selection. *Brain*. 2013;136:3528-3553

178. Bhaskar S, Stanwell P, Cordato D, Attia J, Levi C. Reperfusion therapy in acute ischemic stroke: Dawn of a new era? *BMC Neurol*. 2018;18:8-8

179. Wardlaw JM MV, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2014;2014:CD000213

180. Emberson J LK, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, Grotta J, Howard G, Kaste M, Koga M, von Kummer R,

Lansberg M, Lindley RI, Murray G, Olivot JM, Parsons M, Tilley B, Toni D, Toyoda K, Wahlgren N, Wardlaw J, Whiteley W, del Zoppo GJ, Baigent C, Sandercock P, Hacke W; Stroke Thrombolysis Trialists' Collaborative Group, Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from randomised trials. *Lancet*. 2014;384:1929-1935

181. Goldhoorn RJB, Graaf R, Van Rees JM, Lingsma H, Dippel DWJ, Hinsenveld WH, et al. Endovascular treatment for acute ischemic stroke in patients on oral anticoagulants: Results from the MR CLEAN Registry. *Stroke*. 2020;51:1781-1789

182. Goyal M MB, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CB, van der Lugt A, de Miquel MA, Donnan GA, Roos YB, Bonafe A, Jahan R, Diener HC, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millán M, Davis SM, Roy D, Thornton J, Román LS, Ribó M, Beumer D, Stouch B, Brown S, Campbell BC, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG; HERMES collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723-1731

183. Ciccone A, Valvassori L, Nichelatti M, Sgoifo A, Ponzio M, Sterzi R, Boccardi E. Endovascular treatment for acute ischemic stroke. *New England Journal of Medicine*. 2013;368:904-913

184. Sarraj A, Gupta R. Endovascular treatment for ischemic strokes with large vessel occlusion: Proven therapy and bright future. *Stroke*. 2015;46:1431-1432

185. Jadhav AP, Aghaebrahim A, Jankowitz BT, Haussen DC, Budzik RF, Bonafe A, et al. Benefit of endovascular thrombectomy by mode of onset: Secondary analysis of the DAWN trial. *Stroke*. 2019;50:3141-3146

186. Summers D LA, Wentworth D, Saver JL, Simpson J, Spilker JA, Hock N, Miller E, Mitchell PH; American Heart Association Council on Cardiovascular Nursing and the Stroke Council. Comprehensive overview of nursing and interdisciplinary care of the acute ischemic stroke patient: A scientific statement from the American Heart Association. *Stroke*. 2009;40:2911-2944

187. Hackam DG, Spence JD. Antiplatelet therapy in ischemic stroke and transient ischemic attack: An overview of major trials and meta-analyses. *Stroke (1970)*. 2019;50:773-778

188. Antithrombotic Trialists' (ATT) Collaboration BC, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: Collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373:1849-1860

189. Sandercock PA CC, Kane EJ. Anticoagulants for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2015;2015:CD000024

190. Klijn CJM, Paciaroni M, Berge E, Korompoki E, Kõrv J, Lal A, et al. Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation: A European Stroke Organisation guideline. *Eur Stroke J*. 2019;4:198-223

191. Paciaroni M, Agnelli G, Falocci N, Caso V, Becattini C, Marcheselli S, et al. Early recurrence and cerebral bleeding in patients with acute ischemic stroke and atrial fibrillation: Effect of anticoagulation and its timing: The RAF study. *Stroke*. 2015;46:2175-2182

192. Appleton JP, Sprigg N, Bath PM. Blood pressure management in acute stroke. *Stroke and Vascular Neurology*. 2016

193. Lee M, Ovbiagele B, Hong K-S, Wu Y-L, Lee J-E, Rao NM, et al. Effect of blood pressure lowering in early ischemic stroke: Meta-analysis. *Stroke*. 2015;46:1883-1889

194. Liu S, Li C, Li T, Xiong J, Zhao X. Effects of early hypertension control after ischaemic stroke on the outcome: A meta-analysis. *Cerebrovasc Dis*. 2015;40:270-278

195. Vidale S, Pini C, Arnaboldi M. Antihypertensive therapy after acute ischemic stroke. *JAMA*. 2014;311:2334-2334

196. Tziomalos K, Giampatzis V, Bouziana SD, Spanou M, Kostaki S, Papadopoulou M, et al. Effect of antihypertensive treatment on the long-term outcome of patients discharged after acute ischemic stroke. *Clin Exp Hypertens*. 2017;39:246-250

197. Gorelick PB, Whelton PK, Sorond F, Carey RM. Blood pressure management in stroke. *Hypertension*. 2020;76:1688-1695

198. Chapman N, Huxley R, Warlow C, Woodward M, Anderson C, Bousser MG, et al. Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: The PROGRESS trial. *Stroke*. 2004;35:116-121

199. Lakhan SE SM. Blood pressure lowering treatment for preventing stroke recurrence: A systematic review and meta-analysis. *Int Arch Med*. 2009;2

200. Willmot M, Leonardi-Bee J, Bath PMW. High blood pressure in acute stroke and subsequent outcome: A systematic review. *Hypertension*. 2004;43:18-24

201. Elliott J, Smith M. The acute management of intracerebral hemorrhage: A clinical review. *Anesth Analg*. 2010;110:1419-1427

202. Andrews BT, Chiles BW, III, Olsen WL, Pitts LH. The effect of intracerebral hematoma location on the risk of brain-stem compression and on clinical outcome. *J Neurosurg*. 1988;69:518-522

203. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *The New England journal of medicine*. 2013;368:2355

204. Huhtakangas J, Tetri S, Juvela S, Saloheimo P, Bode MK, Hillbom M. Effect of increased warfarin use on warfarin-related cerebral hemorrhage: A longitudinal population-based study. *Stroke*. 2011;42:2431-2435

205. Nilsson OG, Lindgren A, Ståhl N, Brandt L, Säveland H. Incidence of intracerebral and subarachnoid haemorrhage in southern Sweden. *J Neurol Neurosurg Psychiatry*. 2000;69:601-607

206. Steiner T, Rosand J, Diringer M. Intracerebral hemorrhage associated with oral anticoagulant therapy: Current practices and unresolved questions. *Stroke*. 2006;37:256-262

207. Rosand J, Eckman MH, Knudsen KA, Singer DE, Greenberg SM. The effect of warfarin and intensity of anticoagulation on outcome of intracerebral hemorrhage. *Arch Intern Med*. 2004;164:880-884

208. Kuramatsu JB, Gerner ST, Schellinger PD, Glahn J, Endres M, Sobesky J, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. *JAMA*. 2015;313:824-836

209. Steiner T PS, Griebe M, Hüsing J, Hajda J, Freiberger A, et al. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin k antagonists (INCH): A randomised trial. *Lancet Neurol*. 2016;15:566-573

210. Hanley DFMD, Thompson RE, Rosenblum M, Yenokyan G, Lane K, McBee N, et al. Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): A randomised, controlled, open-label, blinded endpoint phase 3 trial. *Lancet*. 2019;393:1021-1032

211. Mendelow AD GB, Rowan EN, Murray GD, Gholkar A, Mitchell PK, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): A randomised trial. *Lancet*. 2013;382:397-408

212. Takeuchi S, Wada K, Nagatani K, Otani N, Mori K. Decompressive hemicraniectomy for spontaneous intracerebral hemorrhage. *Neurosurg Focus*. 2013;34:E5-E5

213. Stienen MN, Germans M, Burkhardt J-K, Neidert MC, Fung C, Bervini D, et al. Predictors of in-hospital death after aneurysmal subarachnoid hemorrhage: Analysis of a nationwide database (SWISS SOS [SWISSstudy on aneurysmal subarachnoid hemorrhage]). *Stroke*. 2018;49:333-340

214. Oheda M IJ, Moriya S, Kumai T, Kawazoe Y, Nakae S, Kato Y, Hirose Y. Early rebleeding in patients with subarachnoid haemorrhage under intensive blood pressure management. *J Clin Neurosci*. 2015;22

215. van Gijn J, Rinkel GJE. Subarachnoid haemorrhage: Diagnosis, causes and management. *Brain*. 2001;124:249-278

216. Hillman J, Fridriksson S, Nilsson O, Zhengquan YU, SÄVeland H, Jakobsson K-E. Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: A prospective randomized study. *J Neurosurg*. 2002;97:771-778

217. D'Souza S. Aneurysmal subarachnoid hemorrhage. *J Neurosurg Anesthesiol*. 2015;27:222-240

218. Bekelis K, Gottlieb D, Su Y, O'Malley AJ, Labropoulos N, Goodney P, et al. Surgical clipping versus endovascular coiling for elderly patients presenting with subarachnoid hemorrhage. *J Neurointerv Surg*. 2016;8:913-918

219. Luoma A, Reddy U. Acute management of aneurysmal subarachnoid haemorrhage. *Continuing education in anaesthesia, critical care & pain*. 2013;13:52-58

220. Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis*. 2013;35:93-112

221. Bravata DM. Processes of care associated with acute stroke outcomes. *Archives of Internal Medicine* 2010;170

222. Arnold M, Liesirova K, Broeg-Morvay A, Meisterernst J, Schlager M, Mono M, et al. Dysphagia in acute stroke: Incidence, burden and impact on clinical outcome. *PLoS One*. 2016;11

223. Falsetti P, Acciai C, Palilla R, Bosi M, Carpinteri F, Zingarelli A, et al. Oropharyngeal dysphagia after stroke: Incidence, diagnosis, and clinical predictors in patients admitted to a neurorehabilitation unit. *Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association*. 2009;18:329

224. Eiichi Saitoh KP, Yoko Inamoto, Hitoshi Kagaya. *Dysphagia evaluation and treatment: From the perspective of rehabilitation medicine*. Singapore: Springer Singapore : Imprint: Springer; 2018.

225. Suntrup-Krueger S, Minnerup J, Muhle P, Claus I, Schröder Jens B, Marian T, et al. The effect of improved dysphagia care on outcome in patients with acute stroke: Trends from 8-year data of a large stroke register. *Cerebrovasc Dis*. 2018;45:101-108

226. Cohen DL, Roffe C, Beavan J, Blackett B, Fairfield CA, Hamdy S, et al. Post-stroke dysphagia: A review and design considerations for future trials. 2016;11:399-411

227. Donovan NJ, Daniels SK, Edmiaston J, Weinhardt J, Summers D, Mitchell PH. Dysphagia screening: State of the art: Invitational conference proceeding from the state-of-the-art nursing symposium, International Stroke Conference 2012. *Stroke*. 2013;44:e24-e31

228. Palli C, Fandler S, Doppelhofer K, Niederkorn K, Enzinger C, Vetta C, et al. Early dysphagia screening by trained nurses reduces pneumonia rate in stroke patients: A clinical intervention study. *Stroke*. 2017;48:2583-2585

229. Marik PE. Aspiration pneumonitis and aspiration pneumonia. *New England Journal of Medicine*. 2001;344:665-671

230. Dennis M LS, Cranswick G, Forbes J, FOOD Trial Collaboration. FOOD: A multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke. *Health Technol Assess*. 2006;10:iii–iv, ix.

231. Geeganage C, Beavan J, Ellender S, Bath PMW. Interventions for dysphagia and nutritional support in acute and subacute stroke. *Cochrane Database Syst Rev*. 2012;10:CD000323

232. Joundi RA, Saposnik G, Martino R, Fang J, Porter J, Kapral MK. Outcomes among patients with direct enteral vs nasogastric tube placement after acute stroke. *Neurology*. 2018;90:e544-e552

233. Kalra L, Hodsoll J, Irshad S, Smithard D, Manawadu D. Association between nasogastric tubes, pneumonia, and clinical outcomes in acute stroke patients. *Neurology*. 2016; 87 (13): 1352-9

234. Foley N, Teasell R, Salter K, Kruger E, Martino R. Dysphagia treatment post stroke: A systematic review of randomised controlled trials. *Age Ageing*. 2008;37:258-264

235. Wu C-H, Tseng M-C, Chen Y-W, Sung S-F, Yeh P-S, Lin H-J. Indwelling urinary catheterization after acute stroke. *Neurourol. Urodyn*. 2013;32:480-485

236. Kunin CM. Urinary-catheter-associated infections in the elderly. *International Journal of Antimicrobial Agents*. 2006;28:78-81

237. John G, Primmaz S, Crichton S, Wolfe C. Urinary incontinence and indwelling urinary catheters as predictors of death after new-onset stroke: A report of the south London stroke register. *J. Stroke Cerebrovasc. Dis.* 2018;27:118-124

238. Wong AA, Read SJ. Early changes in physiological variables after stroke. *Ann Indian Acad Neurol*. 2008;11:207-220

239. Qureshi AI. Acute hypertensive response in patients with stroke: Pathophysiology and management. *Circulation*. 2008;118:176-187

240. Jones SP, Leathley MJ, McAdam JJ, Watkins CL. Physiological monitoring in acute stroke: A literature review. *J Adv Nurs*. 2007;60:577-594

241. Sandset EC, Anderson CS, Bath PM, Christensen H, Fischer U, Gąsecki D, et al. European Stroke Organisation (ESO) guidelines on blood pressure management in acute ischaemic stroke and intracerebral haemorrhage. *European stroke journal*. 2021:239698732110121

242. Fuentes B, Ntaios G, Putaala J, Thomas B, Turc G, Díez-Tejedor E. European Stroke Organisation (ESO) guidelines on glycaemia management in acute stroke. *Eur Stroke J*. 2018;3:5-21

243. Ntaios G, Dziedzic T, Michel P, Papavasileiou V, Petersson J, Staykov D, et al. European Stroke Organisation (ESO) guidelines for the management of temperature in patients with acute ischemic stroke. *Int J Stroke*. 2015;10:941-949

244. National Institute for Health and Care Excellence. Stroke and transient ischaemic attack in over 16s: Diagnosis and initial management *NICE Guideline*. 2019

245. Robinson TG, Potter JF. Blood pressure in acute stroke. *Age Ageing*. 2004;33:6-12

246. Appleton JP, Sprigg N, Bath PM. Blood pressure management in acute stroke. *Stroke Vasc Neurol*. 2016;1:72-82

247. Liu Y, Yang Y, Jin H, Fan C, Lv P, Sun W, et al. Discrepant relationships between admission blood pressure and mortality in different stroke subtypes. *Journal of the neurological sciences*. 2017;383:47

248. Kim LJ, Gall RS, Nelson EM, Sharman GJ, Thrift GA. Lower systolic blood pressure is associated with poorer survival in long-term survivors of stroke. *Journal of Hypertension*. 2014;32:904-911

249. Leonardi-Bee MWJ, Bath JP, Phillips AGS, Sandercock AGP. Blood pressure and clinical outcomes in the international stroke trial. *Stroke: Journal of the American Heart Association*. 2002;33:1315-1320

250. Muscari A, Puddu GM, Serafini C, Fabbri E, Vizioli L, Zoli M. Predictors of short-term improvement of ischemic stroke. *Neurological Research*. 2013;35:594-601

251. Verschoof MA, Groot AE, Vermeij J-D, Westendorp WF, van den Berg SA, Nederkoorn PJ, et al. Association between low blood pressure and clinical outcomes in patients with acute ischemic stroke. *Stroke*. 2020;51:338-341

252. Roffe C, Corfield D. Hypoxaemia and stroke. *Reviews in clinical gerontology*. 2008;18:299-311

253. Ferdinand P, Roffe C. Hypoxia after stroke: A review of experimental and clinical evidence. *Experimental & translational stroke medicine*. 2016;8:9

254. Rowat AM, Dennis MS, Wardlaw JM. Central periodic breathing observed on hospital admission is associated with an adverse prognosis in conscious acute stroke patients. *Cerebrovascular Diseases*. 2006;21:340-347

255. Roffe C. Hypoxia and stroke. *Age and Ageing*. 2002;31:10-12

256. Stroke Foundation. National acute stroke services framework 2019. 2019. https://strokefoundation.org.au/media/E6682A70FFF0489FA66D28042C0FF472.ashx?la=en

257. Freburger JK LD, Johnson AM, Fraher EP. Physical and occupational therapy from the acute to community setting after stroke: Predictors of use, continuity of care, and timeliness of care. *Arch Phys Med Rehabil*. 2018;99:1077-1089

258. Li Z ZX, Wang K, Wen J. Effects of early mobilization after acute stroke: A meta-analysis of randomized control trials. *J Stroke Cerebrovasc Dis*. 2018;27:1326-1337

259. Julie B, Peter JL, Richard IL, Amanda Gay T, Fiona E, Janice C, et al. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): A randomised controlled trial. *Lancet (London, England)*. 2015;386:46

260. Cumming TB, Churilov L, Collier J, Donnan G, Ellery F, Dewey H, et al. Early mobilization and quality of life after stroke: Findings from AVERT. *Neurology*. 2019;93:e717-e728

261. Momosaki R, Yasunaga H, Kakuda W, Matsui H, Fushimi K, Abo M. Very early versus delayed rehabilitation for acute ischemic stroke patients with intravenous recombinant tissue plasminogen activator: A nationwide retrospective cohort study. *Cerebrovasc Dis*. 2016;42:41-48

262. Dickey L, Kagan A, Lindsay MP, Fang J, Rowland A, Black S. Incidence and profile of inpatient stroke-induced aphasia in Ontario, Canada. *Arch Phys Med Rehabil*. 2010;91:196-202

263. Bersano A, Burgio F, Gattinoni M, Candelise L. Aphasia burden to hospitalised acute stroke patients: Need for an early rehabilitation programme. *Int J Stroke*. 2009;4:443-447

264. Godecke E, Hird K, Lalor EE, Rai T, Phillips MR. Very early poststroke aphasia therapy: A pilot randomized controlled efficacy trial. *Int J Stroke*. 2012;7:635-644

265. Godecke E, Armstrong E, Rai T, Ciccone N, Rose ML, Middleton S, et al. A randomized control trial of intensive aphasia therapy after acute stroke: The very early rehabilitation for speech (VERSE) study. *International journal of stroke*. 2021;16:556-572

266. Breitenstein C, Grewe T, Flöel A, Ziegler W, Springer L, Martus P, Huber W, et al. Intensive speech and language therapy in patients with chronic aphasia after stroke: A randomised, open-label, blinded-endpoint, controlled trial in a health-care setting. *The Lancet*. 2017;389:1528-1538

267. van Zandvoort MJ KR, Nys GM, de Haan EH, Kappelle LJ. Early neuropsychological evaluation in patients with ischaemic stroke provides valid information. *Clin Neurol Neurosurg*. 2005;107:385-392

268. Dong YH, Slavin MJ, Chan BPL, Venketasubramanian N, Sharma VK, Crawford JD, et al. Cognitive screening improves the predictive value of stroke severity scores for functional outcome 3–6 months after mild stroke and transient ischemic attack: An observational study. *BMJ Open*. 2013; 3 (9) e003105-e003105

269. Stolwyk RJ, O'Neill MH, McKay AJD, Wong DK. Are cognitive screening tools sensitive and specific enough for use after stroke? A systematic literature review. *Stroke*. 2014;45:3129-3134

270. Quinn TJ, Elliott E, Langhorne P. Cognitive and mood assessment tools for use in stroke. *Stroke*. 2018;49:483-490

271. Ayerbe L, Ayis S, Wolfe CDA, Rudd AG. Natural history, predictors and outcomes of depression after stroke: Systematic review and meta-analysis. *Br J Psychiatry*. 2013;202:14-21

272. Bartoli F, Di Brita C, Crocamo C, Clerici M, Carrà G. Early post-stroke depression and mortality: Meta-analysis and meta-regression. *Frontiers in Psychiatry*. 2018;9

273. Meader N, Moe-Byrne T, Llewellyn A, Mitchell AJ. Screening for poststroke major depression: A meta-analysis of diagnostic validity studies. *J Neurol Neurosurg Psychiatry*. 2014;85:198-206

274. Lees R, Stott DJ, Quinn TJ, Broomfield NM. Feasibility and diagnostic accuracy of early mood screening to diagnose persisting clinical depression/anxiety disorder after stroke. *Cerebrovasc Dis*. 2014;37:323-329

275. Yaria J, Gil A, Makanjuola A, Oguntoye R, Miranda J, Lazo-Porras M, et al. Quality of stroke guidelines in low- and middle-income countries: A systematic review. *Bulletin of the World Health Organization*. 2021;99:640-652E

276. Bayona HO, Owolabi M, Feng W, Sawers JR, Olowoyo P, Yaria J, et al. Abstract wp418: A systematic comparison of key features of ischaemic stroke prevention guidelines in low- and middle-income vs high-income countries. *Stroke (1970)*. 2017;48

277. Thrift AG, Pandian J, Abd-Allah F, Yaria J, Phan HT, Roth G, et al. The state of stroke services across the globe: Report of world stroke organization–world health organization surveys. *Int J Stroke*. 2021;16:889-901

278. Pandian JD, William AG, Kate MP, Norrving B, Mensah GA, Davis S, et al. Strategies to improve stroke care services in low- and middle-income countries: A systematic review. *Neuroepidemiology*. 2017;49:45-61

279. Baatiema L AA, Sav A, Mnatzaganian G, Chan CK, Somerset S. Barriers to evidence-based acute stroke care in Ghana: A qualitative study on the perspectives of stroke care professionals. *BMJ Open*. 2017;7(4): e015385

280. Chimatiro GL, Rhoda AJ. Scoping review of acute stroke care management and rehabilitation in low and middle-income countries. *BMC Health Serv Res*. 2019;19:789-789

281. Abraham S, Krishnan SV, Thaha F, Balakrishnan JM, Thomas T, Palatty BU. Factors delaying management of acute stroke: An Indian scenario. *International Journal of Critical Illness & Injury Science*. 2017;7:224-230

282. Rhoda A CN, Azaria S, Urimubenshi G. Provision of inpatient rehabilitation and challenges experienced with participation post discharge: Quantitative and qualitative inquiry of African stroke patients. *BMC Health Serv Res*. 2015;15:423

283. Prvu Bettger J, Liu C, Gandhi DBC, Sylaja PN, Jayaram N, Pandian JD. Emerging areas of stroke rehabilitation research in low- and middle-income countries: A scoping review. *Stroke*. 2019;50:3307-3313

284. Fischer F, Lange K, Klose K, Greiner W, Kraemer A. Barriers and strategies in guideline implementation-a scoping review. *Healthcare (Basel)*. 2016;4:36

285. Westfall JM, Mold J, Fagnan L. Practice-based research—"blue highways" on the NIH roadmap. *JAMA*. 2007;297:403-406

286. Grol R GJ. From best evidence to best practice: Effective implementation of change in patients' care. *Lancet*. 2003;362:1225-1230

287. Rudd BN, Davis M, Beidas RS. Integrating implementation science in clinical research to maximize public health impact: A call for the reporting and alignment of implementation strategy use with implementation outcomes in clinical research. *Implement Sci*. 2020;15:103-103

288. Baatiema L, Otim ME, Mnatzaganian G, de-Graft Aikins A, Coombes J, Somerset S. Health professionals' views on the barriers and enablers to evidence-based practice for acute stroke care: A systematic review. *Implement Sci*. 2017;12:74-74

289. Prabhakaran S, Ruff I, Bernstein RA. Acute stroke intervention: A systematic review. *JAMA*. 2015;313:1451-1462

290. Strasser R, Kam SM, Regalado SM. Rural health care access and policy in developing countries. *Annu Rev Public Health*. 2016;37:395-412

291. Muñoz-Venturelli P, Arima H, Lavados P, Brunser A, Peng B, Cui L, et al. Head position in stroke trial (HeadPoST) - sitting-up vs lying-flat positioning of patients with acute stroke: Study protocol for a cluster randomised controlled trial. *Trials*. 2015; 16(1): 256

292. Billot L, Woodward M, Arima H, Hackett ML, Muñoz Venturelli P, Lavados PM, et al. Statistical analysis plan for the head position in stroke trial (HeadPoST): An international cluster cross-over randomized trial. *Int J Stroke*. 2017;12:667-670

293. Van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res*. 2007;16:219-242

294. Anderson CS, Arima H, Lavados P, Billot L, Hackett ML, Olavarría VV, et al. Cluster-randomized, crossover trial of head positioning in acute stroke. *The New England journal of medicine*. 2017;376:2437

Chapter 2 Guideline-recommended care processes to prevent post-stroke infections

Post-stroke infections, particularly pneumonia and urinary tract infections (UTIs), are common complications after acute stroke and are related to increased risk of poor outcome, prolonged hospital stay, and increased cost of care. However, the supporting evidence for the care recommendations for post-stroke infections is at low to moderate grade due to limited studies. This Chapter contains my two papers which focus on the care processes recommended by guidelines to prevent and manage post-stroke infections, including dysphagia screening and assessment (Section 2.1) and early indwelling urinary catheterisation (IUC) (Section 2.2).

The objectives of this chapter are:

1. To determine the associations between a "brief" screen and "detailed" assessment of dysphagia on clinical outcomes in acute stroke patients at 90 days (Section 2.1).

2. To determine the association between IUC and clinical outcomes at 90 days in patients with stroke (section 2.2).

The HeadPoST study, which collected the principal care and management variables during patients' hospitalisation, provided a unique opportunity to examine the utility of these care processes on the key clinical outcomes in a large cohort of acute stroke patients with a heterogeneous characteristic. I used statistical analyses that incorporated the Chi-square test, T-test, Wilcoxon rank-sum test and generalized linear mixed models. Multiple imputations and stratification were used for sensitivity analyses.

The findings showed that the utilisation of these guideline-recommended care processes varied by region and local guidelines. Failing either a dysphagia screening or assessment was associated with increased risks of pneumonia and poor clinical outcomes after acute stroke. Early IUC was associated with death or dependency but not with UTIs. Further studies to explore the appropriate management in patients with dysphagia and IUC are urgently needed.

I co-designed the studies, analysed and interpreted the data, wrote the first drafts of the manuscripts, coordinated and incorporated co-authors' edits, and prepared and submitted the manuscripts, drafted the responses to the editor's and reviewers' comments, and prepared the final drafts of the manuscripts for publication.

2.1 Dysphagia screening and risks of pneumonia and adverse outcomes after acute stroke: an international multicentre study

Dysphagia screening and risks of pneumonia and adverse outcomes after acute stroke: an international multicentre study

Menglu Ouyang, Elizabeth Bowden, Hisatomi Arima, Pablo M. Lavados, Laurent Billot, Maree L. Hackett, Verónica V. Olavarría, Paula Muñoz-Venturelli, Lili Song, Kris Rogers, Sandy Middleton, Octavio M. Pontes-Neto, Tsong-Hai Lee, Caroline L. Watkins, Thompson Robinson, Craig S. Anderson, for the HeadPoST Investigators

Refer to the following 10 pages

✳ ✳ ✳

Dysphagia screening and risks of pneumonia and adverse outcomes after acute stroke: An international multicenter study

Menglu Ouyang[1,2], Elizabeth Boaden[3], Hisatomi Arima[1,4], Pablo M Lavados[5,6,7], Laurent Billot[1], Maree L Hackett[1,3] ⓘ, Verónica V Olavarría[5,6] ⓘ, Paula Muñoz-Venturelli[1,5,6], Lili Song[1,2], Kris Rogers[1], Sandy Middleton[8] ⓘ, Octavio M Pontes-Neto[9], Tsong-Hai Lee[10], Caroline Watkins[3], Thompson Robinson[11] and Craig S Anderson[1,2,12] ⓘ; for the HeadPoST Investigators*

Abstract

Background: Dysphagia is associated with aspiration pneumonia after stroke. Data are limited on the influences of dysphagia screen and assessment in clinical practice.

Aims: To determine associations between a "brief" screen and "detailed" assessment of dysphagia on clinical outcomes in acute stroke patients.

Methods: A prospective cohort study analyzed retrospectively using data from a multicenter, cluster cross-over, randomized controlled trial (Head Positioning in Acute Stroke Trial [HeadPoST]) from 114 hospitals in nine countries. HeadPoST included 11,093 acute stroke patients randomized to lying-flat or sitting-up head positioning. Herein, we report predefined secondary analyses of the association of dysphagia screening and assessment and clinical outcomes of pneumonia and death or disability (modified Rankin scale 3–6) at 90 days.

Results: Overall, 8784 (79.2%) and 3917 (35.3%) patients were screened and assessed for dysphagia, respectively, but the frequency and timing for each varied widely across regions. Neither use of a screen nor an assessment for dysphagia was associated with the outcomes, but their results were compared to "screen-pass" patients, those who failed had higher risks of pneumonia (adjusted odds ratio [aOR] = 3.00, 95% confidence interval [CI] = 2.18–4.10) and death or disability (aOR = 1.66, 95% CI = 1.41–1.95). Similar results were evidence for the results of an assessment for dysphagia. Subsequent feeding restrictions were related to higher risk of pneumonia in patients failed dysphagia screen or assessment (aOR = 4.06, 95% CI = 1.72–9.54).

[1]The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, Australia
[2]The George Institute China at Peking University Health Science Center, Beijing, China
[3]Faculty of Health and Wellbeing, University of Central Lancashire, Preston, Lancashire, UK
[4]Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, Fukuoka, Japan
[5]Department of Neurology and Psychiatry, Clínica Alemana de Santiago, Santiago, Chile
[6]Facultad de Medicina, Clinica Alemana Universidad del Desarrollo, Santiago, Chile
[7]Departamento de Ciencias Neurológicas, Facultad de Medicina, Universidad de Chile Universidad de Chile, Santiago, Chile
[8]Nursing Research Institute, St Vincent's Health (Sydney) Australia, Australian Catholic University, Sydney, Australia

[9]Stroke Service—Neurology Division, Department of Neuroscience and Behavioral Sciences, Ribeirão Preto Medical School, University of Sao Paulo, Sao Paulo, Brazil
[10]Stroke Center and Department of Neurology, Linkou Chang Gung Memorial Hospital and College of Medicine, Chang Gung University, Taoyuan, Taiwan
[11]Department of Cardiovascular Sciences and NIHR Leicester Biomedical Research Centre, University of Leicester, Leicester, UK
[12]Neurology Department, Royal Prince Alfred Hospital, Sydney Health Partners, Sydney, Australia

*Full list of investigators is listed in the Supplemental Appendix.

Corresponding author:
Craig S Anderson, The George Institute for Global Health, PO Box M201, Missenden Road, Sydney, NSW 2050, Australia.
Email: canderson@georgeinstitute.org.au

Conclusions: Failing a dysphagia screen is associated with increased risks of pneumonia and poor clinical outcome after acute stroke. Further studies concentrate on determining the effective subsequent feeding actions are needed to improve patient outcomes.

Introduction

Pneumonia is a common complication of acute stroke, which increases the likelihood of death and poor recovery, and costs of care.[1–3] As dysphagia is also common and associated with aspiration pneumonia,[4–6] stroke management guidelines recommend that health professionals screen for this impairment before their patients receive any oral intake of food, fluid, or medications.[7–12] However, the evidence base supporting this recommendation is of moderate grade, with only one cluster clinical trial of implementing protocols that included dysphagia screening/assessment in conjunction with fever and hyperglycemia management showing improved short- and long-term clinical outcomes.[13] A small "before-and-after" study showed that the implementation of dysphagia screening by nurses reduced pneumonia and length of stay in hospital,[14] while delays in screening and assessment for dysphagia in patients were associated with pneumonia in the UK national stroke registry.[15] Although a range of simple and systematic approaches exist for the assessment of dysphagia, data are limited on how well these are incorporated into clinical pathways and influence feeding actions and clinical outcomes in practice.[14] The international Head Positioning in Acute Stroke Trial (HeadPoST) data set,[16] therefore, provides an opportunity to examine the utility of screening and assessment of dysphagia, and feeding actions, on key clinical outcomes in a large cohort of stroke patients with a broad range of characteristics who were recruited from 114 hospitals in nine countries.

Methods

Design

This study is a predefined secondary analysis of HeadPoST, the design and main results of which are outlined in detail elsewhere.[16] In brief, HeadPoST was an international, multicenter, cluster cross-over, randomized controlled trial of two different head positions in 11,093 adult patients with acute stroke undertaken between March 2015 and November 2016. Patients were excluded if they had resolved neurological symptoms consistent with a transient ischemic attack, a clear contraindication to either head position, any medical condition that would compromise adherence to the protocol or assigned head position, or refusal to participate. The main results showed there were no significant differences in disability outcomes and risks between those assigned to the lying-flat or sitting-up head positions for at least 24 h after hospital admission. The study was approved by ethics committees of participating sites. Consent was obtained from all patients or appropriate surrogates for participation, use of medical data, and central follow-up assessment.

Assessments

After central randomization, stratified by country, centers were required to implement the first assigned intervention position until a target number of consecutive patients was reached, before crossing over to apply the other intervention to a similar number of consecutive patients. Data collection included the time, result, and action of any: dysphagia screen, defined as the use of a simple brief noninvasive bedside test, such as a drinking a sip of water; and any dysphagia assessment, defined as a more systematic examination performed by a speech pathologist/therapist or qualified clinician, according to local standard protocols. Only data pertaining to the first performed dysphagia screen/assessment were recorded. In practice, patients should have a dysphagia assessment after failing a dysphagia screen,[12] and the results used to inform a local treatment plan to prevent aspiration pneumonia. As this was a pragmatic study, the specific practitioner, tool, and approach to any dysphagia screen/assessment were not specified in the protocol. Moreover, the study protocol allowed some flexibility in the assigned head position: to address any potential investigator concerns over harms, those patients allocated to the lying-flat position could be turned to their side; and patients assigned to either head position could have this interrupted for short intervals (≤3 nonconsecutive periods for <30 min) for feeding or mobility over the required 24 h of applying the intervention, if it was considered necessary.

Outcome

The primary outcome for these analyses was pneumonia, reported as a serious adverse event, and classified according to the following predefined criteria[17]: "definite" pneumonia included ≥ 3 features of new or worsening cough, increased respiratory rate, oxygen desaturation, fever $> 38°C$, leukocytosis or leukopenia, and purulent secretions, rales or bronchial breath sounds over the chest together with positive radiological abnormalities (patchy infiltration, lobar consolidation, or pleural effusion); "probable" pneumonia was defined as ≥ 3 of the listed features but without any radiological abnormalities; and "uncertain" pneumonia was < 3 features with or without an abnormal X-ray. The secondary outcome was death or disability, defined as scores 3–6 on the modified Rankin scale (mRS) on blinded assessment at 90 days postrandomization.

Statistical analysis

Both individual and hospital baseline characteristics were assessed in univariate analyses. Predictors of dysphagia screening (or assessment) and the outcomes of interest were determined by chi-square test for categorical variables, t-test for approximately normally distributed variables, and Wilcoxon rank-sum test for skewed continuous variables. Variables identified with P values < 0.2 were included in multivariable models. All potentially significant predictors were included in multilevel logistic regression models to estimate associations (Supplemental Tables S1 and S2). The primary analyses were the associations between the use of a dysphagia screen (as a quality of stroke care performance measure, yes vs. no) and its result (fail vs. pass) on the outcomes of pneumonia and death or disability (mRS: 3–6), independent of having a dysphagia assessment. Secondary analyses were for associations of a dysphagia assessment according to dysphagia screen status (unscreened, pass, and fail) and clinical outcomes. A complete case data set was used to build models for analyzing each of the association. The term "unadjusted" was used in an initial, binomial logistic regression, hierarchical mixed model, where adjustment was made for the study design with fixed effects of head position (lying-flat vs. sitting-up) and cross-over period, and random effects of cluster and interaction between cluster and cross-over period. Sequential multilevel models were then "adjusted," first for region of recruitment and then with the addition of prespecified baseline covariates and hospital characteristics. A further analysis was conducted to explore the influence of feeding restrictions on clinical outcomes in patients who failed either screening or assessment. Any interactions between significant variables and dysphagia screen/assessment were checked in each level of the

models, and only those that were significant ($P < 0.01$) were included in the final model. Associations between exposures and outcomes were assessed across the predefined subgroups of the main trial. Multiple imputations were used for sensitivity analysis due to 12% missing data on 90-day clinical outcome. Ten imputed data sets were generated and the odds ratios (ORs) were pooled from the imputation analysis. Data are reported with OR and 95% confidence intervals (CIs), and a standard level of significance was used ($P < 0.05$). No adjustments were made for multiplicity or missing data. All analyses were performed with SAS Software version 9.3 (SAS Institute, Cary, NC).

Results

Frequency and time of dysphagia screen and assessment

Among 11,093 HeadPoST participants, there were 15 patients without any details on the use of dysphagia screening or assessment. Overall, there were 8784 (79.2%) and 3917 (35.3%) patients who had a screen and assessment for dysphagia, respectively, but the frequency and timing for each varied significantly across regions (Table 1). Frequency of dysphagia screening was low in China (69.2%) and South America (61.5%) compared to Australia/UK (91.4%) and India/Sri Lanka (87.0%). Conversely, the frequency of dysphagia assessment was highest in South America (62.3%) compared to the other regions (range, 23.3%–35.5%). Overall, median times from admission to dysphagia screen and assessment were 2.2 h (interquartile range (IQR) = 0.8–6.3) and 12.5 h (IQR = 1.8–28.0), respectively, but this varied from approximately 1 to 38 h across regions, being shortest in China and longest in South America (Table 1). The majority of dysphagia assessments were undertaken subsequent to dysphagia screening; only 3% had an assessment recorded before a dysphagia screen.

Baseline and hospital characteristics by screening and assessment

Patients without a dysphagia screen were younger, had greater premorbid disability, and more severe neurological impairment at the time of presentation (Supplemental Table S3). At hospital level, patients from hospitals with a stroke unit, guidelines for acute stroke treatment, local special pathways from stroke care, local protocols for swallow dysfunction, and speech pathologists were more likely to receive screening (Supplemental Table S4). In comparison, in hospital with available protocol for swallow dysfunction, neurologists, dysphagia specialist nurses, and speech

Table 1. Frequency and timing of dysphagia screening and assessment in 11,093 stroke patients, by region of recruitment

Region	Dysphagia screen performed				Dysphagia assessment performed			
	N (%)	P value[a]	Time from hospital arrival Median (IQR), hours	P value[b]	N (%)	P value[a]	Time from hospital arrival Median (IQR), hours	P value[b]
Overall (N = 11,093)	8784 (79.2)		2.2 (0.8–6.3)		3917 (35.3)		12.5 (1.8–28.0)	
Australia/UK (N = 4761)	4338 (91.4)	<0.0001	2.6 (1.1–5.7)	<0.0001	1684 (35.5)	<0.0001	20.0 (6.2–34.1)	<0.0001
China[c] (N = 4652)	3218 (69.2)		1.2 (0.5–3.4)		1488 (32.0)		1.4 (0.7–4.4)	
India/Sri Lanka (N = 770)	670 (87.0)		6.5 (1.5–19.0)		179 (23.3)		19.0 (6.8–48.0)	
South America (N = 910)	558 (61.5)		26.7 (12.8–46.6)		566 (62.3)		37.5 (20.9–54.2)	

IQR: interquartile range.
[a]P value obtained from Chi-square test.
[b]P value obtained from Mann–Whitney Test (Wilcoxon rank-sum test).
[c]Includes Taiwan.

pathologists, patients were more likely to have further dysphagia assessment (Supplemental Table S5).

Results of dysphagia screen and further assessment

Overall, 22.8% (2004/8784) of patients failed a dysphagia screen (Table 2; Supplemental Figure S1). Compared to those who passed, dysphagia screen-fail patients were significantly older, with greater premorbid disability, cardiovascular disease and chronic obstructive pulmonary disease, and more severe baseline neurological impairment (Table 2). Of the 6778 patients who passed the dysphagia screen, 1775 (26.2%) proceeded to

a dysphagia assessment, which was passed by the great majority (96.1%). There were 2292 patients who did not have a dysphagia screen, of whom 739 (32.2%) proceeded to a dysphagia assessment (Supplemental Figure S1). They were older, more often female, with greater premorbid dependency and more severe baseline neurological impairment without coma, and more often placed on a feeding restriction regime, compared to those without a dysphagia assessment (Supplemental Table S6). Of the 2003 dysphagia screen-fail patients, there were 1402 (70.0%) who proceeded to a dysphagia assessment; they tended to have milder neurological impairment compared to the 601 patient who did not have a dysphagia assessment (Supplemental Table S7).

Table 2. Baseline characteristics of patients, by result of dysphagia screen

Baseline characteristics	Pass N = 6778	Fail N = 2004	P value
Age, years	66.9 ± 13.6	72.5 ± 14.1	<0.0001
Male	4215 (62.2)	1062 (53.0)	<0.0001
Pathological subtype			
Acute ischemic stroke	5749 (85.0)	1715 (86.0)	<0.0001
Intracerebral hemorrhage	492 (7.3)	211 (10.6)	
Uncertain	523 (7.7)	69 (3.5)	
GCS score	15 (15–15)	14 (11–15)	<0.0001
Severe (3–8)	67 (1.0)	117 (5.8)	<0.0001
NIHSS score	4 (2–6)	11 (6–18)	<0.0001
Severe ≥ 15	258 (3.8)	705 (35.2)	<0.0001
Pre-stroke mRS score			<0.0001
Independent (0–1)	5504 (81.2)	1474 (73.6)	
Mild disability but independent (2)	676 (10.0)	206 (10.3)	
Disabled (3–5)	590 (8.7)	317 (15.8)	
Prior cardiovascular disease[a]	3373 (49.8)	1137 (56.7)	<0.0001
Prior COPD	238 (3.5)	91 (4.6)	0.030
Time to screen, hours	2.0 (0.8–5.8)	2.7 (1.0–10.5)	<0.0001
>24 h	405 (6.5)	262 (14.0)	<0.0001
Feeding restrictions	750 (11.2)	1681 (84.1)	<0.0001

Note: Data are n (%), mean ± SD, or median (interquartile range). GCS: Glasgow coma scale; NIHSS: National Institute of Health Stroke Scale; COPD: chronic obstructive pulmonary disease; mRS: modified Rankin scale.
[a]Includes history of heart disease, stroke, or diabetes mellitus.

Patients who neither had a screen nor assessment were younger, had lower NIHSS scores, were less dependent, and free of prior medical history, but with higher GCS scores at baseline (Supplemental Table S8).

Pneumonia outcome

Overall, 362 (3.3%) patients developed pneumonia, but the frequency varied significantly across regions and according to the use and results of a dysphagia screening and assessment (Supplemental Table S9). In particular, the frequency of pneumonia was higher in those who had dysphagia screen (or assessment), and especially in those who failed, and it was also associated with longer times to having a dysphagia screen (and assessment) (Supplemental Tables S9 and S10).

In multivariable analysis adjusted both individual and hospital level of characteristics, there was no association between the use of dysphagia screen and pneumonia (adjusted odds ratio (aOR) = 1.20, 95% CI = 0.82–1.75; Figure 1(a)). However, compared to those who passed a dysphagia screen, screen-fail patients had a significantly higher risk of pneumonia (1.5% vs. 10.0%; aOR = 3.00, 95% CI = 2.19–4.10) (Supplemental Table S9; Figure 2(a), Model 2). Similarly, there was no association between the use of dysphagia assessment and risk of pneumonia (Supplemental Figure S2(A)).

Death and disability at 90-day outcome

There were 12% (1345/11,093) of patients with missing 90-day clinical outcome data, who were younger and with greater premorbid disability compared to those with complete data (Supplemental Table S12). There was no association between the use of dysphagia screen itself and poor clinical outcome (death or disability) (aOR = 0.96, 95% CI = 0.81–1.13; Figure 1(b)). However, there was a significant association between those who failed compared to those who passed a dysphagia screen (68.1% vs. 30.8%, $P < 0.0001$; aOR = 1.66, 95% CI = 1.41–2.95; Supplemental Table S9 and Figure 2(b)). Compared to patients who did not have a dysphagia assessment, those who did had a higher risk of poor outcome (47.5% vs. 34.6%, $P < 0.0001$; Supplemental Table S9). There was a significant association between dysphagia assessment and poor outcome in patients who passed a dysphagia screen (aOR = 1.39, 95% CI = 1.14–1.69; Supplemental Figure S2(B)). The significance of this association varied by region (Supplemental Figure S3). Failing a dysphagia assessment was significantly associated with increased risks of pneumonia (aOR = 3.04, 95% CI = 2.11–4.39) and poor outcome (aOR = 2.22, 95% CI = 1.76–2.80; Supplemental Figure S4).

Figure 1. Outcomes by the use of dysphagia. Poor outcome refers to death or disability (scores 3–6 on the mRS) at 90 days. *Unadjusted refers to adjustment for study design features in a mixed logistic regression model with fixed period, fixed head position treatment, random cluster, and random cluster cross-over period. †Model 1 (country level) includes adjustment for region of recruitment (Australia and UK, China includes Taiwan, India and Sri Lanka, and South America). ‡Model 2 (individual level) for analysis includes variables in model 1 and age as continuous, sex, premorbid function (mRS scores: 0–1 as independent; 2 as mild disability but independent; 3–5 as disabled), NIHSS (National Institutes of Health Stroke Scale) as continuous, stroke type (acute ischemic, intracerebral hemorrhage, or uncertain), past history of cardiovascular disease (heart disease, diabetes mellitus, or stroke), past history of chronic obstructive pulmonary disease, and current smoker. §Model 3 (hospital level) for (a) further adjusted number of stroke patients admitted annually, academic hospital, location of hospital, local protocol for swallow dysfunction, available of neurologists, dysphagia specialist nurses, and speech pathologists. For (b) further adjusted present of dedicated stroke unit and guidelines for acute treatment of stroke care. OR: odds ratio; CI: confidence interval.

(a)	Pneumonia OR (95% CI)	(b)	Poor Outcome OR (95% CI)
Unadjusted *	0.96 (0.67, 1.38)		0.90 (0.78, 1.04)
Model 1†	0.89 (0.62, 1.28)		0.88 (0.76, 1.01)
Model 2‡	1.18 (0.81, 1.71)		0.97 (0.82, 1.15)
Model 3§	1.20 (0.82, 1.75)		0.96 (0.81, 1.13)
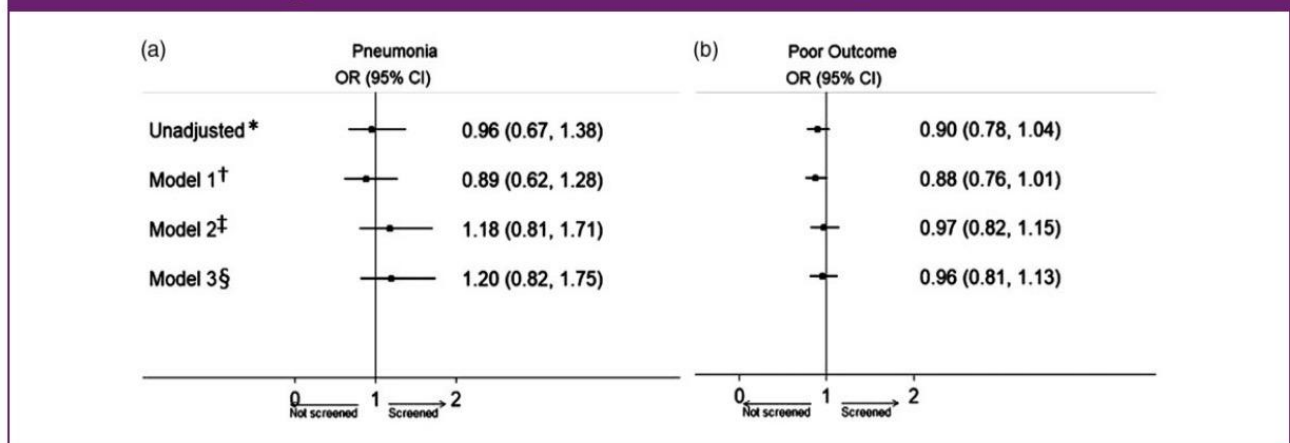
Figure 2. Outcomes by results of dysphagia screen. Poor outcome refers to death or disability (scores 3–6 on the mRS) at 90 days. *Unadjusted refers to adjustment for study design features in a mixed logistic regression model with fixed period, fixed head position treatment, random cluster, and random cluster cross-over period. [†]Model 1 (country level) includes adjustment for region of recruitment (Australia and UK, China includes Taiwan, India and Sri Lanka, and South America). [‡]Model 2 (individual level) for analysis includes variables in model 1 and age as continuous, sex, premorbid function (mRS scores: 0–1 as independent; 2 as mild disability but independent; 3–5 as disabled), NIHSS (National Institutes of Health Stroke Scale) as continuous, stroke type (acute ischemic, intracerebral hemorrhage, or uncertain, past history of cardiovascular disease (heart disease, diabetes mellitus, or stroke), past history of chronic obstructive pulmonary disease, and current smoker status. [§]Model 3 (hospital level) for (a) further adjusted number of stroke patients admitted annually, academic hospital, location of hospital, local protocol for swallow dysfunction, available of neurologists, dysphagia specialist nurses, and speech pathologists; and (b) further adjusted present of dedicated stroke unit and guidelines for acute treatment of stroke care. OR: odds ratio; CI: confidence interval.
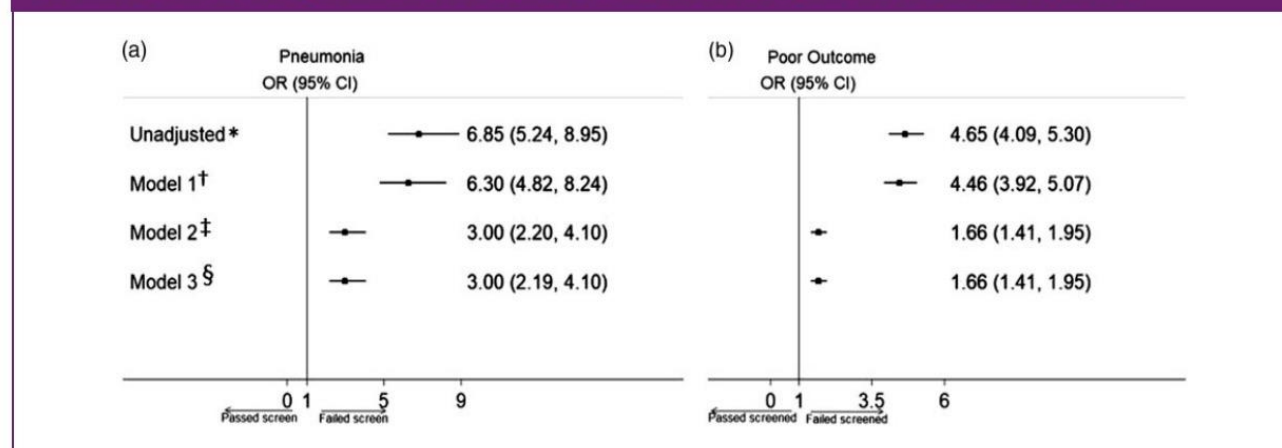
Subgroup analysis

There was consistency in the relation between the use of dysphagia screening and pneumonia and poor outcome across patient subgroups (Supplemental Figures S5 and S6). Although there was no influence of head positioning on pneumonia, there was a lower risk of poor outcome in patients who were allocated to the lying-flat position (aOR = 0.88, 95% CI = 0.77–1.00; Supplemental Figure S7). Similarly, there was no heterogeneity across subgroups in the results according to either a pass or fail on a dysphagia screen on pneumonia and poor outcome (Supplemental Figures S8 and S9). The effect of failing dysphagia screen is also consistent in patients with different head positions of the patients (Supplemental Figure S10(B)).

Influence of feeding restrictions

Patients who failed dysphagia screen were more likely to be placed on feeding restrictions compared to those passed (84.1% vs. 11.2%, $P < 0.0001$; Table 2). The incidence of pneumonia and poor outcome were more in patients had feeding restrictions compared to those did not (9.5% vs. 0.9%, $P < 0.0001$ and 67.6% vs. 28.7%, $P < 0.0001$, respectively; Supplemental Table S9). In the stratified analysis, subsequent use of feeding restrictions were related to higher risk of pneumonia,

especially for patients failed a dysphagia screen or dysphagia assessment (11.9% vs. 1.8%, $P < 0.0001$; Supplemental Table S12 and aOR = 4.06, 95% CI = 1.72–9.54; Supplemental Figure S11(A)). There was considerable regional variation in the feeding regimes provided to patients who failed a dysphagia screen, although the use of a nasogastric tube was the most common method (Supplemental Table S13).

Sensitivity analysis

With adjustment of both baseline and hospital characteristics, and the use of multiple imputation for missing outcome, the results were similar to our primary analyses (Supplemental Figures S12 and S13).

Discussion

In this large multinational study, we found no clear association between the use of a simple screen or detailed assessment of dysphagia regardless of the test results, as a quality of care measure, and either pneumonia or poor functional outcome after acute stroke. However, patients who failed either of these tests were clearly at increased risks of these adverse outcomes. The risk of pneumonia varied widely across regions and was related to the timing of dysphagia screen and assessment.

The overall 3% frequency of pneumonia in our study was lower than reported in many other studies,[15,17,18] but similar to that of a large registry study.[19] The patients in our study were likely subjected to rigorous assessment and management of dysphagia by virtue of their participation in a clinical trial, where pneumonia was an expected adverse outcome. However, it is likely that selection bias and variable definitions influence the detection and reporting of pneumonia across studies. As in a real-life registry-based study, our protocol included consecutive patients with acute stroke. However, we did not specify any particular procedures for investigators to follow, and the assessment and management of dysphagia were performed according to local protocols.

Dysphagia screening, assessment, and management vary across countries in the context of specifications and interpretation of guidelines for stroke management.[9–12] In our study, the median times from admission to screening and assessing dysphagia in Australia and UK were similar to another study conducted during 2013–2014.[15] In China, dysphagia screens and assessments were performed at approximately the same time, although guidelines in this country make no specific recommendation regarding when or how to conduct them.[10] Another UK stroke registry study has shown an association between delayed screen and assessment of dysphagia and increased risk of pneumonia.[15] In our study, dysphagia screening was most delayed in South America, which may in part explain the higher rate of pneumonia (6.5%) there compared to other regions.

We found no evidence of an association between the use of dysphagia screening and the risk of adverse outcomes. Another cluster clinical trial also showed no association of dysphagia screening and risk of pneumonia but rather a relation with lower risk of death and severe disability,[13] which may have been due to an effect of other components of the care bundle targeting fever and hyperglycemia. However, our study shows that patients who fail a dysphagia screen are at increased risk of pneumonia and poor clinical outcome, which is consistent with other studies.[13,14,20,21] The majority (84%) of patients who failed dysphagia screening were placed on feeding restrictions. These data are consistent with guideline recommendation for routine use of dysphagia screening in patients with acute stroke, with subsequent use of feeding restrictions or early dysphagia treatment in those who fail.

Another finding from our study was the increased risk of pneumonia or poor clinical outcome in "screen-fail" or "assessment-fail" patients and particularly those placed on restricted feeding. We assume that it might be related to the mixed methods of feeding practices we measured, some of which might introduce adverse effect. A previous retrospective study has shown that the presence of nasogastric feeding was associated with reduced functional recovery and increased mortality after stroke.[22] However, there is randomized evidence of early use of nasogastric tubes in dysphagia patients and lower risk of adverse outcomes,[22] while dysphagia therapy programs appear to reduce the risk of pneumonia in the acute phase of stroke.[8] We were unable to assess for any association of individual feeding actions on outcomes, as patients were often on multiple feeding restriction regimes. It is likely that analyses are complicated by indication bias, where high-risk patients receive the intervention of interest, as our stratified analyses showed that patients who passed a dysphagia screen but subsequently had a dysphagia assessment had higher risks of poor clinical outcome compared to other patients. Further studies concentrate on evaluating different methods of feeding actions subsequently after failing dysphagia screen will be essential to improve patient's clinical outcomes.

In our study, it is interesting to note that a quarter of patients passed a dysphagia screen yet went on to also receive a dysphagia assessment, and majority (96%) of them were reconfirmed as passed. Some of them may have deteriorated after screen and therefore required further assessment; however, many may not have. This duplicated assessing for dysphagia was also noted in the QASC (Quality in Acute Stroke Care) trial, with similar proportion (97%) also deemed safe to swallow by the speech pathologist.[13] Further examination of the reason for double swallowing surveillance in stroke patients is warranted. From another perspective, such inefficient duplicated assessment is costly and time-consuming, especially for some low-resourced settings. We recommend patients who had passed a screen and with no further deterioration should not be reviewed by a health professional.

We acknowledge several limitations, including the inability to prespecify (or standardize) the methods of screening and assessment used across participating centers. As such, we were unable to provide any details regarding the type and quality of screening and assessments approaches undertaken for dysphagia and for other aspects of background management. Another factor is that participants in our study are likely to have received a greater attention to standard of care processes including dysphagia monitoring and feeding actions because of the specific nature of our clinical trial assessing the influence of head positioning on stroke outcomes. However, this was a prespecified secondary analysis of a large international trial based on local protocol by regions. Our findings reflect usual practice according to current guideline recommendations across countries. A major strength of our study is the large sample size of patients with a broad range of characteristics from a range of health-care

settings with variable resourcing levels. Moreover, selection bias was likely reduced compared to most conventional individual patient randomized clinical trials, by the inclusion of consecutive stroke patients within a cluster cross-over design. We also considered the influences of institutional factors in multilevel models that included adjustment for various hospital characteristics.

Conclusions

The utility of dysphagia screening and assessment varies according to countries and local guidelines. Failing a dysphagia screen was associated with higher risk of pneumonia and poor outcome from acute stroke. Subsequent feeding restrictions are related to increased risk of adverse outcomes. Further randomized controlled trials that evaluating the effects of feeding actions are urgent to improve patient's outcome.

Author contributions

CSA, HA, MLH, CW, and LS contributed to the concept and rationale for the study. MO did the statistical analysis with assist from KR. MO wrote the first draft of manuscript with input from CSA. All authors have seen and approved the final version of the manuscript for publication.

ORCID iDs

Maree L Hackett (iD) https://orcid.org/0000-0003-1211-9087
Verónica V Olavarría (iD) https://orcid.org/0000-0003-4300-9921
Sandy Middleton (iD) https://orcid.org/0000-0002-7201-4394
Craig S Anderson (iD) https://orcid.org/0000-0002-7248-4863

References

1. Koennecke HC, Belz W, Berfelde D, et al. Factors influencing in hospital mortality and morbidity in patients treated on a stroke unit. *Neurology* 2011; 77: 965–972.
2. Hannawi Y, Hannawi B, Rao CP, Venkatasubba Suarez J and Bershad EM. Stroke associated pneumonia: major advances and obstacles. *Cerebrovascular Dis* 2013; 35: 430–443.
3. Katzan L, Dawson V, Thomas L, Votruba E and Cebul D. The cost of pneumonia after acute stroke. *Neurology* 2007; 68: 1938–1943.
4. Rofes L, Arreola V, Almirall J, et al. Diagnosis and management of oropharyngeal dysphagia and its nutritional and respiratory complications in the elderly. *Gastroenterol Res Pract* 2011; 2011: 1–13.
5. Titsworth LW, Abram J, Fullerton A, et al. Prospective quality initiative to maximize dysphagia screening reduces hospital-acquired pneumonia prevalence in patients with stroke. *Stroke* 2013; 44: 3154–3160.
6. Joundi RA, Martino R, Saposnik G, Giannakeas V, Fang J and Kapral MK. Predictors and outcomes of dysphagia screening after acute ischaemic stroke. *Stroke* 2017; 48: 900–906.
7. Cohen DL, Roffe C, Beavan J, et al. Post-stroke dysphagia: a review and design considerations for future trials. *Int J Stroke* 2016; 11: 399–411.
8. Smith EE, Kent DM, Bulsara R, et al. Effect of dysphagia screening strategies on clinical outcomes after stroke. *Stroke* 2018; 49: e123–e128.
9. Indian Stroke Association Consensus Statement. Recommendations for the early management of acute ischaemic stroke a consensus statement for healthcare professionals from the India Stroke Association, https://www.stroke-india.org/stroke.pdf (2014, accessed June 24, 2018).
10. Chinese Cerebrovascular Association. 2014 Chinese guidelines for acute ischemic stroke treatment and management. *Chin J Neurol* 2015; 48: 246–248.
11. Scottish Intercollegiate Guidelines Network. Guideline 119: management of patients with stroke: identification and management of dysphagia a national guideline, http://www.sign.ac.uk/assets/sign119.pdf (2011, accessed June 24, 2018).
12. Stroke Foundation Australia. Chapter 3 of 8: Acute medical and surgical management: dysphagia. Clinical guidelines for stroke management, https://www.magicapp.org/app#/gMOUYuideline/2280 (2017, accessed June 29, 2018).
13. Middleton S, McElduff P, Ward J, et al. Implementation of evidence-based treatment protocols to manage faver, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. *Lancet* 2011; 378: 1699–1706.

14. Palli C, Fandler S, Doppelhofer K, et al. Early dysphagia screening by trained nurses reduces pneumonia rate in stroke patients: a clinical intervention study. *Stroke* 2017; 48: 2583–2585.

15. Bray BD, Smith CJ, Cloud GC, et al. The association between delays in screening for and assessing dysphagia after acute stroke and the risk of stroke associated pneumonia. *J Neurol Neurosurg Psychiatry* 2017; 88: 25–30.

16. Anderson CS, Arima H, Lavados P, et al. Cluster-randomized, crossover trial of head positioning in acute stroke. *New Engl J Med* 2017; 376: 2437–2447.

17. Smith CJ, Kishore AK, Vail A, et al. Diagnosis of stroke-associated pneumonia: recommendations from the pneumonia in stroke consensus group. *Stroke* 2015; 46: 2335–2340.

18. Finlyson O, Kapral M, Hall R, Asllani E, Selchen D and Saposnik G. Risk factors, inpatients care, and outcomes of pneumonia after ischaemic stroke. *Neurology* 2011; 77: 1338–1345.

19. Lakshminarayan K, Tsai AW, Tong X, et al. Utility of dysphagia screening results in predicting poststroke pneumonia. *Stroke* 2010; 41: 2849–2854.

20. Joundi RA, Martino R, Saposnik G, Giannakeas V, Fang J and Kapral MK. Predictors and outcomes of dysphagia screening after acute ischaemic stroke. *Stroke* 2017; 48: 900–906.

21. Geeganage C, Beavan J, Ellender S and Bath PM. Interventions for dysphagia and nutritional support in acute and subacute stroke. *Cochrane Database Syst Rev* 2012; 10: CD000323.

22. Schwarz M, Coccetti A, Murdoch A and Cardell E. The impact of aspiration pneumonia and nasogastric feeding on clinical outcomes in stroke patients. *J Clin Nursing* 2018; 27: e235–e241.

2.2 Prognostic significance of early urinary catheterization after acute stroke: secondary analyses of the international HeadPoST trial

Paper published in International Journal of Stroke as

Prognostic significance of early urinary catheterization after acute stroke: secondary analyses of the international HeadPoST trial

Menglu Ouyang, Laurent Billot, Lili Song, Xia Wang, Christine Roffe, Hisatomi Arima, Pablo M. Lavados, Maree L. Hackett, Verónica V. Olavarría, Paula Muñoz-Venturelli, Sandy Middleton, Octavio M. Pontes-Neto, Tsong-Hai Lee, Caroline L. Watkins, Thompson Robinson, Craig S. Anderson, for the HeadPoST Investigators

http://doi.org/ 10.1177/1747493020908140.

Refer to the following 7 pages

∗ ∗ ∗

Prognostic significance of early urinary catheterization after acute stroke: Secondary analyses of the international HeadPoST trial

Menglu Ouyang[1,2] ◉, Laurent Billot[1] ◉, Lili Song[1,2], Xia Wang[1] ◉,
Christine Roffe[3], Hisatomi Arima[1,4], Pablo M Lavados[5],
Maree L Hackett[1,6] ◉, Verónica V Olavarría[5] ◉,
Paula Muñoz-Venturelli[1,7], Sandy Middleton[8] ◉,
Octavio M Pontes-Neto[9], Tsong-Hai Lee[10], Caroline L Watkins[6],
Thompson G Robinson[11] and Craig S Anderson[1,2,7,12,13] ◉

Abstract

Background: An indwelling urinary catheter (IUC) is often inserted to manage bladder dysfunction, but its impact on prognosis is uncertain. We aimed to determine the association of IUC use on clinical outcomes after acute stroke in the international, multi-center, cluster crossover, Head Positioning in Acute Stroke Trial (HeadPoST).

Methods: Data were analyzed on HeadPoST participants (n = 11,093) randomly allocated to the lying-flat or sitting-up head position. Binomial, logistic regression, hierarchical mixed models were used to determine associations of early insertion of IUC within seven days post-randomization and outcomes of death or disability (defined as "poor outcome," scores 3–6 on the modified Rankin scale) and any urinary tract infection at 90 days with adjustment of baseline and post-randomization management covariates.

Results: Overall, 1167 (12%) patients had an IUC, but the frequency and duration of use varied widely across patients in different regions. IUC use was more frequent in older patients, and those with vascular comorbidity, greater initial neurological impairment (on the National Institutes of Health Stroke Scale), and intracerebral hemorrhage as the underlying stroke type. IUC use was independently associated with poor outcome (adjusted odds ratio (aOR): 1.40, 95% confidence interval (CI): 1.13–1.74), but not with urinary tract infection after adjustment for antibiotic treatment and stroke severity at hospital separation (aOR: 1.13, 95% CI: 0.59–2.18). The number exposed to IUC for poor outcome was 13.

Conclusions: IUC use is associated with a poor outcome after acute stroke. Further studies are required to inform appropriate use of IUC.

[1]The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, Australia
[2]The George Institute China at Peking University Health Science Center, Beijing, China
[3]Department of Neurosciences, Royal Stoke University Hospital, Stoke-on-Trent, UK
[4]Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, Fukuoka, Japan
[5]Departmento de Neurologia and Psiquiatria, Clínica Alemana de Santiago, Servicio de Neurología, Unidad de Neurología Vascular, Vitacura, Chile
[6]Faculty of Health and Wellbeing, University of Central Lancashire, Preston, Lancashire, UK
[7]Center for Clinical Studies, School of Medicine—Clínica Alemana, ICIM, Universidad del Desarrollo, Santiago, Chile

[8]Nursing Research Institute, St Vincent's Health Australia, Australian Catholic University, Sydney, Australia
[9]Stroke Service—Neurology Division, Department of Neuroscience and Behavioral Sciences, Ribeirão Preto Medical School, University of Sao Paulo, Ribeirão Preto, Brazil
[10]Stroke Center and Department of Neurology, Linkou Chang Gung Memorial Hospital and College of Medicine, Chang Gung University, Taoyuan
[11]Department of Cardiovascular Sciences and NIHR Leicester Biomedical Research Centre, University of Leicester, Leicester, UK
[12]Neurology Department, Royal Prince Alfred Hospital, Sydney Health Partners, Sydney, Australia
[13]Heart Health Research Center, Beijing, China

Corresponding author:
Craig S Anderson, The George Institute for Global Health, PO Box M201, Missenden Rd., Sydney, NSW 2050, Australia.
Email: canderson@georgeinstitute.org.au

Bladder dysfunction is common after acute stroke, affecting at least one third of patients.[1] A urodynamic study suggested frequencies of urinary incontinence of 73% and 64%, and urinary retention of 13% and 52%, in patients with acute intracerebral hemorrhage (ICH) and ischemic stroke, respectively.[2] An indwelling urine catheter (IUC) is often inserted to manage these conditions,[3] but the benefits may be offset by increased mortality and morbidity, especially in the context of incontinence.[4,5] Guidelines[6,7] therefore recommend cautious use of IUC and for their early removal to avoid urinary tract infection (UTI) and other sepsis. However, these recommendations are based on level C grade of evidence, since the data are derived from studies limited by small sample size, retrospective design, and incomplete adjustment for confounding. We aimed to determine associations of IUC use and 90-day clinical outcomes in stroke patients with a broad range of characteristics who participated in the international Head Positioning in Acute Stroke Trial (HeadPoST).[8]

Methods

Study population

HeadPoST was an international, multicenter, cluster crossover, clinical trial that involved 11,093 adults (≥18 years) with acute stroke randomly allocated to the lying flat or sitting up head position soon at 114 hospitals in nine countries from March 2015 to November 2016.[8] A guardian consent process was used to implement the randomized intervention as a policy of usual service delivery to a pre-defined patient cluster; patients provided consent for use of their medical record data and centralized telephone follow-up. HeadPoST is registered at ClinicalTrials.gov (NCT02162017).

Procedures

Demographic, medical history, and clinical information, included the severity of neurological impairment on the National Institutes of Health Stroke Scale (NIHSS), were collected at baseline. Data of IUC use, including insertion date, along with other pre-defined management interventions, repeat NIHSS, and an assessment of functional status on the simplified modified Rankin scale (mRS) were collected at day 7 post-randomization (or at hospital separation if earlier). Recorded IUC use was assumed as the first insertion after hospital admission and duration of use was censored at day 7. Trained staff, blind to treatment allocation, contacted patients not known to have died by telephone to assess their functional status on the mRS at 90 days. The primary outcome for these analyses was death or dependency (mRS scores 3–6). The secondary outcome was UTI identified from details related to serious adverse events (SAEs) reported by site investigators to the end of follow-up at 90 days.[8]

Statistical analysis

Binomial, logistic regression, hierarchical mixed models were used to adjust for the fixed effects of head position (lying-flat vs. sitting-up) and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period. The term "unadjusted" was used for convenience in defining this initial mixed model. Potential confounders at baseline and day 7 post-randomization (P value < 0.2) in univariate analyses (Table 1; Supplemental Tables S1 and S2) defining associations of IUC and outcomes were included in sequential hierarchical logistic regression models with (model I) country groups according to region, (model II) baseline characteristics, and (model III) management covariates. As the NIHSS and mRS scores at day 7 (or earlier) were correlated (Spearman's rank correlation = 0.72), the former scale was used in model III to adjust for early neurological change. As there was a high proportion of missing day 90 mRS scores (12%), multiple imputation was conducted for a sensitivity analysis with all covariates (include outcome variable) in the mixed model for analysis (method was described in Supplemental Material). Considering UTI as an intermediate variable for IUC and poor functional outcome, an additional sensitivity analysis was conducted to assess the strength of association in patients without UTI. Pre-specified subgroup analyzes considered head position, age, sex, baseline neurological severity (NIHSS score), and medical history. To assist in understanding the adverse consequences of IUC use, we calculated a number needed to expose for poor outcome using the adjusted odds

Table 1. Characteristics of 11,093 patients by urinary catheter use

Characteristics	Urinary catheter inserted		P value[a]
	Yes (N = 1167)	No (N = 9829)	
Age, years	71.3 ± 13.9	67.5 ± 13.7	<0.0001
Male	610 (52.3)	5999 (61.0)	<0.0001
Region			<0.0001
Australia/UK	535 (45.8)	4154 (42.3)	
China (incl. Taiwan)	266 (22.8)	4371 (44.5)	
India/Sri Lanka	259 (22.2)	507 (5.2)	
South America	107 (9.2)	797 (8.1)	
Hypertension	630 (54.0)	4948 (50.3)	0.140
Previous stroke	272 (23.3)	2314 (23.5)	0.854
Coronary artery disease	192 (16.5)	1337 (13.6)	0.008
Atrial fibrillation	227 (19.5)	936 (9.5)	<0.0001
Heart failure	70 (6.0)	337 (3.4)	<0.0001
Diabetes mellitus	252 (21.6)	1956 (20.0)	0.642
Stroke category			<0.0001
AIS	950 (81.5)	8442 (86.1)	
ICH	192 (16.5)	728 (7.4)	
Uncertain	24 (2.1)	637 (6.5)	
NIHSS at admission	12.0 (6.0, 18.0)	4.0 (2.0, 7.0)	<0.0001
GCS score at admission	14.0 (11.0, 15.0)	15.0 (14.0, 15.0)	<0.0001
Pre-morbid mRS 0–1[b]	881 (75.5)	7782 (79.2)	0.008
NIHSS at 7 days	9.0 (4.0, 16.0)	2.0 (1.0, 5.0)	<0.0001
mRS at 7 days	4.0 (3.0, 5.0)	2.0 (1.0, 3.0)	<0.0001
ICU admission	242 (20.7)	274 (2.8)	<0.0001
ASU admission	824 (70.6)	5716 (58.2)	<0.0001
Antibiotic treatment	526 (45.1)	1146 (11.7)	<0.0001
Underwent surgery[c]	29 (2.5)	7 (0.1)	<0.0001

Note: Data are n (%), mean (SD) and median (IQR). AIS: acute ischaemic stroke; SD: standard deviation; IQR: interquartile range; ASU: acute stroke unit; GCS: Glasgow coma scale; ICH: intracerebral hemorrhage; ICU: intensive care unit; mRS: modified Rankin scale; NIHSS: National Institutes of Health Stroke Scale.
[a]P values from the Student's t-test or Wilcoxon rank-sum test for continuous variables, and the Chi-squared test or Fisher's extract test for categorical variables.
[b]Estimated functional grade score 0–1 on the mRS.
[c]Includes decompressive hemicraniectomy, open craniotomy, minimally invasive surgery, and intraventricular drainage of ICH.

ratio (aOR) obtained in models.[9] Data are reported with 95% confidence intervals (CIs), and a two-sided $P < 0.05$ was considered statistically significant. All analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC).

Data sharing

Individual participant data used in these analyses can be shared by formal request with protocol from any qualified investigator to the Research Office of The George Institute for Global Health, Australia.

Results

Patient characteristics for IUC insertion

Of the 11,093 randomized HeadPoST patients (mean age 68 ± 14 years; 60% male), 1167 (11.6%) had an IUC inserted during their hospitalization, but this figure varied widely across regions: highest for participants in India/Sri Lanka (33.8%), followed in decreasing frequency by those in South America, Australia/ UK, and China (including Taiwan) (Supplemental Table S3). The median duration over seven days of IUC insertion was five days (interquartile range (IQR): 3–7) (Supplemental Table S3).

Table 1 shows that the highest likelihood of IUC use was in older patients, and those with history of heart disease, greater initial neurological impairment, and a diagnosis of ICH. In particular, most (70.7%) older patients (≥ 65 years) had an IUC. Similarly, day 7 data indicate that IUC use was related to greater neurological impairment and physical disability, defined by higher NIHSS and mRS scores, respectively. Moreover, IUC use was more frequent after an admission to an intensive care or acute stroke unit, and in those who received antibiotics within the seven days, as compared to those without an IUC (Table 1).

IUC and outcomes

Median duration of IUC use in patients with a poor outcome (death or dependency, mRS 3–6) was significantly higher than in those with good functional recovery (six vs. five days, $P = 0.013$; Supplemental Table S4). Compared to patients without an IUC, those with IUC had a greater likelihood of a poor outcome (76.6% vs. 34.7%; $P < 0.0001$; Supplemental Table S5). Table 2 shows that the increased odds of poor outcome with IUC use persisted after adjustment for imbalance in baseline characteristics and post-randomization management variables (model III aOR: 1.40, 95% CI: 1.13–1.74) and after multiple imputation of missing outcome data (aOR: 1.36, 95% CI: 1.14–1.63). A significant interaction was found for IUC use and baseline NIHSS score (P for interaction 0.0019; Supplemental Figure S1). The number needed to be exposed to an IUC for harm (death or dependency) was 13.

Overall, only 0.7% (76/11,093) patients had a UTI (Supplemental Table S5), and this was more likely in those with IUC (1.5% vs. 0.6%, $P = 0.0002$; Supplemental Table S5). The median time to diagnosis of UTI was 17 (IQR: 5–36) days; but only 38% (29/76) of UTI events occurred within day 7/discharge (Supplemental Figure S2). However, in those patients

Table 2. Association of urinary catheter use and death or dependency at 90 days

Model	Complete case dataset		Multiple imputation dataset	
	aOR (95% CI)	P value	aOR (95% CI)	P value
Unadjusted[a]	5.44 (4.54–6.39)	<0.0001	5.17 (4.44–6.02)	<0.0001
Model I[b]	5.27 (4.49–6.18)	<0.0001	5.01 (4.31–5.83)	<0.0001
Model II[c]	2.31 (1.91–2.78)	<0.0001	2.21 (1.85–2.64)	<0.0001
Model III[d]	1.40 (1.13–1.74)	0.002	1.36 (1.14–1.63)	0.001

aOR: adjusted odds ratio; CI: confidence interval.
[a]Binomial logistic regression model with adjustment for the fixed effects of head position (lying-flat vs. sitting-up) and crossover period, and random effects of cluster, and random interaction effects between cluster and crossover period.
[b]Model I adjusted for region (Australia/UK, China including Taiwan, India/Sri Lanka, South America).
[c]Model II is model I with further adjustment for baseline covariates of age as a continuous variable, sex, estimated premorbid grade 0 or 1 on the mRS, baseline NIHSS score as a continuous variable, history of heart disease (any heart failure, atrial fibrillation or coronary artery disease), diabetes mellitus or stroke, and pathological stroke type.
[d]Model III is model II further adjusted for individual variables at day 7 or earlier hospital separation, including intensive care unit admission, acute stroke unit admission, antibiotic use, and NIHSS score as a continuous variable.

Table 3. Association of urinary catheter use and urinary tract infection within 90 days

Model	Original dataset		Multiple imputation	
	aOR (95% CI)	P value	aOR (95% CI)	P value
Unadjusted[a]	2.85 (1.62–4.99)	0.0003	2.85 (1.62–4.99)	0.0003
Model I[b]	2.58 (1.47–4.53)	0.001	2.58 (1.47–4.53)	0.001
Model II[c]	2.08 (1.13–3.82)	0.018	2.05 (1.12–3.75)	0.020
Model III[d]	1.13 (0.59–2.18)	0.707	1.18 (0.63–2.19)	0.610

aOR: adjusted odds ratio; CI: confidence interval.
[a]Binomial logistic regression model with adjustment for the fixed effects of head position (lying-flat vs. sitting-up) and crossover period, and random effects of cluster, and random interaction effects between cluster and crossover period.
[b]Model I adjusted for region (Australia/UK, China including Taiwan, India/Sri Lanka, and South America).
[c]Model II is model I with further adjustment for baseline covariates of age as a continuous variable, sex, estimated premorbid grade 0 or 1 on the mRS, baseline NIHSS score as a continuous variable, history of heart disease (any heart failure, atrial fibrillation or coronary artery disease), diabetes mellitus or stroke, and pathological stroke type.
[d]Model III is model II further adjusted for individual variables at day 7 or earlier hospital separation, including intensive care unit admission, acute stroke unit admission, antibiotic use, and NIHSS score as a continuous variable.

with UTI, there was no clear difference in the median duration of IUC compared to those without UTI (4 (3–6) vs. 5 (3–7) days; P = 0.17) (Supplemental Table S4). Table 3 shows this association in the initial adjusted analysis (model II, aOR: 2.08, 95% CI: 1.13–3.82), but lost significance after adjustment for post-randomization management variables that included antibiotic use and day 7 (or hospital discharge) neurological severity (model III, aOR: 1.13, 95% CI: 0.59–2.18). These associations remained after multiple imputation (model III, OR: 1.18, 95% CI: 0.63–2.19). In patients who received an IUC, duration of early use was not associated poor outcome (aOR: 1.03, 95% CI: 0.93–1.14; Supplemental Table S6).

Subgroup analysis

The odds of poor outcome being higher in females (P for interaction 0.01), the elderly (age > 80 years; P for interaction 0.006), and those with mild neurological impairment (NIHSS scores of 0–4; P for interaction < 0.0001) compared in other subgroups (Supplemental Figure S3). No heterogeneity was found for stroke subtypes (P for interaction 0.47; Supplemental Figure S3), nor among subgroups for outcome in those with UTI (Supplemental Figure S4).

Role of UTI on poor outcome

Patients with UTI were more likely to have a poor 90-day outcome compared to those without UTI (71.9% vs. 39.0%; P < 0.0001; Supplemental Table S2), but not after adjusting for all confounders (aOR: 1.46, 95% CI: 0.70–3.04; Supplemental Table S7). The positive association of IUC and poor outcome persistent after including UTI as a confounder in the primary analysis (aOR: 1.41, 95% CI: 1.13–1.75; Supplemental Table S7). Sensitivity analysis shows that the positive association of IUC use and poor outcome was also present in patients without UTI, and of the same magnitude as identified in the primary analysis of the overall population (aOR: 1.43, 95% CI: 1.15–1.78; Supplemental Table S8).

Discussion

In these secondary analyses of a large population of patients with acute stroke, we have shown that inserting an IUC was associated with a poor functional outcome after adjusting for various prognostic and management confounders, including a diagnosis of UTI and early in-hospital antibiotic use.

Overall, approximately 1 in 10 stroke patients in our study had an IUC inserted, but the frequency was higher in the elderly and those with a history of heart disease, greater baseline neurological deficit, and ICH as the cause. As such, the lower overall frequency of IUC in our study than reported in registries (20%–30%)[4,5,10] may reflect the selective nature of the clinical trial population which included patients with predominantly mild to moderate neurological severity, despite the pragmatic design and broad inclusion criteria. Yet, our data are consistent with others in showing an association of IUC with increasing age and stroke severity.[4,11] Clearly, critical ill patients with more severe deficits are at increased risk of bladder dysfunction and adverse outcomes, and therefore, they require more intensive monitoring and interventional procedures, such as IUC insertion.

Explanations for the adverse consequences of IUC insertion not so clear cut.[5] While an IUC may compromise early mobilization and rehabilitation and cause an inflammatory reaction from subclinical urosepsis.[12] Another explanation for the significant association of IUC and poor outcome is indication bias, whereby patients at risk of poor recovery (old age or severe disability) are more likely to receive an IUC as part of their management. Our subgroup analyses showed the adverse effect of IUC to be greater in patients with mild deficits (NIHSS scores 0–4) and early residual disability (mRS 0–2), suggesting caution in considering an IUC in such patients. Protocols outlining indications and management of IUC may help reduce complications and improve outcomes.[13,14] Moreover, the finding elsewhere of females with poor functional stroke outcome[15] having higher rates of inappropriate IUC use[16] may explain our finding of sex differences in the prognostic significance of IUC.

A recent meta-analysis has shown a wide frequency (3%–44%) of UTI after stroke according to study design and setting.[17] Once again, the low (0.7%) frequency of UTI in HeadPoST compared to an observational study[18] may relate to selection and observer bias, and diagnosis based on reported SAEs rather than systematic surveillance. However, our approach was arguably more clinically relevant in using a "clinically significant" endpoint and in showing attenuation of the association of IUC use and UTI after adjustment for antibiotic use and level of functional impairment. Our findings are therefore contrary to a previous hospital-based study showing a significant association of IUC and UTI,[19] but these results were based on small sample where UTIs were reported without standard diagnostic criteria, and there was no adjustment for other variables, such as antibiotic use. Our study also contrasts with another study which found an association of UTI and poor functional outcome (mRS 3–5) at the time of hospital discharge,[20] but is consistent with another study where adjustments were made for prognostic covariates.[5] Nonetheless, we recognize that the small number of cases of UTI in our study restricted our ability to undertake stratified analyzes or adjust for a large number of covariates.

Strengths of our study include the large sample size of participants with a broad range of characteristics managed in a range of health-care settings. Moreover, we were able to adjust for a large number of potential confounding prognostic factors in different multivariable models. However, in any observational study, there is the potential for incomplete adjustment, while the lack of systematic screening for UTI and reliance on SAE data, likely biased reported events toward those that were more clinically significant or symptomatic. We also had very limited information of the type of IUCs used, their indication, timing of removal, and relationship in the use of antibiotics. The data of censored assessment of all hospital management also limited the utility analysis of IUC duration and outcomes.

In summary, IUC use is associated with a poor functional outcome after acute stroke, after adjustment for a range of important prognostic and management factors. Further studies are required to establish causal pathways and inform guideline recommendations regarding the appropriate indications for IUC to decreases potential risks and promote recovery in vulnerable patients.

Author contributions

CSA and MO contributed to the concept and rationale for the study. MO undertook statistical analyses with assist from LB. MO wrote the first draft of manuscript with input from CSA. All authors commented upon and approved the final version of the manuscript for publication.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MLH holds a National Health and Medical Research Council of Australia (NHMRC) Career Development Fellowship. SM was a member of the NHMRC Research Committee during 2015–2018. TGR is a senior investigator at National Institutes for Health Research (NIHR). CSA holds an NHMRC Senior Principal Research Fellowship and reports honoraria and travel reimbursement from Takeda, Boehringer Ingelheim, and Amgen outside of this study. The other authors have no disclosures to report.

ORCID iDs

Menglu Ouyang 🄳 https://orcid.org/0000-0001-7917-6858
Laurent Billot 🄳 https://orcid.org/0000-0002-4975-9793
Xia Wang 🄳 https://orcid.org/0000-0002-1684-7076
Maree L Hackett 🄳 https://orcid.org/0000-0003-1211-9087
Verónica V Olavarría 🄳 https://orcid.org/0000-0003-4300-9921
Sandy Middleton 🄳 https://orcid.org/0000-0002-7201-4394
Craig S Anderson 🄳 https://orcid.org/0000-0002-7248-4863

Supplemental material

Supplemental material for this article is available online.

References

1. Kong KH and Young S. Incidence and outcome of post-stroke urinary retention: a prospective study. *Arch Phys Med Rehabil* 2000; 81: 1464–1467.
2. Ersoz M, Tunc H, Akyuz M and Ozel S. Bladder storage and emptying disorder frequencies in hemorrhagic and ischemic stroke patients with bladder dysfunction. *Cerebrovasc Dis* 2005; 20: 395–399.
3. Poisson NS, Johnston CS and Josephson AS. Urinary tract infections complicating stroke: mechanisms, consequences, and possible solutions. *Stroke* 2010; 41: e180–e184.
4. John G, Primmaz S, Crichton S and Wolfe C. Urinary incontinence and indwelling urinary catheters as predictors of death after new-onset stroke: a report of the South London stroke register. *J Stroke Cerebrovasc Dis* 2018; 27: 118–124.
5. Wu CH, Tseng MC, Chen YW, Sung SF, Yeh PS and Lin HJ. Indwelling urinary catheterization after acute stroke. *Neurourol Urodyn* 2013; 32: 480–485.
6. Powers JW, Rabinstein AA, Ackerson MT, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2018; 49: e46–e99.
7. Bowen A, James M and Young G; Intercollegiate Stroke Working Party. *National clinical guideline for stroke*, 5th ed. London: Royal College of Physicians, 2016.
8. Anderson CS, Arima H, Lavados P, et al. Cluster-randomized, crossover trial of head positioning in acute stroke. *N Engl J Med* 2017; 376: 2437–2447.
9. Bender R and Blettner M. Calculating the "number needed to be exposed" with adjustment for confounding variables in epidemiological studies. *J Clin Epidemiol* 2002; 55: 525–530.
10. Net P, Karnycheff F, Vasse M, Bourdain F, Bonan B and Lapergue B. Urinary tract infection after acute stroke: impact of indwelling urinary catheterization and assessment of catheter-use practices in French stroke centers. *Rev Neurol* 2018; 174: 145–149.
11. Cowey E, Smith LN, Booth J and Weir CJ. Urinary catheterization in acute stroke: clinical realities. A mixed methods study. *Clin Rehabil* 2012; 26: 470–479.
12. Bernhardt BJ, English BC, Johnson BL and Cumming BT. Early mobilization after stroke: early adoption but limited evidence. *Stroke* 2015; 46: 1141–1146.
13. Kim HJ, Chun MH, Han EY, Yi JH and Kim D-K. The utility of a bladder scan protocol using a portable ultrasonographic device in subacute stroke patients. *Disabil Rehabil* 2012; 34: 486–490.
14. Felix K. Decreasing catheter associated urinary tract infection in a long term acute care hospital. *Am J Infect Control* 2016; 44: S89.
15. Mizrahi EH, Waitzman A, Arad M and Adunsky A. Gender and the functional outcome of elderly ischemic stroke patients. *Arch Gerontol Geriatr* 2012; 55: 438.
16. Hu F-W, Chang C-M, Su P-F, Chen H-Y and Chen C-H. Gender differences in inappropriate use of urinary catheters among hospitalized older patients. *J Women Aging* 2019; 31: 165–175.
17. Westendorp W, Nederkoorn P, Vermeij J-D, Dijkgraaf M and de Beek DV. Post-stroke infection: a systematic review and meta-analysis. *BMC Neurol* 2011; 11: 110.
18. Stenzelius K, Laszlo L, Madeja M, Pessah-Rasmusson H and Grabe M. Catheter-associated urinary tract infections and other infections in patients hospitalized for acute stroke: a prospective cohort study of two different silicone catheters. *Scand J Urol* 2016; 50: 483–488.
19. Stott DJ, Falconer A, Miller H, Tilston JC and Langhorne P. Urinary tract infection after stroke. *Int J Med* 2009; 102: 243–249.
20. Popović N, Stefanović-Budimkić M, Mitrović N, et al. The frequency of poststroke infections and their impact on early stroke outcome. *J Stroke Cerebrovasc Dis* 2013; 22: 424.

Chapter 3 Observation on abnormal physiological parameters

Physiological parameters of blood pressure (BP) and oxygen saturation (SaO_2) are often altered after acute stroke. Although clinical guidelines recommend monitoring these physiological parameters and responding to any abnormal conditions, evidence is still scarce, particularly in less frequent scenarios of low BP and oxygen desaturation after stroke. This Chapter contains my two studies which focus on abnormal physiological parameters, including low presenting BP in acute stroke (Section 3.1) and the lowest SaO_2 recorded in the first 24 hours after hospital admission (Section 3.2).

The objectives of this chapter are:

1. To define the characteristics and prognostic significance of low BP early after the onset of acute stroke (Section 3.1).

2. To determine the strength of association between oxygen desaturation and clinical outcomes in patients with stroke (section 3.2).

The HeadPoST study is a systematic assessment of a broad range of large sampled patients and the collection of clinical data at baseline and during hospitalisation, which provided an opportunity for these analyses. I used descriptive statistics to report differences across the BP categories with ANOVA and Kruskal-Wallis test; and Chi-square test, t-test, Wilcoxon rank-sum test for SaO_2 categorized levels. Restricted Cubic Spline was used to visualise the relationships between continuous BP and SaO_2 and clinical outcomes, respectively. Generalized linear mixed models with adjustment of potential confounders were conducted to report the associations.

The findings outlined a 'J-shaped' relationship between presenting BP and death or dependency, with a similar revered 'J-shaped' relationship found in the lowest SaO_2 and clinical outcomes. Patients with low presenting BP and oxygen desaturation are associated with an increased risk of adverse outcomes, suggesting clinicians should closely monitor these vulnerable patients and take appropriate management to improve clinical outcomes.

I co-designed the studies, analysed and interpreted the data, wrote the first drafts of the manuscripts, coordinated and incorporated co-authors' edits, and prepared and submitted the manuscripts, drafted the responses to the editor's and reviewers' comments, and prepared the final drafts of the manuscripts for publication.

3.1 Low blood pressure and adverse outcomes in acute stroke: HeadPoST study explanations

Paper published in Journal of Hypertension as

Low blood pressure and adverse outcomes in acute stroke: HeadPoST study explanations

Menglu Ouyang, Paula Muñoz-Venturelli, Laurent Billot, Xia Wang, Lili Song, Hisatomi Arima, Pablo M. Lavados, Maree L. Hackett, Verónica V. Olavarría, Alejandro Brunser, Sandy Middleton, Octavio M. Pontes-Neto, Tsong-Hai Lee, Caroline L. Watkins, Thompson Robinson, Craig S. Anderson, for the HeadPoST Investigators

∗ ∗ ∗

Original Article

OPEN

Low blood pressure and adverse outcomes in acute stroke: HeadPoST study explanations

Menglu Ouyang[a,b], Paula Muñoz-Venturelli[a,c,d], Laurent Billot[a], Xia Wang[a], Lili Song[a,b], Hisatomi Arima[a,e], Pablo M. Lavados[d], Maree L. Hackett[a,f], Verónica V. Olavarría[d], Alejandro Brunser[d], Sandy Middleton[g], Octavio M. Pontes-Neto[h], Tsong-Hai Lee[i], Caroline L. Watkins[f], Thompson Robinson[j], and Craig S. Anderson[a,b,c,k,l]

Objective: As uncertainties exist over underlying causes, we aimed to define the characteristics and prognostic significance of low blood pressure (BP) early after the onset of acute stroke.

Methods: Post hoc analyzes of the international Head Positioning in acute Stroke Trial (HeadPoST), a pragmatic cluster-crossover randomized trial of lying flat versus sitting up in stroke patients from nine countries during 2015–2016. Associations of baseline BP and death or dependency [modified Rankin scale (mRS) scores 3–6] and serious adverse events (SAEs) at 90 days were assessed in generalized linear mixed models with adjustment for multiple confounders. SBP and DBP was analysed as continuous measures fitted with a cubic spline, and as categorical measures with low (<10th percentile) and high (≥140 and ≥90 mmHg, respectively) levels compared with a normal range (≥10th percentile; 120–139 and 70–89 mmHg, respectively).

Results: Among 11 083 patients (mean age 68 years, 39.9% women) with baseline BP values, 7.2 and 11.7% had low SBP (<120 mmHg) and DBP (<70 mmHg), respectively. Patients with low SBP were more likely to have preexisting cardiac and ischemic stroke and functional impairment, and to present earlier with more severe neurological impairment than other patients. Nonlinear 'J-shaped' relationships of BP and poor outcome were apparent: compared with normal SBP, those with low SBP had worse functional outcome (adjusted odds ratio 1.27, 95% confidence interval 1.02–1.58) and more SAEs, particularly cardiac events, with adjustment for potential confounders to minimize reverse causation. The findings were consistent for DBP and were stronger for ischemic rather than hemorrhagic stroke.

Conclusion: The prognostic significance of low BP on poor outcomes in acute stroke was not explained by reverse causality from preexisting cardiovascular disease, and propensity towards greater neurological deficits and cardiac events. These findings provide support for the hypothesis that low BP exacerbates cardiac and cerebral ischemia in acute ischemic stroke.

Keywords: acute stroke, blood pressure, hypotension, outcome, trial

Abbreviations: AIS, acute ischemic stroke; BP, blood pressure; CI, confidence interval; GLM, generalized linear mixed model; HeadPoST, Head Positioning in acute Stroke Trial; ICH, intracerebral hemorrhage; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SAE, serious adverse events

INTRODUCTION

Blood pressure (BP) is often altered in acute stroke [1–3], typically as an acute hypertensive (physiological) response (SBP ≥140 mmHg and/or DBP ≥90 mmHg within 24 h of symptom onset), presumably related to cerebral ischemia and/or elevated intracranial pressure. Observational studies are consistent in showing that high BP is positively associated with adverse clinical outcomes [4,5]. However, randomized controlled trials of blood pressure lowering have produced mixed results [6,7],

although any benefits on functional recovery appear more likely for intracerebral hemorrhage (ICH) [7] than acute ischemic stroke (AIS) [8]. Although the prognostic significance of the less frequent situation of low presentation BP (variously defined by SBP <120, <130, or <155 mmHg) in an acute stroke is well recognized [9–14], uncertainties exist over whether this represents a risk factor or risk marker in relation to premorbid factors in final few years of life [15] or critical cerebral injury from impaired perfusion pressure in acute stroke. Herein, we report post hoc secondary analyses of the Head Positioning in acute Stroke Trial (HeadPoST) dataset, where the systematic assessment of a large and broad range of relatively unselected patients provided us with an opportunity to determine relationships of low baseline BP and the patterns of functional recovery and serious adverse events (SAEs), overall and by major pathological subtype of acute stroke.

METHODS

Study design

HeadPoST was an international, pragmatic, multicenter, cluster crossover, clinical trial involving 11 093 adults (≥18 years) with acute stroke who were randomly allocated to the lying flat or sitting up head position at a median time of 14 h (interquartile range 5–35 h) after symptom onset at 114 hospitals in nine countries between March 2015 and November 2016 [16].

Standard protocol approvals, registrations, and patient consents

Relevant hospital ethics committees or institutional review boards approved the study, which included the use of a cluster guardian consent to allow implementation of the randomized intervention as a policy of usual service delivery for a predefined patient cluster; patients only provided written consent for use of their medical record data and release of personal information to allow centralized telephone interview for follow-up at 90 days. The study is registered at ClinicalTrials.gov (NCT02162017).

Procedures

Demographic information, clinical data, including the severity of neurological impairment according to the National Institutes of Health Stroke Scale (NIHSS). The NIHSS is a measure of neurological impairment caused by a stroke, composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score, ranging from 0 to 42. Baseline BP were collected at the time of presentation/admission to hospital. Trained and certified staff, blind to treatment allocation, contacted patients not known to have died by telephone to assess their functional status on the modified Rankin scale (mRS) at 90 days. The mRS is a global, seven-level assessment of disability, in which scores of 0 or 1 indicate good function without or with symptoms but no disability, scores of 2 indicates slight disability, 3 to 5 indicate increasing levels of disability (and

dependency), and a score of 6 indicates death. The primary outcome for these analyses was death or dependency (mRS scores 3–6), and secondary outcomes were all-cause and cause-specific SAEs, as reported by site investigators and coded centrally according to standard definitions.

Statistical analysis

Descriptive statistics were reported across categories with ANOVA for normally distributed data, Kruskal–Wallis test for skewed continuous variables, and chi-squared test for categorical variables. Generalized linear mixed (GLM) models were built with initial adjustment for the study design of the fixed effects of head position (lying-flat versus sitting-up) and cross-over period, random effects of cluster, and random interaction effects between cluster and cross-over period; and then adjusted for clinical risk factors with P less than 0.1 (listed in Table 1 and Supplemental Table e-1, http://links.lww.com/HJH/B455) to determine the estimates of low SBP and DBP on outcomes, respectively. Restricted cubic splines was used to visualize the relationships of baseline SBP and DBP as continuous variables and outcomes in the models, fitted with three to five knots with placement recommended by Harrell [17] and optimal knots selected according to the likelihood ratio test and Aikaike information classification (AIC). The point of lowest odds ratio (OR) was used as the optimal reference. To explore associations of categorical BP and clinical outcomes, the first decile of BP (121 mmHg for SBP and 68 mmHg for DBP) were used to define the ranges of low BP in the study population (<120 mmHg in SBP and <70 mmHg in DBP being considered for meaningful interpretability). High BP was defined as at least 140 and at least 90 mmHg in SBP and DBP, respectively, according to guidelines [18]. The primary analysis were according to the intention-to-treat population, with stratified analyses conducted by final diagnoses of AIS or ICH. Prespecified subgroup analyses were performed by ethnicity (Asian vs. non-Asian), use of intensive BP-lowering treatment, preuse of antihypertensive agents, and randomized head position. In view of the high proportion (12%) of missing 90-day mRS data, multiple imputation was conducted as a sensitivity analysis with all missing covariates and outcome variable imputed [19] in a mixed model for analysis of the main results (see Supplemental Appendix, http://links.lww.com/HJH/B455). Data are reported with OR and 95% confidence intervals (CI), with a two-sided P less than 0.05 considered statistically significant. All analyses were performed with SAS version 9.3 (SAS Institute, Cary, North Carolina, USA) and STATA version 15 (StataCorp, College Station, Texas, USA).

Data availability

Individual de-identified participant data used in these analyses may be shared by request from any qualified investigator via the Research Office of The George Institute for Global Health, Australia.

RESULTS

A total of 11 083 patients (mean age 68 years, 39.9% women) had baseline BP recorded, of whom 64.7% had a history of hypertension and 85.6% had a final diagnosis of AIS (Table 1

TABLE 1. Baseline characteristics by categories of SBP

Variable	Overall	SBP (mmHg)			P value
		<120	120–139	≥140	
Number of patients	11083	795 (7.2)	2393 (21.6)	7895 (71.2)	
Age (years)	68 (13.8)	65 (15.5)	66 (14.6)	69 (13.2)	<0.0001
Female	4423 (39.9)	300 (37.7)	888 (37.1)	3235 (41.0)	0.0012
Region					<0.0001
Australia and UK	4754 (42.9)	390 (49.1)	971 (40.6)	3393 (43.0)	
China and Taiwan	4652 (42.0)	245 (30.8)	1056 (44.1)	3351 (42.4)	
South America	910 (8.2)	83 (10.4)	179 (7.5)	645 (8.2)	
India and Sri Lanka	770 (6.9)	77 (9.7)	187 (7.8)	506 (6.4)	
Clinical features					
Final pathological type of stroke					<0.0001
AIS	9467 (85.6)	675 (85.1)	2086 (87.4)	6701 (85.1)	
ICH	930 (8.4)	39 (4.9)	123 (5.1)	768 (9.8)	
Uncertain	696 (6.0)	79 (10.0)	178 (7.5)	405 (5.1)	
Severity of neurological impairment, NIHSS score[a]	4 (2–8)	5 (2–10)	4 (2–8)	4 (2–8)	0.0002
Score ≥15	1207 (11.1)	112 (14.3)	240 (10.2)	855 (11.0)	0.0079
SBP (mmHg)	151 (136–171)	110 (105–116)	130 (125–134)	162 (150–180)	<0.0001
DBP (mmHg)	85 (76–97)	70 (61–75)	80 (70–84)	90 (80–100)	<0.0001
Time from onset (h)	7.5 (2.3–26.8)	6.4 (2.0–25.3)	8.9 (2.5–31.8)	7.2 (2.3–25.9)	<0.0001
Medical history					
Hypertension	7148 (64.7)	382 (48.2)	1310 (54.8)	5456 (69.3)	<0.0001
Current treatment	5616 (50.7)	322 (40.6)	1055 (44.1)	4238 (53.7)	0.0007
Number of antihypertensive agents	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	0.0030
Diabetes mellitus	2650 (24.0)	159 (20.1)	546 (22.9)	1945 (24.7)	0.0054
Atrial fibrillation	1189 (10.8)	112 (14.1)	287 (12.0)	790 (10.1)	0.0002
Coronary disease	1540 (14.0)	141 (17.8)	361 (15.1)	1038 (13.2)	0.0003
Heart failure	413 (3.8)	53 (6.7)	105 (4.4)	255 (3.3)	<0.0001
Previous stroke	2605 (23.6)	189 (23.9)	571 (23.9)	1845 (23.4)	0.8779
Smoking	2124 (19.4)	177 (22.7)	519 (21.9)	1428 (18.3)	<0.0001
High level of premorbid function (mRS 0–1)[b]	8733 (78.9)	603 (75.9)	1860 (77.8)	6270 (79.5)	0.0205
Hypercholesterolemia	2731 (24.6)	215 (27.3)	591 (24.8)	1925 (24.5)	0.2175
COPD/emphysema	406 (3.7)	37 (4.7)	78 (3.3)	291 (3.7)	0.1809
Medications					
Aspirin/other antiplatelet	5398 (48.7)	387 (48.7)	1249 (52.2)	3762 (47.7)	0.0005
Anticoagulation	951 (8.6)	87 (11.0)	223 (9.3)	641 (8.1)	0.0088
Statin/other lipid lowering	2295 (20.7)	188 (23.6)	501 (20.9)	1606 (20.3)	0.2219

Data are mean (SD), median (IQR), and n (%). Analyses were ANOVA test for normally distributed variables, Kruskal–Wallis test for skewed continuous variables, and chi-squared test for categorical variables. AIS, acute ischemic stroke; COPD, chronic obstructive pulmonary disease; ICH, intracerebral hemorrhage; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; UK, United Kingdom.
[a]NIHSS is a measure of neurological impairment caused by a stroke, composed of 11 items, each of which scores a specific ability from 0 up to 4. For each item, a score of 0 typically indicates normal function in that specific ability, whereas a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score, ranging from 0 to 42.
[b]The mRS represents a global, seven-level assessment of disability, in which score of 0 or 1 indicate good function without or with symptoms but no disability, score of 2 indicates slight disability, scores of 3–5 indicate increasing levels of disability (and dependency), and a score of 6 indicates death.

and Table e-1, http://links.lww.com/HJH/B455). Overall, their mean baseline SBP and DBP were 155 and 87 mmHg, respectively, and 7.2% were defined as having low SBP (<120 mmHg). Compared with other patients, those with low SBP were younger, less likely to have history of hypertension, and more likely to have comorbid heart disease and functional impairment, and greater neurological impairment and strokes without brain imaging confirmation (Table 1). In multivariable analysis, history of atrial fibrillation, coronary disease, heart failure and current smoking were related to increased risk of low BP at presentation (Table e-2, http://links.lww.com/HJH/B455).

Low SBP and clinical outcomes

After adjustment for study design and various potential confounding baseline factors, restricted cubic splines regression curves show a nonlinear 'J-shaped' relationship

between baseline SBP and death or dependency, with the odds increasing for SBP levels less than 130 mmHg (Fig. 1a) and in those with a final diagnosis of AIS rather than ICH (Fig. 2). Patients with low SBP had an increased risk of death or dependency in the main analysis (adjusted OR 1.27, 95% CI 1.02–1.58; Fig. 3), which was consistent after multiple imputation (adjusted OR 1.26, 95% CI 1.02–1.56; Fig. 3). Risks of death and any SAE were also higher in patients with low SBP, with the latter related to an increased risk of cardiac events (Table 2). Similar J-shaped relationships were found for SBP and SAEs, with adjusted OR increasing with SBP less than 140 mmHg (Fig. 1b). Compared with those with AIS, ICH patients were more likely to present with high SBP (≥140 mmHg; Table 1), which significantly increased the risk of SAEs compared with those with normal SBP (adjusted OR 2.31, 95% CI 1.16–4.60; Figure e-1A, http://links.lww.com/HJH/B455).

(a) SBP and death or dependency at 90 days

(b) SBP and SAEs within 90 days
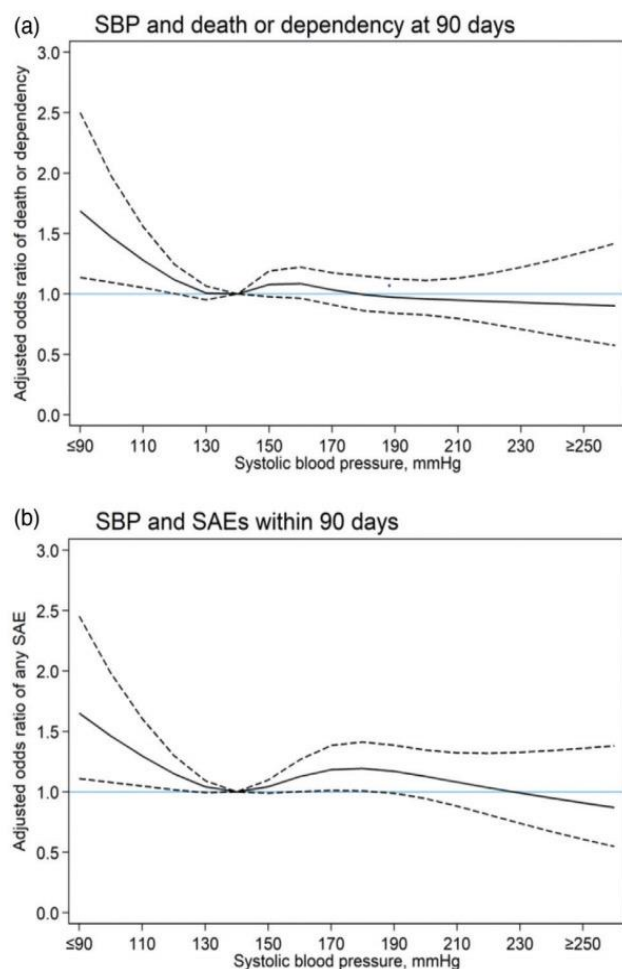
FIGURE 1 Restricted cubic spline of baseline SBP and clinical outcomes at 90 days. Generalized linear mixed models were used with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and potential baseline confounders of age, sex, region, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, coronary heart disease, National Institutes of Health Stroke Scale score, pathological stroke type, premorbid score 0–1 on the modified Rankin scale, aspirin/other antiplatelet treatment, anticoagulant treatment, time from stroke onset to hospital arrival and current smoking. (a) Spline fitted with five knots (percentiles 5th, 27.5th, 50th, 72.5th, 95th) for SBP; (b) Spline fitted with four knots (percentiles 5th, 35th, 65th, 95th) for SBP. Reference SBP 140 mmHg. Solid line indicates odds ratios; dotted line indicates 95% confidence intervals. SAE, serious adverse events.

(a) AIS patients

(b) ICH patients
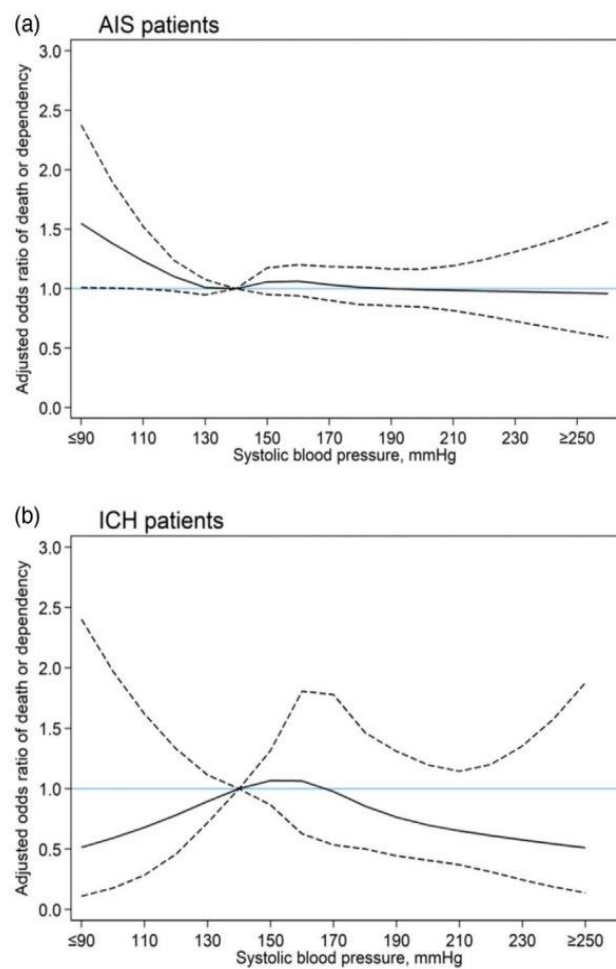
FIGURE 2 Restricted cubic spline of baseline SBP and 90-day death or dependency, by stroke subtype. Generalized linear mixed model fitted were used with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and potential baseline confounders of age, sex, region, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, coronary heart disease, National Institutes of Health Stroke Scale score, pathological stroke type, premorbid score 0–1 on the modified Rankin scale, aspirin/other antiplatelet treatment, anticoagulant treatment, time from stroke onset to hospital arrival and current smoking. Splines fitted with five knots (percentiles 5th, 27.5th, 50th, 72.5th, 95th) for SBP. Reference SBP 140 mmHg. Solid line indicates odds ratios; dotted line indicates 95% confidence intervals. AIS, acute ischemic stroke; ICH, intracerebral hemorrhage.

Low DBP and clinical outcomes

A similar relationship applied for DBP, with odds of poor outcome increasing with DBP levels less than 90 mmHg, overall and in those with AIS and ICH (Figures e-2A, http://links.lww.com/HJH/B455 and e-3, http://links.lww.com/HJH/B455). Similar associations were identified for low DBP and poor outcome, where patients with low DBP had an increased risk of death or dependency in the main analysis (adjusted OR 1.25, 95% CI 1.06–1.48), which was consistent after multiple imputation (adjusted OR 1.20, 95% CI 1.03–1.40) (Figure e-4, http://links.lww.com/HJH/B455). There was a nonlinear relationship between DBP and SAE (Figure e-2B, http://links.lww.com/HJH/B455), but this association was not significant when compared with a normal range (70–89 mmHg) of DBP (Figure e-1B, http://links.lww.com/HJH/B455).

Subgroup analysis

Heterogeneity was found in the association between low BP and outcome, comparing Asian ($n = 4947$) and non-Asian ($n = 4428$) patients, with the former having a significantly higher risk of poor outcome at 90 days (SBP, adjusted OR 1.53, 95% CI 1.11–2.11, Figure e-5, http://links.lww.com/HJH/B455; DBP, adjusted OR 1.38, 95% CI 1.05–1.81, Figure e-6, http://links.lww.com/HJH/B455). However, for non-Asian patients, high BP was associated with lower risk of poor outcome (SBP, adjusted OR 0.78, 95% CI 0.65–0.94, Figure e-5, http://links.lww.com/HJH/B455; DBP, adjusted OR 0.80, 95% CI 0.68–0.94, Figure e-6, http://links.lww.com/HJH/B455). No heterogeneity was found in subgroup analysis by use of intensive BP lowering during hospitalization, prior use of antihypertensive treatment, or randomized head positioning, and death or
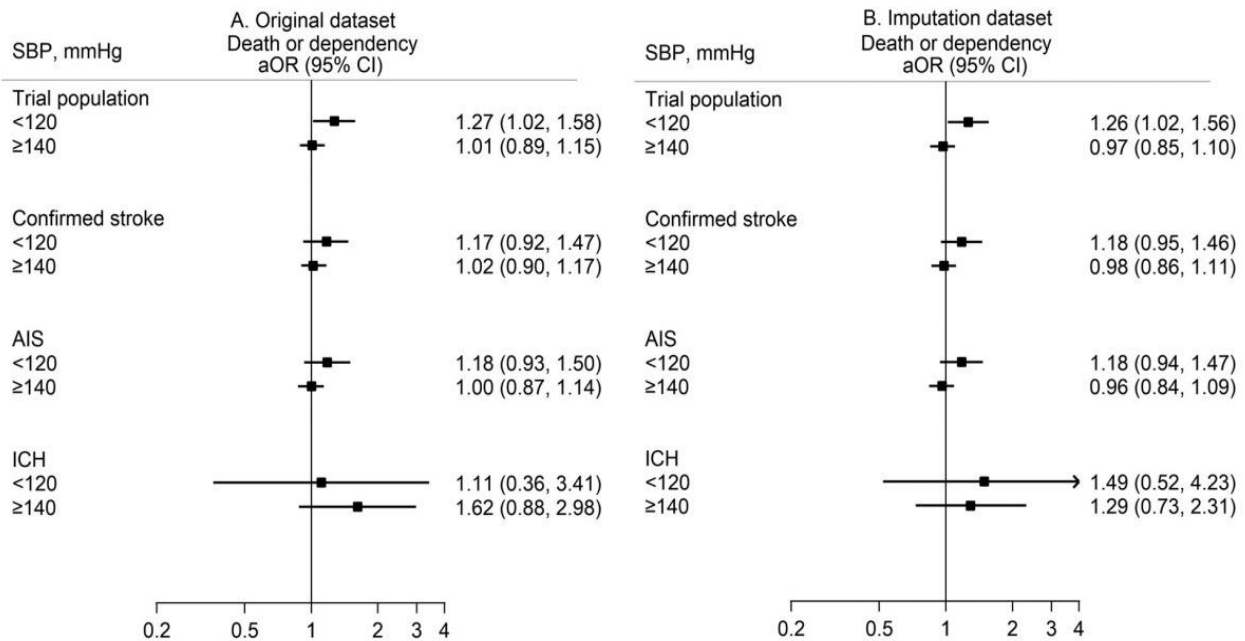
FIGURE 3 Association of categorical baseline SBP and 90-day death or dependency, by dataset. Generalized linear mixed model fitted were used with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and potential baseline confounders of age, sex, region, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, coronary heart disease, National Institutes of Health Stroke Scale score, pathological stroke type, premorbid score 0–1 on the modified Rankin scale, aspirin/other antiplatelet treatment, anticoagulant treatment, time from stroke onset to hospital arrival and current smoking. Reference SBP 120–139 mmHg. Boxes indicate point estimate of odds ratios, solid line indicates 95% confidence intervals. AIS, acute ischemic stroke; aOR, adjusted odds ratio; CI, confidence interval; ICH, intracerebral hemorrhage; OR, odds ratio.

dependency (Figures e-5, http://links.lww.com/HJH/B455 and e-6, http://links.lww.com/HJH/B455).

DISCUSSION

In these secondary analyzes of a large and heterogenous international clinical cohort, low BP early after hospital presentation for acute stroke was associated with increased odds of poor clinical outcome after full adjustment for many potential confounding factors. The findings of consistency in the association for both SBP and DBP on functional recovery and cardiac SAEs, and being greater for AIS than ICH, provides support for the common concern for an interaction between low BP and cardiac and cerebral hypoperfusion and ischemia [1].

Most guidelines provide recommendations on the management of BP in AIS [20] and particularly ICH [20,21], principally as hypertension is a commonly observed phenomenon [22–24] with a well documented relation to increased adverse outcomes [25]. Although less frequently observed, low BP is also clearly not a benign phenomenon. Previous observational studies have found J-curve relationships between BP and adverse outcomes in relation to various heart diseases [26–28], and proposing 'reverse causation' as the basis for the progression of heart failure with premorbid comorbidities and frailty [29]. Similarly for stroke, one study has shown that low SBP (<120 mmHg) after recent AIS is related to increased recurrent stroke and vascular death [30], whereas another showed that diastolic hypotension increased the risks of death, myocardial

TABLE 2. Outcomes at 90 days by baseline SBP

| Outcome | SBP (mmHg) | | | P value |
	<120	120–139	≥140	
Death or dependency (mRS[a] 3–6)	296/669[b] (44.2)	778/2084[b] (37.3)	2746/6986[b] (39.3)	0.0060
Disability (mRS[a] 3–5)	228/669 (34.1)	607/2084 (29.1)	2189/6986[b](31.3)	0.0349
Death	68/669 (8.7)	171/2084 (7.3)	557/6986 (7.2)	0.3308
SAE	138/795[c] (17.4)	303/2393[c] (12.7)	1098/7895[c] (13.9)	0.0040
Recurrent stroke	43/795 (5.4)	104/2393 (4.4)	380/7895 (4.8)	0.4289
Cardiac or other vascular events	26/795 (3.3)	40/2393 (1.7)	169/7895 (2.1)	0.0247
Pneumonia	23/795 (2.9)	54/2393 (2.3)	215/7895 (2.7)	0.4103
Other infection	11/795 (1.8)	28/2393 (1.2)	79/7895 (1.0)	0.1326
Other SAE	28/795 (3.5)	60/2393 (2.5)	197/7895 (2.5)	0.2134

Data are n/N (%); P value from chi-squared test. mRS, modified Rankin scale; SAE, serious adverse event.
[a]The mRS represents a global, seven-level assessment of disability, in which scores of 0 or 1 indicate good function without or with symptoms but no disability, score of 2 indicates slight disability, scores of 3–5 indicate increasing levels of disability (and dependency), and a score of 6 indicates death.
[b]N is according to total number of patients at 90-day follow-up.
[c]N is according to total number of patients randomized.

infarction [31], and recurrent vascular events including stroke [32]. There is a strong argument that a reduction in systematic BP may worsen cerebral ischemia in relation to altered cerebral autoregulation in the vulnerable penumbral region of AIS [33], whereas comorbidity and greater neurological severity in those presenting with hypotension, may partly explain the increase in SAEs shown in previous acute stroke trials [34]. Although low BP in frail older patients might be a harbinger of preterminal decline [35], we found the increased risk of adverse events in stroke patients with low BP persisted after adjustment for premorbid disability and comorbid heart disease.

Our study also found that the prognostic significance of low BP was modified by ethnicity, with Asian patients having a worse outcome irrespective of BP than non-Asians, who had a comparably lower odds of death or dependency from low BP. Although some studies have also shown poorer functional outcome in Asian compared with European stroke patients [36], there are limited data specifically pertaining to ethnicity and low BP. Yet, ethnic disparities in cardiovascular risk factor control, as well as acute stroke care, and regional differences in rehabilitation, might explain some of this variation [37].

In addition to the large sample size and systematic recording of outcomes, key strengths of our study were the steps taken to adjust for many potential confounding factors and to minimize potential reverse causation. Moreover, the generalizability of the results is enhanced by the use of broad inclusion criteria applied to AIS and ICH patients recruited in multiple countries. However, as the HeadPoST study was a pragmatic clinical trial focused on different head positions after stroke, there were limited in-hospital BP measures recorded for the study or these were measured BP according to local protocols, although any effect of BP misclassification would be to attenuate the strength of associations. In addition, we did not have data concerning dose of prior antihypertensive therapy nor use of other cardiac medications, although the frequency of hypertension and number of antihypertensive agents were greater in those patients presenting with elevated BP. Other limitations related to these being secondary analyses with relatively small number of patients in subgroups, variable cut-points to define BP categories, and missing or misclassification of confounding covariates.

In conclusion, our study has shown that low presenting BP, both SBP and DBP, are associated with poor outcome after acute stroke, even after taking account of these patients being a particularly high-risk group from having preexisting cardiac or cerebral cardiovascular comorbidity and dependency/frailty; and of the severity of neurological injury. As well as alerting clinicians to the care of these vulnerable patients, there may be merit in further studies being undertaken to better define the mechanisms of low BP on the cerebral circulation, and the most appropriate management strategies for low BP.

ACKNOWLEDGEMENTS

Conflicts of interest

REFERENCES

1. Tikhonoff V, Zhang H, Richart T, Staessen JA. Blood pressure as a prognostic factor after acute stroke. *Lancet Neurol* 2009; 8:938–948.
2. Sare GM, Geeganage C, Bath PMW. High blood pressure in acute ischaemic stroke – broadening therapeutic horizons. *Cerebrovasc Dis* 2009; 27:156–161.
3. Qureshi AI. Acute hypertensive response in patients with stroke: pathophysiology and management. *Circulation* 2008; 118:176–187.
4. Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and subsequent outcome: a systematic review. *Hypertension* 2004; 43:18–24.
5. Miller J, Kinni H, Lewandowski C, Nowak R, Levy P. Management of hypertension in stroke. *Ann Emerg Med* 2014; 64:248.
6. Sandset EC, Bath P, Boysen G, Jatuzis D, Korv J, Luders S, *et al.*, SCAST Study Group. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. *Lancet* 2011; 377:741–750.
7. Moullaali TJ, Wang X, Martin RH, Shipes VB, Robinson TG, Chalmers J, *et al*. Blood pressure control and clinical outcomes in acute intracerebral haemorrhage: a preplanned pooled analysis of individual participant data. *Lancet Neurol* 2019; 18:857.
8. Anderson CS, Huang Y, Lindley RI, Chen X, Arima H, Chen G, *et al.*, ENCHANTED Investigators and Coordinators. Intensive blood pressure reduction with intravenous thrombolysis therapy for acute

ischaemic stroke (enchanted): an international, randomised, open-label, blinded-endpoint, phase 3 trial. *Lancet (London, England)* 2019; 393:877–888.

9. Vemmos KN, Tsivgoulis G, Spengos K, Zakopoulos N, Synetos A, Manios E, *et al*. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. *J Intern Med* 2004; 255:257–265.

10. Stead GL, Gilmore MR, Decker WW, Weaver LA, Brown DR. Initial emergency department blood pressure as predictor of survival after acute ischemic stroke. *Neurology* 2005; 65:1179–1183.

11. Wohlfahrt P, Redfield MM, Lopez-Jimenez F, Melenovsky V, Kane GC, Rodeheffer RJ, *et al*. Impact of general and central adiposity on ventricular-arterial aging in women and men. *JACC Heart Fail* 2014; 2:489–499.

12. Kim LJ, Gall RS, Nelson EM, Sharman GJ, Thrift GA. Lower systolic blood pressure is associated with poorer survival in long-term survivors of stroke. *J Hypertens* 2014; 32:904–911.

13. Liu Y, Yang Y, Jin H, Fan C, Lv P, Sun W, *et al*., ChinaQUEST (Quality Evaluation of Stroke Care and Treatment) Investigators. Discrepant relationships between admission blood pressure and mortality in different stroke subtypes. *J Neurol Sci* 2017; 383:47–51.

14. Verschoof MA, Groot AE, Vermeij J-D, Westendorp WF, van Den Berg SA, Nederkoorn PJ, *et al*. Association between low blood pressure and clinical outcomes in patients with acute ischemic stroke. *Stroke* 2020; 51:338–341.

15. Ravindrarajah CR, Hazra HDN, Hamada CS, Charlton CJ, Jackson CS, Dregan CA, *et al*. Systolic blood pressure trajectory, frailty, and all-cause mortality >80 years of age: cohort study using electronic health records. *Circulation* 2017; 135:2357–2368.

16. Anderson CS, Arima H, Lavados P, Billot L, Hackett ML, Olavarría VV, *et al*., HeadPoST Investigators and Coordinators. Cluster-randomized, crossover trial of head positioning in acute stroke. *N Engl J Med* 2017; 376:2437-2447.

17. Harrell FE. *Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis*. New York, New York: Springer; 2001.

18. Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, *et al*. Clinical practice guidelines for the management of hypertension in the community: a statement by the american society of hypertension and the international society of hypertension. *J Clin Hypertens (Greenwich)* 2013; 16:14–26.

19. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, *et al*. Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. *BMJ* 2009; 338:b2393.

20. Powers JW, Rabinstein AA, Ackerson MT, Adeoye CO, Bambakidis MN, Becker CK, *et al*., American Heart Association Stroke Council. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke* 2018; 49:e46–e110.

21. Hemphill CJ, Greenberg MS, Anderson SC, Becker RK, Bendok LB, Cushman NM, *et al*. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2015; 46:2032–2060.

22. Leonardi-Bee MWJ, Bath JP, Phillips AGS, Sandercock AGP, IST Collaborative Group. Blood pressure and clinical outcomes in the international stroke trial. *Stroke* 2002; 33:1315–1320.

23. Bangalore S, Schwamm L, Smith EE, Hellkamp AS, Suter RE, Xian Y, *et al*., Get With the Guidelines-Stroke Steering Committee and Investigators. Blood pressure and in-hospital outcomes in patients presenting with ischaemic stroke. *Eur Heart J* 2017; 38:2827–2835.

24. Appleton JP, Sprigg N, Bath PM. Blood pressure management in acute stroke. *Stroke Vasc Neurol* 2016; 1:72–82.

25. Ahmed N, Wahlgren N, Brainin M, Castillo J, Ford GA, Kaste M, *et al*. Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis: retrospective analysis from Safe Implementation of Thrombolysis in Stroke-international Stroke Thrombolysis Register (SITS-ISTR). *Stroke* 2009; 40:2442–2449.

26. Lee SE, Lee H-Y, Cho H-J, Choe W-S, Kim H, Choi J-O, *et al*. Reverse j-curve relationship between on-treatment blood pressure and mortality in patients with heart failure. *JACC Heart Fail* 2017; 5:810.

27. Vidal-Petiot E, Ford I, Greenlaw N, Ferrari R, Fox KM, Tardif J-C, *et al*., CLARIFY Investigators. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. *Lancet* 2016; 388:2142–2152.

28. Böhm M, Schumacher H, Teo KK, Lonn EM, Mahfoud F, Mann JFE, *et al*. Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ontarget and transcend trials. *Lancet* 2017; 389:2226–2237.

29. Böhm M, Young R, Jhund PS, Solomon SD, Gong J, Lefkowitz MP, *et al*. Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (lcz696) in patients with chronic heart failure and reduced ejection fraction: results from PARADIGM-HF. *Eur Heart J* 2017; 38:1132–1143.

30. Ovbiagele B, Diener H-C, Yusuf S, Martin RH, Cotton D, Vinisko R, *et al*., PROFESS Investigators. Level of systolic blood pressure within the normal range and risk of recurrent stroke. *JAMA* 2011; 306:2137.

31. Flint AC, Conell C, Ren X, Banki NM, Chan SL, Rao VA, *et al*. Effect of systolic and diastolic blood pressure on cardiovascular outcomes. *N Engl J Med* 2019; 381:243–251.

32. Park JH, Ovbiagele B. Poststroke diastolic blood pressure and risk of recurrent vascular events. *Eur J Neurol* 2017; 24:1416–1423.

33. Potter JF, Robinson TG, Ford GA, Mistri A, James M, Chernova J, *et al*. Controlling hypertension and hypotension immediately poststroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. *Lancet Neurol* 2009; 8:48.

34. Hesse LK, Fulton HR, Abdul-Rahim RA, Lees RK, VISTA Collaborators. Characteristic adverse events and their incidence among patients participating in acute ischemic stroke trials. *Stroke* 2014; 45:2677–2682.

35. Supiano MA, Pajewski NM, Williamson JD. Systolic blood pressure and mortality: role of reverse causation. *J Am Geriatr Soc* 2018; 66:205–206.

36. McNaughton H, Feigin V, Kerse N, Barber PA, Weatherall M, Bennett D, *et al*., Auckland Regional Community Stroke Study Group. Ethnicity and functional outcome after stroke. *Stroke* 2011; 42:960–964.

37. Tuhrim S. Ethnic disparities in stroke: Epidemiology, acute care, and postacute outcomes. *Stroke* 2005; 36:386–387.

3.2 Oxygen desaturation and adverse outcomes in acute stroke: secondary analysis of HeadPoST study

Paper published in Clinical Neurology and Neurosurgery as

Oxygen desaturation and adverse outcomes in acute stroke: secondary analysis of HeadPoST study

Menglu Ouyang, Christine Roffe, Laurent Billot, Lili Song, Xia Wang, Laurent Billot, Paula Muñoz-Venturelli, Pablo M. Lavados, Thompson Robinson, Sandy Middleton, Verónica V. Olavarría, Caroline L. Watkins, Tsong-Hai Lee, Alejandro M. Brunser, Octavio M. Pontes-Neto, Maree L. Hackett, Craig S. Anderson, for the HeadPoST Investigators

Refer to the following 6 pages

∗ ∗ ∗
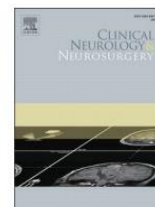
Oxygen desaturation and adverse outcomes in acute stroke: Secondary analysis of the HeadPoST study

Menglu Ouyang [a,b], Christine Roffe [c], Laurent Billot [a], Lili Song [a,b], Xia Wang [a], Paula Muñoz-Venturelli [a,d,e], Pablo M. Lavados [d], Thompson Robinson [f], Sandy Middleton [g], Verónica V. Olavarría [d], Caroline L. Watkins [h], Tsong-Hai Lee [i], Alejandro M. Brunser [d], Octavio M. Pontes-Neto [j], Maree L. Hackett [a,h], Craig S. Anderson [a,b,k,l,*]

[a] The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, Australia
[b] The George Institute China at Peking University Health Science Center, Beijing, China
[c] Stroke Research, School of Medicine, Keele University, Staffordshire, UK
[d] Unidad de Neurología Vascular, Servicio de Neurología, Departamento de Neurología y Psiquiatría, Clínica Alemana de Santiago, Chile
[e] Clinical Research Center, Instituto de Ciencias e Innovación en Medicina, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile
[f] Department of Cardiovascular Sciences and NIHR Leicester Biomedical Research Centre, University of Leicester, Leicester, UK
[g] Nursing Research Institute, St Vincent's Health (Sydney) Australia, Australian Catholic University, Sydney, Australia
[h] Faculty of Health and Care, University of Central Lancashire, Preston, Lancashire, UK
[i] Stroke Center and Department of Neurology, Linkou Chang Gung Memorial Hospital and College of Medicine, Chang Gung University, Taoyuan, Taiwan
[j] Stroke Service - Neurology Division, Department of Neuroscience and Behavioral Sciences, Ribeirão Preto Medical School, University of Sao Paulo, Ribeirão Preto, SP, Brazil
[k] Neurology Department, Royal Prince Alfred Hospital, Sydney Health Partners, Sydney, Australia
[l] Heart Health Research Center, Beijing, China

A R T I C L E I N F O	A B S T R A C T
	Objective: Uncertainty exists over the prognostic significance of low arterial oxygen saturation (SaO_2) in acute stroke. We aimed to determine the strength of association of SaO_2 and adverse outcomes among participants of the international Head Positioning in acute Stroke Trial (HeadPoST). *Methods:* Post-hoc analyzes of HeadPoST, a pragmatic cluster-crossover randomized trial of lying flat versus sitting up head positioning in 11,093 patients (age $\geq$18 years) with acute stroke at 114 hospitals in 9 countries during 2015–2016. Associations of the lowest recorded SaO_2 level, as a continuous measure and as a cut-point for desaturation (SaO_2 <93%), in the first 24 h and clinical outcomes of death or dependency (modified Rankin scale [mRS] scores 3–6) and any serious adverse event (SAE) at 90 days, were assessed in generalized linear mixed models adjusted for baseline and in-hospital management confounders. *Results:* There was an inverse J-shaped association between SaO_2 and death or dependency, with a nadir for optimal outcome at 96–97%. Patients with SaO_2 desaturation were older, and had greater neurological impairment, premorbid disability and cardiorespiratory disease. Desaturation was not clearly associated with death or dependency (adjusted odds ratio [aOR] 1.19, 95% confidence interval [CI] 0.95–1.48) but was with SAEs (aOR 1.34, 95% CI 1.07–1.68), without heterogeneity by head position, cardiac-respiratory comorbidity, or other pre-specified subgroups. *Conclusions:* Any change in SaO_2 outside of 96–97% is associated with poorer outcome after acute stroke. *Clinical trial registration:* HeadPoST is registered at ClinicalTrials.gov (NCT02162017).

1. Introduction

Hypoxia is common in patients who have suffered an acute stroke,

the result of many factors including the severity of the neurological deficit, dysphagia, sleep apnea, and cardiac or respiratory disease [1]. Given that it can cause harms, such as worsening of the cerebral lesion,

* Correspondence to: George Institute for Global Health, PO Box M201, Missenden Rd, NSW 2050, Australia.
E-mail address: canderson@georgeinstitute.org.au (C.S. Anderson).

guidelines are consistent in recommending that patients with an acute stroke, as well as anyone with a critical illnesses, be carefully monitored and for supplementary oxygen to be used when the levels of arterial oxygen saturation (SaO_2) fall below 93% or 94% [2–4]. Although randomized trials have not shown a benefit from the routine use of supplementary oxygen in acute stroke [5–8], prompt correction of SaO_2 desaturation is likely to improve outcomes, although supporting evidence is limited [1]. The few studies that have evaluated the influence of different head positions in bed suggest that SaO_2 improves with head elevation or sitting up [9,10], but these data are derived from small samples where high-risk patients have been excluded [11]. Herein, we present post-hoc analyzes of the large international, Head Positioning in Acute Stroke Trial (HeadPoST) dataset [12], to determine any associations between the lowest SaO_2 recorded during patient monitoring in the first 24 h after hospital admission for acute stroke and 90-day clinical outcomes; and whether this was modified by head position or comorbid cardiorespiratory illness.

2. Methods

2.1. Study population

HeadPoST was a multicenter, cluster crossover, clinical trial in 11,093 adults (age ≥18 years) with presumed acute stroke (both ischemic and hemorrhagic) randomly allocated to the lying flat or sitting up head position soon after presentation at 114 hospitals in 9 countries between March 2015 and November 2016 [8]. A guardian consent process was used to implement the randomized intervention as a policy of usual service delivery to a pre-defined patient cluster; patients provided consent for the use of their medical record data and centralized telephone follow-up. HeadPoST is registered at ClinicalTrials.gov (NCT02162017).

2.2. Procedures

Demographic, medical history and clinical information, including the severity of neurological impairment on the National Institutes of Health Stroke Scale (NIHSS), were recorded at baseline. Data were collected on the lowest SaO_2 within the first 24 h as part of a protocol for standard monitoring of vital signs and adherence to the allocated head position. Trained staff, blind to treatment allocation, contacted patients not known to have died, by telephone to assess their functional status on the modified Rankin scale (mRS) at 90 days. The primary outcome for these analyzes was death or dependency (mRS scores 3–6). Secondary outcomes were all-cause and cause-specific, serious adverse events (SAEs), reported by site investigators during the hospital stay to the end of follow-up at 90 days (see appendix for list of SAEs) [8].

2.3. Statistical analysis

Continuous relationships of lowest SaO_2 level and clinical outcomes were visualized using restricted cubic splines fitted with 3–5 knots for placement, as recommended by Harrell [13], with optimal knots selected according to the likelihood ratio test and Aikaike information classification (AIC). Associations were also assessed according to SaO_2 desaturation as a binary variable, defined as < 93% by the 1st decile of distribution and according to clinical guideline recommended threshold for use of supplementary oxygen [14]. These levels were assessed by generalized linear mixed (GLM) models that were built with adjustment for the fixed effects of head position (lying-flat versus sitting-up) and cross-over period, random effects of cluster, random interaction effects between cluster and crossover period, and potential confounding baseline (Model 1) and relevant hospital management variables (Model 2) (with P < 0.20 from Table 1). A sensitivity analysis used a SaO_2 < 92%, another popular definition of desaturation [15]. Due to the high proportion of missing data in SaO_2 and baseline blood glucose level,

Table 1

Baseline characteristics and hospital management by lowest level of arterial oxygen saturation (SaO_2) in the first 24 h after acute stroke.

Variables	Lowest SaO_2		
	< 93% (n = 784 [9.7%])	93–100% (n = 7283 [90.3%])	P value
Age	72.7 (13.00)	68.6 (14.00)	< 0.001
Female	354 (45.2)	2987 (41.0)	0.025
Region			< 0.001
Australia/UK	418 (53.3)	3958 (54.5)	
China/Taiwan	176 (22.5)	2194 (30.1)	
India/Sri Lanka	44 (5.6)	457 (6.3)	
South America	146 (18.6)	674 (9.3)	
Premorbid mRS scores 2–5	196 (25.1)	1401 (19.3)	< 0.001
NIHSS score	6 (3–13)	4 (2–9)	< 0.001
≥ 15	169 (21.8)	842 (11.8)	< 0.001
Systolic blood pressure, mmHg	152 (135–176)	152 (135–172)	0.749
Blood glucose level, mmol/L	6.5 (5.6–8.5)	6.1 (5.3–7.7)	< 0.001
Time from symptom onset to hospital arrival, hrs	4.1 (1.8–14.1)	6.2 (2.1–23.5)	< 0.001
Medical history and medications			
Heart failure	49 (6.3)	279 (3.9)	0.001
COPD/emphysema	72 (9.3)	262 (3.6)	< 0.001
Hypertension	541 (69.2)	4621 (63.6)	< 0.001
Atrial fibrillation	117 (15.0)	875 (12.1)	0.017
Coronary heart disease	114 (14.7)	1027 (14.2)	0.719
Diabetes mellitus	202 (25.8)	1705 (23.5)	0.143
Hyperlipidemia	245 (31.5)	2051 (28.3)	0.060
Previous stroke	178 (22.8)	1598 (22.0)	0.619
Other major health conditions	184 (23.8)	1318 (18.3)	< 0.001
Current smoker	127 (16.4)	1275 (17.7)	0.352
Antiplatelet use in AIS	318 (48.1)	3092 (50.4)	0.270
Anticoagulant use in AIS	82 (12.4)	529 (8.7)	0.002
Dysphagia	264 (34.2)	1370 (19.0)	< 0.001
Final diagnosis			0.431
Acute ischemic stroke	664 (84.7)	6143 (84.4)	
AIS subtype			< 0.001
Large vessel occlusion	168 (25.3)	1896 (30.9)	
Cardioembolic	146 (22.0)	922 (15.0)	
Lacunar	158 (23.5)	1600 (26.1)	
Other	194 (29.2)	1725 (28.1)	
Intracerebral haemorrhage	74 (9.4)	629 (8.6)	
Presence of intraventricular blood	16 (22.2)	188 (30.1)	0.165
Haematoma volume	10 (3–15)	10 (3–15)	0.446
Not AIS/ICH*	46 (5.9)	504 (6.9)	
Hospitalisation management			
Reperfusion therapy† for AIS	151 (22.8)	1030 (16.8)	< 0.001
Surgical procedures‡ for ICH	3 (4.1)	4 (0.6)	0.005
Withdraw active care	26 (3.4)	66 (0.9)	< 0.001
Endotracheal intubation	21 (2.7)	60 (0.8)	< 0.001

Data are mean (SD), median (IQR), and n (%)
Analyses were T-test for normally distributed variables, Wilcoxon rank sum test for skewed continuous variables, and Chi-squared test for categorical variables. AIS denotes acute ischemic stroke, COPD chronic obstructive pulmonary disease, ICH intracerebral haemorrhage, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale, UK United Kingdom
*includes transient ischemic attack, migraine, seizure, functional weakness, syncope, transient global amnesia, metabolic disorder, tumour or other sources
†Reperfusion therapy includes recombinant tissue-type plasminogen activator (rt-PA) treatment (intravenous or intra-arterial) or endovascular clot retrieval
‡ICH surgical procedures include decompressive hemicarnectomy, open craniotomy surgical evacuation, minimally invasive surgery or intraventricular drainage

multiple imputation was also used as another form of sensitivity analysis (Model 3), where all covariates and outcomes [16] were used with a fully conditional specification of 20 imputed sets through PROC MI according to fully conditional method (FCS) methods. A propensity score matching approach was also conducted as a sensitivity analysis to address variable imbalance between the two groups in exploring associations of desaturation and clinical outcomes (described in

supplemental materials). Pre-specified subgroup analysis considered participating region, age, stroke subtype, baseline neurological severity, pre-morbid function, presence of dysphagia, allocated head position, comorbid cardiorespiratory disorder (i.e. heart failure or chronic obstructive pulmonary disease [COPD] / emphysema), and time from the onset of symptoms to hospital arrival. Estimates are presented as adjusted odds ratios (aOR) and 95% confidence intervals (CI), and a two-sided $P < 0.05$ was considered statistically significant. All analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC).

3. Data sharing

Individual participant data used in these analyses can be shared by formal request, with the protocol from any qualified investigator, to the Research Office of The George Institute for Global Health, Australia.

4. Results

There were 8067 (73%) patients (mean age 69 years; 58.6% male) from the total study population with data on their lowest SaO_2 level recorded in the 24 h after hospital admission (Supplemental Fig. S1): the median lowest SaO_2 was 95% (IQR 94%–97%) and the 1st decile was 93% (Supplemental Fig. S2). Participants who lacked data on SaO_2 were significantly more often from China, had greater prior strokes and co-morbid conditions of COPD/emphysema and ischemic stroke, with adjustment of study design (Supplemental Table S1). Among the 8067 patients with SaO_2 recorded, 784 (9.7%) met the definition of SaO_2 desaturation (<93%), and they were older, more often female, arrived

A. Death or dependency at 90 days

B. Serious adverse events (SAE) within 90 days
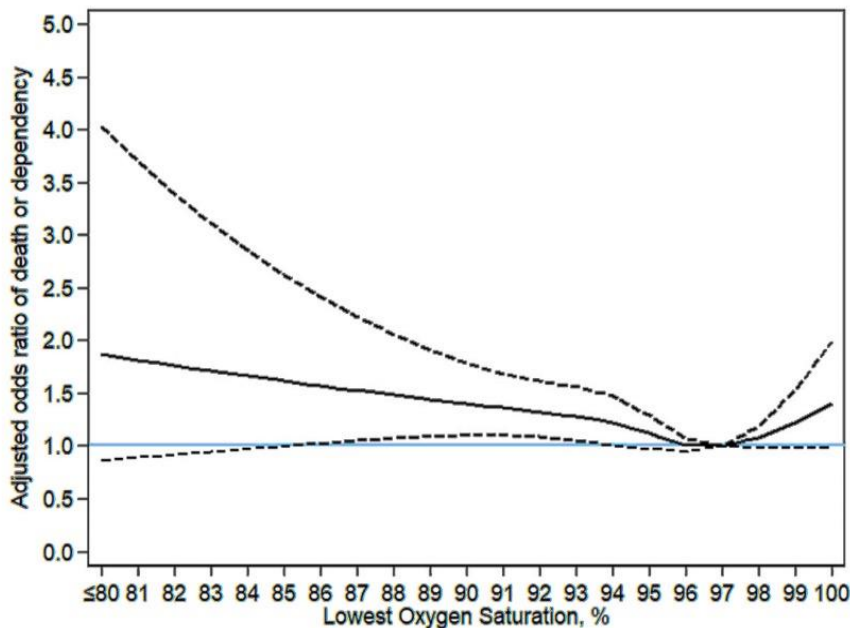
Fig. 1. Relationship of lowest arterial oxygen saturation (SaO_2) in first 24 h of acute stroke and clinical outcomes A. Death or dependency at 90 days B. Serious adverse events (SAE) within 90 days Footnote: Generalized linear mixed models with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and region, age, sex, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, National Institutes of Health Stroke Scale score, pre-morbid score 0–1 on the modified Rankin scale, dysphagia, hyperlipidemia, other major health conditions, chronic obstructive pulmonary disease, stroke subtype, antithrombotic treatment, time from symptom onset to hospital arrival, withdraw active care, endotracheal intubation, reperfusion therapy for ischemic stroke and surgical procedures for haemorrhagic stroke A. Spline fitted with 4 knots (percentiles 5th, 35th, 65th, 95th) for SaO_2, with 97% as reference. Solid line indicates adjusted odds ratio; dotted lines indicates 95% confidence intervals. B. Spline fitted with 3 knots (percentiles 25th, 50th, 75th) for SaO_2 with 100% as reference. Solid line indicates adjusted odds ratio; dotted lines indicates 95% confidence intervals.
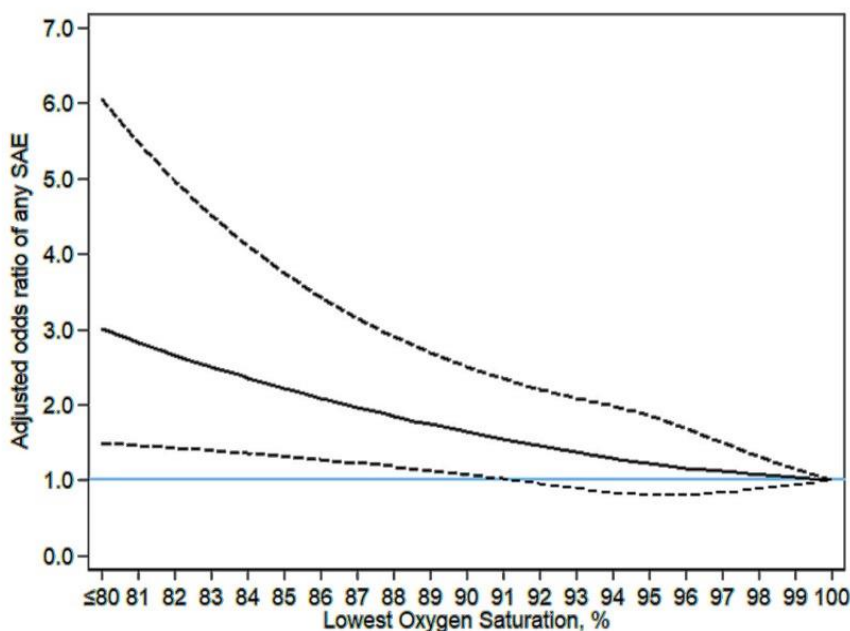
earlier to hospital, had greater neurological severity, higher baseline blood glucose, more premorbid disability, cardiac and respiratory co-morbidities and dysphagia, than other patients (Table 1).

Fig. 1A shows a reverse J-shape relationship between the lowest SaO_2 in first 24 h post-stroke and death or dependency, with a nadir at 96–97%. When analyzed as a binary variable, patients with SaO_2 desaturation (<93%) had a higher odds, albeit non-significant, association of death or dependency (55.6% vs. 40.0%; aOR 1.19, 95% CI 0.95–1.48; Table 2). The relationship of SaO_2 and SAEs was inverse linear, with a decrease in SAEs as SaO_2 increased (Fig. 1B), which translated into a significant association between SaO_2 desaturation (<93%) and any SAE (aOR 1.34, 95% CI 1.07–1.68; Table 2). These results were consistent after multiple imputation (Table 2), when using a lower cut-point of < 92% for SaO_2 desaturation (Supplemental Table S2), and after pro-pensity score matching to adjust unbalanced covariates (Supplemental Tables S3 and S4). Although desaturation was associated with stroke-specific SAEs in Model 1 (aOR 1.54, 95% ci 1.12–2.12), the signifi-cance was lost after adjustment of hospital management variables (aOR 1.38, 95% CI 0.98–1.93; Table 2).

There was no evidence of heterogeneity in the association between SaO_2 desaturation across subgroups for death or dependency (Supple-mental Fig. S3), and for SAEs (Supplementary Fig. S4). In particular, there was no clear modification of these associations by different head position, comorbid cardiorespiratory disease, and dysphagia, nor was there any heterogeneity across regions. However, significant higher odds of poor outcome were found in males and without dysphagia (Fig. S3). Moreover, minor stroke, ICH, lying flat, and presence of cardiac-respiratory comorbidity, were all related to a higher odds of SAEs in subgroup analysis (Fig. S4). The level of the lowest SaO_2 at which the spline for death and disability had its nadir was consistent across stroke subtypes (Supplementary Figs. S5), but varied across re-gions: ranging between 95% and 98% (Supplementary Figs. S6). Post-hoc power calculations underlying these analyzes based on the observed outcomes are outlined in the Appendix (Supplementary Table S5).

5. Discussion

In these secondary analyzes of a large clinical cohort, patients with the lowest SaO_2 of around 96–97% early after the onset of stroke had a better clinical outcome compared to others with either lower or higher levels of SaO_2. Patients with SaO_2 desaturation were more often older, frailer, and had greater neurological impairment, than other patients,

which placed them at higher odds of adverse outcomes.

Our results are consistent with the conclusions drawn from a recent review of hypoxia in stroke, where there is no clear association of SaO_2 desaturation, as a binary cut-point variable, and adverse functional outcome [1]. Although another study showed that hypoxic (SaO_2 <93%) patients treated with supplemental oxygen had improved neurological function by one week, this might have been a chance finding due to the small sample and/or an imbalance in baseline neurological severity between the groups [17]. As some studies have shown an increased odds of adverse outcomes at much lower cut points to define hypoxia (SaO_2 <90%) [18], our finding of a poor outcome in patients with higher levels of SaO_2 might be due to reverse causality, where supplementary oxygen had been used in high-risk patients. This is supported the significant relationship between desaturation and stroke-specific SAEs being elim-inated after adjustment of aspects of hospital management. As the normal range of SaO_2 in healthy adults is 95–98% [19], the finding of poor outcome associated with SaO_2 at full concentration (100%) sup-ports the potential for mechanisms such as oxidative stress to be exac-erbated by over-aggressive use of oxygen treatment [20,21]. Other studies have shown that inappropriately high oxygen therapy is asso-ciated with greater mortality without any improvement in patient-centred outcomes [22]. As such, guidelines recommend that supplementary oxygen should not be used routinely, but instead restricted to those with evidence of desaturation, with a SaO_2 of 94–96% being a reasonable treatment target [3,14].

Compared to other studies [23–25] suggesting that females have greater respiratory effort and are less prone to ischemic injury than males, we could not find any heterogeneity by sex, nor according to the presence of dysphagia or neurological severity; but this might be due to incomplete adjustment for confounding, such as the use of supplemen-tary oxygen in sicker patients. Similarly, although there was no clear influence of head position on the association of SaO_2 desaturation and poor outcome, the higher odds of SAEs in those who were lying flat could have been due to reduced lung expansion and gas exchange [10], and risk of aspiration, especially in the presence of dysphagia [26]. Moreover, the smaller sample size of subgroup analyzes and different national standards of care, could have influenced the varying nadir of SaO_2 for optimal outcome across regions.

A strength of our study was the inclusion of a large sample of patients with a broad range of characteristics who were managed across a variety of health systems. However, there are several limitations, one which being the high proportion of missing data, which may have introduced further bias on top of selection bias pertaining to the data being derived

Table 2
Association of arterial oxygen saturation (SaO_2) and clinical outcomes at 90 days after acute stroke.

Outcome	SaO_2		Model 1		Model 2		Model 3	
	< 93%	93–100%	aOR (95% CI)	P value	aOR (95% CI)	P value	aOR (95% CI)	P value
Death or dependency	380/683* (55.6)	2503/6266* (40.0)	1.20 (0.96–1.50)	0.102	1.19 (0.95–1.48)	0.133	1.16 (0.97–1.39)	0.106
Any SAEs	197/784† (25.1)	1085/7283† (14.9)	1.41 (1.13–1.76)	0.002	1.34 (1.07–1.68)	0.012	1.26 (1.03–1.52)	0.023
Acute stroke	70/784 (8.9)	364/7283 (5.0)	1.54 (1.12–2.12)	0.008	1.38 (0.98–1.93)	0.063		
Cardiac/other vascular disease	27/784 (3.4)	168/7283 (2.3)	1.12 (0.70–1.79)	0.631	1.12 (0.70–1.80)	0.624		
Pneumonia	49/784 (5.1)	212/7283 (2.9)	1.18 (0.79–1.76)	0.433	1.12 (0.74–1.68)	0.597		
Other infection	12/784 (1.5)	86/7283 (1.2)	0.97 (0.49–1.92)	0.923	0.95 (0.47–1.89)	0.875		
Other SAEs	38/784 (4.5)	252/7283 (3.4)	1.29 (0.88–1.90)	0.200	1.28 (0.87–1.89)	0.208		

Data are n/N (%)

aOR adjusted odds ratio, CI denotes confidence interval, SAEs serious adverse events,

*Denominators represent the total number of patients with follow-up to 90-days

†Denominators represent the total number of randomized patients

Model 1: aOR obtained from generalized linear mixed models with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and baseline variables of age, sex, region, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, National Institutes of Health Stroke Scale score, pre-morbid score 0–1 on the modified Rankin scale, dysphagia, hyperlipidemia, other major health conditions, chronic obstructive pulmonary disease, stroke type, antithrombotic treatment, and time from symptom onset to hospital arrival

Model 2: further adjusted management variables include withdraw active care, endotracheal intubation and reperfusion therapy for ischemic stroke during hospi-talisation and surgical procedures for intracerebral haemorrhage during hospitalisation

Model 3: imputation dataset analysis based on the variables adjusted in Model 2 with additional adjustment of imputed blood glucose level

from a clinical trial population. Despite consistency of the results after multiple imputation, the assumption that missingness occurred at random for these analyzes may not have applied, and thus the observed data may not have been sufficient to explain the association. Another major limitation is the availability of only a single exposure measure, that of the lowest recorded SaO_2 in the first 24 h after hospital admission, being recorded as a measure of safety to the allocated head position. A full appreciation of the role of desaturation would require data on the timing of SaO_2 desaturation, its change, purpose of measurement, and its management. As SaO_2 is physiologically dynamic, a single measure will not adequately capture the frequency and duration of episodes of SaO_2 desaturation [18], and chance and bias further complicate post-hoc analyzes with variable cut-off points for SaO_2. Taken together with issues of indication bias and reduced power in subgroup analysis and of disease-specific SAEs, any associations may not be causal, and caution should be applied when interpreting these results.

In summary, a SaO_2 of 96–97% is associated with optimal functional recovery from acute stroke, with poor outcomes evident at both lower and higher values without any clear influence of head position or cardiorespiratory disease this association. Further research is required to determine the potential impact of avoiding SaO_2 desaturation and/or over-correction to full SaO_2 concentration in acute stroke.

Author contributions

CSA and MO contributed to the concept and rationale for the study. MO undertook statistical analyzes with assistance from LB. MO wrote the first draft of manuscript with input from CSA. All authors commented upon and approved the final version of the manuscript for publication.

Statement of ethics

The appropriate ethics committee at each participating centre approved the study protocol. A senior executive officer at each centre acted as a 'guardian' and provided institutional consent for this low-risk intervention to be implemented as part of routine nursing care in each cluster. Written informed consent was sought from all patients or approved surrogates for ongoing assessments and data collection.

Disclosures

PML reports grants from The George Institute for Global Health and Clínica Alemana de Santiago, during the conduct of the study; and non-financial support from Boehringer Ingelheim, grants and personal fees from Bayer and AstraZeneca, and grants from CONICYT, outside the submitted work. MLH holds a National Health and Medical Research Council of Australia (NHMRC) Career Development Fellowship. VVO reports grants from The George Institute for Global Health and Clínica Alemana de Santiago, during the conduct of the study; and research grants from Boehringer Ingelheim and CONICYT outside the submitted work. PMV reports grants from The George Institute for Global Health and Clínica Alemana de Santiago, during the conduct of the study; and research grants from CONICYT, outside the submitted work. CR has received funding from the UK National Institute for Health Research (NIHR) for a trial of routine oxygen supplementation in acute stroke as well as other stroke studies; and she is a member of the Data Safety Monitoring committee for the EU FP7 funded PROOF study assessing the effects of high flow oxygen treatment during mechanical thrombectomy. SM was a member of the NHMRC Research Committee during 2015–2018. OMPN received grants for the Brazilian Stroke Research Network by DECIT/MS and CNPQ (402388/2013-5) for conduct this study. TGR is an NIHR Senior Investigator. CSA is an NHMRC Senior Investigator and grants, honoraria and travel reimbursement from Takeda outside of this study. The other authors have no disclosures to report.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.clineuro.2021.106796.

References

[1] P. Ferdinand, C. Roffe, Hypoxia after stroke: A review of experimental and clinical evidence, Exp. Transl. Stroke Med 8 (2016) 9.

[2] Bowen AJM, Young, G. National clinical guideline for stroke prepared by the intercollegiate stroke working party. 2016.

[3] W.J. Powers, A.A. Rabinstein, T. Ackerson, O.M. Adeoye, N.C. Bambakidis, K. Becker, J. Biller, M. Brown, B.M. Demaerschalk, B. Hoh, E.C. Jauch, C. S. Kidwell, T.M. Leslie-Mazwi, B. Ovbiagele, P.A. Scott, K.N. Sheth, A. M. Southerland, D.V. Summers, D.L. Tirschwell, C. American Heart Association Stroke, 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the american heart association/american stroke association, Stroke 49 (2018) e46–e99.

[4] C. The European Stroke Organisation Executive, the ESOWC, Guidelines for management of ischaemic stroke and transient ischaemic attack 2008, Cereb. Dis. 25 (2008) 457–507.

[5] C. Roffe, T. Nevatte, J. Sim, J. Bishop, N. Ives, P. Ferdinand, R. Gray, G. Stroke Oxygen Study Investigators and the Stroke OxygenStudy Collaborative, Effect of routine low-dose oxygen supplementationon death and disability in adults with acute strokethe stroke oxygen study randomized clinical trial, JAMA 318 (2017) 1125–1135.

[6] A.B. Singhal, T. Benner, L. Roccatagliata, W.J. Koroshetz, P.W. Schaefer, E.H. Lo, F. S. Buonanno, R.G. Gonzalez, A.G. Sorensen, A pilot study of normobaric oxygen therapy in acute ischemic stroke, Stroke 36 (2005) 797–802.

[7] M.V. Padma, A. Bhasin, R. Bhatia, A. Garg, M.B. Singh, M. Tripathi, K. Prasad, Normobaric oxygen therapy in acute ischemic stroke: a pilot study in indian patients, Ann. Indian Acad. Neurol. 13 (2010) 284–288.

[8] K. Ali, A. Warusevitane, F. Lally, J. Sim, S. Sills, S. Pountain, T. Nevatte, M. Allen, C. Roffe, The stroke oxygen pilot study: A randomized controlled trial of the effects of routine oxygen supplementation early after acute stroke–effect on key outcomes at six months, PLoS One 8 (2014), 59274.

[9] J. Elizabeth, J. Singarayar, J. Ellul, D. Barer, M. Lye, Arterial oxygen saturation and posture in acute stroke, Age Ageing 22 (1993) 269–272.

[10] A.M. Rowat, J.M. Wardlaw, M.S. Dennis, C.P. Warlow, Patient positioning influences oxygen saturation in the acute phase of stroke, Cereb. Dis. 12 (2001) 66–72.

[11] H.J. Chatterton, V.M. Pomeroy, L. Clayton, R.C. Tallis, M. Connolly, E.B. Farragher, The effect of body position on arterial oxygen saturation in acute stroke, J. Gerontol. A Biol. Sci. Med Sci. 86 (2000), 149-149.

[12] C.S. Anderson, H. Arima, P. Lavados, L. Billot, M.L. Hackett, V.V. Olavarría, P. Muñoz Venturelli, A. Brunser, B. Peng, L. Cui, L. Song, K. Rogers, S. Middleton, J. Y. Lim, D. Forshaw, C.E. Lightbody, M. Woodward, O. Pontes-Neto, H.A. De Silva, R.T. Lin, T.H. Lee, J.D. Pandian, G.E. Mead, T. Robinson, C. Watkins, C. HeadPoST Investigators and, Cluster-randomized, crossover trial of head positioning in acute stroke, New Engl. J. Med. 376 (2017) 2437–2447.

[13] F.E. Harrell Jr., Regression modeling strategies: With applications to linear models, logistic and ordinal regression, and survival analysis, Springer International Publishing AG, Cham: Cham, 2015.

[14] Stroke Foundation. Clinical guidelines for stroke management. 2019.

[15] British Thoracic Society Standards of Care Committee, Guidelines for the management of community acquired pneumonia in adults, Thorax 56 (2001) iv1–iv64.

[16] J.A.C. Sterne, I.R. White, J.B. Carlin, M. Spratt, P. Royston, M.G. Kenward, A. M. Wood, J.R. Carpenter, Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls, BMJ 338 (2009), b2393 b2393-b2393.

[17] C. Roffe, K. Ali, A. Warusevitane, S. Sills, S. Pountain, M. Allen, J. Hodsoll, F. Lally, P. Jones, P. Crome, The sos pilot study: A rct of routine oxygen supplementation early after acute stroke–effect on recovery of neurological function at one week, PLoS One 6 (2011), 19113.

[18] A.M. Rowat, M.S. Dennis, J.M. Wardlaw, Hypoxaemia in acute stroke is frequent and worsens outcome, Cereb. Dis. 21 (2006) 166–172.

[19] A.J. Williams, Assessing and interpreting arterial blood gases and acid-base balance, BMJ 317 (1998) 1213–1216.

[20] G. Hedenstierna, C.S. Meyhoff, Oxygen toxicity in major emergency surgery—anything new? Intensive Care Med 45 (2019) 1802–1805.

[21] R.P. Weenink, S.W. de Jonge, R.A. van Hulst, T.T. Wingelaar, P. van Ooij, R. V. Immink, B. Preckel, M.W. Hollmann, Perioperative hyperoxyphobia: Justified or not? Benefits and harms of hyperoxia during surgery, J. Clin. Med 9 (2020) 642.

[22] D.K. Chu, L.H. Kim, P.J. Young, N. Zamiri, S.A. Almenawer, R. Jaeschke, W. Szczeklik, H.J. Schünemann, J.D. Neary, W. Alhazzani, Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (iota): a systematic review and meta-analysis, Lancet 391 (2018) 1693–1705.

[23] Ulanova M., Gekalyuk A., Agranovich I., Khorovodov A., Rezunbaeva V., Borisova E., et al. Stress-induced stroke and stomach cancer: Sex differences in oxygen saturation. Oxygen Transport to Tissue XXXVIII. 2016:135–140.

[24] S. Levental, E. Picard, F. Mimouni, L. Joseph, T.Y. Samuel, R. Bromiker, D. Mandel, N. Arish, S. Goldberg, Sex-linked difference in blood oxygen saturation, Clin. Respir. J. 12 (2018) 1900–1904.

[25] S.R. Mayoral, G. Omar, A.A. Penn, Sex differences in a hypoxia model of preterm brain damage, Pedia Res 66 (2009) 248–253.

[26] S. Singh, S. Hamdy, Dysphagia in stroke patients, Post. Med J. 82 (2006) 383–391.

Chapter 4 Quantifying regional variations in components of acute stroke unit care (ASU) in the international HeadPoST study

ASU is acknowledged as being able to improve survival and functional recovery for patients affected by stroke. The treatment effect is homogeneous across a range of patient characteristics in all age groups and different stroke subtypes. However, studies are limited on variations of ASU care processes across regions, especially in low- and middle-income countries. This Chapter contains one of my studies which aims to quantify regional variations in the various components of care processes by ASU admission.

The HeadPoST trial collected in-hospital management variables that covered the essential standard care processes, as recommended by clinical guidelines, from a wide range of settings in nine countries. This allowed me to compare variations in care processes across four economically-defined regional groups. I used descriptive analysis to compare differences in care processes according to ASU admission, within and across grouped regions. In order to estimate the regional variations in the ASU care, generalized linear mixed models were used with adjustment for the study design and potential patient- and hospital-level confounders.

My findings showed significant variations in the ASU care processes across regions, with lower probabilities of receiving reperfusion therapy and multidisciplinary care in low economic-level regions compared to high economic-level regions. Efforts are required to eliminate the disparities of acute stroke care across lower economic-level regions to improve patient outcomes.

I designed this study, analysed and interpreted the data, wrote the first draft of the manuscript, coordinated and incorporated co-authors' edits, prepared and submitted the manuscript, drafted the responses to editor's and reviewers' comments, and prepared the final draft of the manuscript for publication.

Paper published in Journal of the Neurological Sciences as

Quantifying regional variations in components of acute stroke unit (ASU) care in the international HeadPoST study

Menglu Ouyang, Yao Zhang, Xia Wang, Lili Song, Laurent Billot, Thompson Robinson, Pablo M. Lavados, Hisatomi Arima, Maree L. Hackett, Verónica V. Olavarría, Paula Muñoz-Venturelli, Sandy Middleton, Caroline L. Watkins, Octavio M. Pontes-Neto, Tsong-Hai Lee, Alejandro M. Brunser, Craig S. Anderson, for the HeadPoST Investigators

Refer to the following 6 pages

✳ ✳ ✳
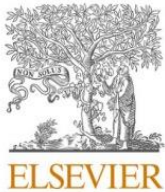
Quantifying regional variations in components of acute stroke unit (ASU) care in the international HeadPoST study

Menglu Ouyang [a,b], Yao Zhang [c], Xia Wang [a], Lili Song [a,b], Laurent Billot [a], Thompson Robinson [d], Pablo M. Lavados [e], Hisatomi Arima [f], Maree L. Hackett [a,g], Verónica V. Olavarría [e], Paula Muñoz-Venturelli [a,h], Sandy Middleton [i], Caroline L. Watkins [g], Octavio M. Pontes-Neto [j], Tsong-Hai Lee [k], Alejandro M. Brunser [e], Craig S. Anderson [a,b,h,l,m,*]

[a] The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, Australia
[b] The George Institute China at Peking University Health Science Center, Beijing, China
[c] Department of Neurology, Shenyang First People's Hospital, Shenyang, China
[d] Department of Cardiovascular Sciences and NIHR Leicester Biomedical Research Centre, University of Leicester, Leicester, UK
[e] Unidad de Neurología Vascular, Servicio de Neurología, Departmento de Neurologia y Psiquiatria, Clínica Alemana de Santiago, Facultad de Medicina, Clínica Alemana, Universidad del Desarrollo, Chile
[f] Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, Fukuoka, Japan
[g] Faculty of Health and Wellbeing, University of Central Lancashire, Preston, Lancashire, UK
[h] Centro de Estudios Clínicos, Instituto de Ciencias e Innovación en Medicina, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile
[i] Nursing Research Institute, St Vincent's Health Network Sydney, St Vincent's Hospital, Melbourne and Australian Catholic University, Sydney, Australia
[j] Stroke Service - Neurology Division, Department of Neuroscience and Behavioral Sciences, Ribeirão Preto Medical School, University of Sao Paulo, Ribeirão Preto, SP, Brazil
[k] Stroke Center and Department of Neurology, Linkou Chang Gung Memorial Hospital and College of Medicine, Chang Gung University, Taoyuan, Taiwan
[l] Neurology Department, Royal Prince Alfred Hospital, Sydney Health Partners, Sydney, Australia
[m] Heart Health Research Center, Beijing, China

ARTICLE INFO

ABSTRACT

Objective: Access to acute stroke unit (ASU) care is known to vary worldwide. We aimed to quantify regional variations in the various components of ASU care.

Method: Secondary analysis of the Head Positioning in acute Stroke Trial (HeadPoST), an international, multi-centre, cluster crossover trial of head-up versus head-down positioning in 11,093 acute stroke patients at 114 hospitals in 9 countries. Patients characteristics and 11 standard components of processes of care were described according to ASU admission within and across four economically-defined regional groups (Australia/UK, China [includes Taiwan], India/Sri Lanka, and South America [Brazil/Chile/Colombia]). Variations in process of ASU care estimates were obtained in hierarchical mixed models, with adjustment for study design and potential patient- and hospital-level confounders.

Results: Of 11,086 patients included in analyses, 59.7% (*n* = 6620) had an ASU admission. In China, India/Sri Lanka and South America, ASU patients were older, had greater neurological severity and more premorbid conditions than non-ASU patients. ASU patients were more likely to receive reperfusion therapy and multidisciplinary care within regions, but the components of care varied across regions. With Australia/UK as reference, patients in other regions had a lower probability of receiving reperfusion therapy, especially in India/Sri Lanka (adjusted odds ratio [aOR] 0.27, 95% confidence interval [CI] 0.12–0.63) and multidisciplinary care (mainly in formal dysphagia assessment, physiotherapy and occupational therapy).

Conclusion: There is significant variation in the components of stroke care across economically-defined regions of the world. Ongoing efforts are required to reduce disparities and optimise health outcomes, especially in resource poor areas.

Clinical trial registration: HeadPoST is registered at ClinicalTrials.gov (NCT02162017).

---

* Corresponding author at: The George Institute for Global Health, PO Box M201, Missenden Rd., NSW 2050, Australia.
E-mail address: canderson@georgeinstitute.org.au (C.S. Anderson).

1. Introduction

National guidelines universally recommend well-organised, inter-disciplinary, acute stroke unit (ASU) care [1–4], based upon consistent evidence from systematic reviews and individual trials showing improved survival and functional recovery [5,6], with the treatment effect being consistent across a range of patient characteristics within all age groups and different stroke subtypes [7–10]. However, such care is absence or only partially established in many hospitals around world [11]. While ASU care is relatively well-defined in high resource settings, less attention has been given to its availability and appropriateness in low- and middle- income countries (LMICs), where most of the global burden of stroke occurs [12,13]. Previous studies have shown large variations in the organisation of stroke care across hospitals which may compromise effective ourcomes, as significant associations between receipt of evidence-based care and clinical outcomes were reported in our international, multicentre, Head Positioning in acute Stroke Trial (HeadPoST) [7,14]. Despite acknowledging variations in stroke care pathways, access to ASU, and other aspects of stroke care [14,15], few studies have systematically quantified how the specific components of ASU care may differ across regions of the world [16]. Herein, we quantify the components of ASU care, within and across hospitals, in four participating income-grouped geographical regions for patients who participated in the HeadPoST. This study included a large and broad range of relatively unselected patients with acute stroke with systematic assessment of their management and outcome.

2. Methods

2.1. Study design and population

This descriptive study is a secondary analysis using data prospec-tively collected from 114 hospitals in nine countries in the HeadPoST study. In brief, HeadPoST was an international, multicentre, cluster crossover, randomised trial that involved 11,093 adults (≥18 years) with acute stroke who were randomly allocated to lying flat (head down) or sitting up (head up) positioning between March 2015 and November 2016 [17]. Patients were excluded if they had early resolu-tion of their neurological symptoms consistent with a transient ischae-mic attack; a clear contraindication to either head position; any medical condition that would compromise adherence to the protocol or assigned head position; or refused participation. A cluster guardian consent process was used to implement the randomised intervention as a policy of usual service delivery to a pre-defined patient cluster; patients pro-vided consent for use of their medical record data and centralised tele-phone follow-up. HeadPoST study is registered at ClinicalTrials.gov (NCT02162017).

2.2. Procedures

ASU admission and processes of care were derived from hospital management data collected at Day 7 post-randomisation (or at hospital separation, if earlier). Eleven in-hospital processes of care data of evidence-based guideline recommendations and/or clinical quality of care indicators were assessed [18–20], including reperfusion treatment (thrombolysis or endovascular clot retrieval), antiplatelet therapy for acute ischaemic stroke (AIS), anticoagulant for atrial fibrillation (AF), blood pressure (BP) lowering, dysphagia screening, formal dysphagia assessment for those failed screening, feeding assistance in those with dysphagia, and components of multidisciplinary care including physio-therapy, occupational therapy and psychological therapy (Supplemental Table S1). Baseline data collection included demography, medical his-tory and clinical information, including severity of neurological impairment on the National Institutes of Health Stroke Scale [21] (NIHSS). Patients were re-grouped into four principle geographical re-gions and world bank country income levels: [22] Australia/UK, China

(includes Taiwan), India/Sri Lanka, and South America (including Brazil/Chile/Colombia). Outcomes were time to hospital discharge, death, and functional outcomes on the modified Rankin scale [23] (mRS), as determined by trained staff, blind to treatment allocation, through telephone interviews at 90-days of follow-up.

2.3. Statistical analysis

Randomised patients with no record of ASU care were excluded from analyses. Differences in baseline characteristics and processes of care were compared according to ASU admission within and between grouped regions; where there were limited data, standardised differ-ences (SD) were used to describe any imbalances. For outcomes by ASU admission, univariate analyses were reported with Chi-square and Wil-coxon rank-sum tests. To estimate regional variations in the processes of ASU care, logistic regression hierarchical mixed models were used with adjustment for the study design (with fixed effects of head position and crossover period, and random effects of cluster and interaction between cluster and crossover period) and potential baseline confounders related to patient (age, sex, neurological severity [NIHSS score], and patho-logical stroke subtype) and hospital (academic status, size, and location) factors. Data are reported with odds ratios (OR) and 95% confidence intervals (CI), and a standard level of significance ($P < 0.05$) was used. All analyses were performed with SAS Enterprise 7.1 (SAS Institute, Cary, NC), and R Studio 3.6.3 was used for data visualisation.

2.4. Data sharing

Individual participant data used in these analyses can be shared by formal request and protocol from any qualified investigator to the Research Office of The George Institute for Global Health, Australia.

3. Results

A total of 11,086 patients were included in these analyses: their average age was 68.0 (±13.8) years, 39.9% were female, 85.6% had AIS, and 59.7% received ASU care (Supplementary Table S2). Table 1 shows that ASU admission varied from 98.2% in Australia/UK, 84.0% in India/Sri Lanka, 41.3% in South America, and 20.0% in China, with associated regional variations in the distribution of patient characteristics and processes of care. In Australia/UK, care processes were generally balanced, except for ASU patients being less likely to have dysphagia assessment and more likely to receive physiotherapy and occupational therapy, compared to non-ASU patients. In China, ASU patients were older, more often had AIS and greater neurological impairment but fewer pre-morbid health problems, compared to other patients. More-over, ASU patients were more likely to receive reperfusion therapy, antihypertensive treatment, dysphagia screening and formal assess-ment, assisted feeding, and input from an occupational therapist than patients on other wards in China (Fig. 1). Although ASU patients in India/Sri Lanka had less severe neurological impairment and greater pre-morbid health problems, they received more multidisciplinary care than patients on other wards (Fig. 1). Finally, in South America, ASU patients were older, had more history of hypertension (Table 1) and greater use of reperfusion therapy, intensive BP lowering, and physio-therapy, occupational and psychological therapy but less screening or assessment for dysphagia (Fig. 1).

There were significant variations in a range of processes of ASU care, except early use of antiplatelets and psychological therapy, in adjusted analyses with Australia/UK as the reference group (Fig. 2). ASU patients in India/Sri Lanka had the lowest probability of receiving reperfusion therapy (adjusted odds ratio [aOR] 0.27, 95%CI 0.12–0.63) but highest probability of receiving anticoagulation for AF, whereas Chinese ASU patients were more likely to receive early BP lowering (aOR 2.50, 95% CI 1.10–5.68) and less likely to receive oral BP lowering treatment for secondary prevention (aOR 0.49, 95% CI 0.36–0.67). ASU patients in

South America were the least likely to have dysphagia screening (aOR 0.07, 95% CI 0.01–0.37) but together with those in India/Sri Lanka, were more likely to receive feeding assistance (aOR 5.83, 95% CI 2.47–13.74, and aOR 2.41, 95% CI 1.15–5.00, respectively). The probability of receiving allied health care (formal dysphagia assessment, physiotherapy and occupational therapy) was much lower in all regions compared to Australia/UK (Fig. 2).

Time from hospital arrival to discharge was longest in China and shortest in Australia/UK (median 11.0 [IQR 8.0–15.0] days vs. 4.0 [IQR 2.0–10.]; Supplementary Table S3). Within regions, there were no significant differences in time to discharge in Australia/UK and South America by ASU admission, but this was prolonged for patients without ASU care in China and ASU patients in India/Sri Lanka (Supplementary Table S3). Death and functional outcomes also varied across regions (Supplementary Fig. 1): case fatality was greatest in India/Sri Lanka (12.3%) and lowest in China (3.5%) (Supplementary Table S3), whilst death and dependence (mRS scores 3–6) in patients admitted ASU was significantly lower in India/Sri Lanka compared to those without ASU care (Supplementary Table S3).

4. Discussion

In these post-hoc analyses of the large international HeadPoST study, we have shown considerable regional variations in patient characteristics, processes of care, and outcomes according to the receipt of ASU care, where admission was highest in Australia/UK and lowest in China. Except for patients in Australia/UK, those admitted to ASU differed in age, neurological severity and comorbid risk factors, and were generally more likely to receive reperfusion therapy and multidisciplinary team care.

Our study confirms findings elsewhere, that ASU is more accessible and available in high-income countries compared to LMIC [24]. The fragmentation of care and absence of standardised healthy policies also undermine access to ASU care [25]. However, some of this variation may reflect differences in definitions, concepts and approaches to monitoring; for example, use of neuro-intensive care and neurosurgery for stroke patients is high in China [26,27], and interdisciplinary vascular units, which combine stroke with cardiac care, are popular in Brazil [28,29]. As shown in various national registries in China and India [30–32], the patients who are more likely to receive ASU care are those who are old, have AIS, greater neurological severity and more vascular risk factors.

Our finding of lower thrombolysis treatment rates for AIS patients in China and India/Sri Lanka, compared to Australian/UK patients, is consistent with Asian registries [32,33]. Underlying barriers for thrombolysis in Asia include delayed presentation from the onset of symptoms, concerns over harm, inexperience, and high cost of thrombolysis treatment when there is no health insurance coverage [31,34,35]. Although ASU care is defined as multidisciplinary and a Level I guideline recommendation, early rehabilitation is less common in China and India/Sri Lanka, and many other resource settings in LMICs, in part due to limited availability of allied healthcare professionals and ethnic/cultural differences in the understanding of 'passive' and 'active' rehabilitation [11,33,36,37]. Additionally, compared to AU/UK, the recommendation for assessment by a speech pathologist and assisted feeding is explicit stroke management guidelines in China and India [38,39], which also influences their implementation into practice [40]. The consistent high use of antiplatelet therapy across

Table 1
Patient baseline characteristics according to acute stroke unit (ASU) admission by region.

Variable	AU/UK			China (includes Taiwan)			India/Sri Lanka			South America[b]		
	ASU care			ASU care			ASU care			ASU care		
	Yes	No	SD[a]	Yes	No	SD[a]	Yes	No	SD[a]	Yes	No	SD[a]
Number of patients	4669 (98.2)	88 (1.9)		931 (20.0)	3721 (80.0)		647 (84.0)	123 (16.0)		373 (41.3)	534 (58.7)	
Age, yr	72.5 (±13.9)	71.7 (±14.1)	0.05	66.5 (±12.0)	63.9 (±12.0)	0.22	61.3 (±13.1)	60.0 (±14.0)	0.09	70.4 (±13.8)	67.4 (±14.2)	0.21
Female	2122 (45.4)	37 (42.0)	0.07	350 (37.6)	1253 (33.7)	0.08	239 (36.9)	34 (27.6)	0.20	173 (46.4)	218 (40.8)	0.11
Pre-morbid disability[c]	1036 (22.2)	22 (26.5)	0.10	150 (16.1)	807 (21.7)	0.14	112 (17.3)	11 (8.9)	0.25	84 (22.6)	114 (21.4)	0.03
Stroke subtype												
AIS	3767 (81.1)	65 (73.9)	0.17	855 (91.8)	3323 (89.3)	0.11	560 (86.6)	98 (79.7)	0.26	336 (90.1)	463 (86.7)	0.30
ICH	355 (7.6)	9 (10.2)		64 (6.9)	338 (9.1)		83 (12.8)	25 (20.3)		28 (7.5)	28 (5.2)	
Uncertain	522 (11.2)	14 (15.9)		12 (1.3)	59 (1.6)		4 (0.6)	0 (0.0)		9 (2.4)	43 (8.1)	
NIHSS score	4.0 (2.0–10.0)	5.0 (2.0–13.0)	0.13	4.0 (2.0–8.0)	3.0 (2.0–6.0)	0.25	7.0 (4.0–12.0)	12.0 (8.0–18.0)	0.66	6.0 (3.0–11.0)	5.0 (3.0–11.0)	0.02
Severe, score ≥ 15	674 (14.8)	18 (20.9)	0.13	56 (6.0)	142 (3.9)	0.21	106 (16.4)	47 (38.2)	0.55	64 (17.3)	97 (18.2)	0.13
Coronary heart disease	730 (15.8)	9 (10.2)	0.17	114 (12.3)	506 (13.6)	0.04	76 (11.8)	16 (13.0)	0.04	38 (10.3)	50 (9.6)	0.02
Atrial fibrillation	837 (18.3)	23 (26.4)	0.20	66 (7.1)	151 (4.1)	0.13	20 (3.1)	3 (2.4)	0.04	36 (9.8)	41 (7.9)	0.07
Heart failure	250 (5.4)	3 (3.4)	0.10	17 (1.8)	74 (2.0)	0.01	11 (1.7)	1 (0.8)	0.08	20 (5.4)	37 (7.1)	0.07
Diabetes mellitus	986 (21.2)	11 (12.5)	0.23	226 (24.4)	848 (22.8)	0.04	265 (41.0)	41 (33.3)	0.16	112 (30.0)	163 (30.7)	0.01
Prior stroke	895 (19.3)	10 (11.4)	0.22	252 (27.1)	1124 (30.2)	0.07	93 (14.4)	11 (8.9)	0.17	96 (25.8)	125 (23.5)	0.05
Hypertension	2940 (63.3)	47 (53.4)	0.20	610 (65.5)	2438 (65.5)	<0.01	375 (58.0)	62 (50.4)	0.15	264 (71.0)	411 (77.7)	0.15
COPD	269 (5.8)	5 (5.7)	<0.01	19 (2.0)	58 (1.6)	0.04	11 (1.7)	3 (2.4)	0.05	21 (5.8)	20 (3.8)	0.09
Current smoker	633 (13.8)	7 (8.0)	0.19	253 (27.3)	959 (25.8)	0.03	90 (14.0)	22 (17.9)	0.11	57 (15.4)	104 (19.7)	0.11
Dysphagia	1069 (23.2)	30 (34.1)	0.24	102 (11.0)	413 (11.2)	0.01	131 (20.2)	49 (39.8)	0.44	98 (26.3)	151 (28.4)	0.05

Data are N (%), mean (±standard deviation) or median (interquartile range). AF donates atrial fibrillation, AIS acute ischaemic stroke, ASU acute stroke unit, AU Australia, BP blood pressure, COPD chronic obstructive pulmonary disease, ICH intracerebral haemorrhage, mRS modified Rankin scale, NIHSS National Institute of Health Stroke Scale, SD standardised difference, UK United Kingdom.
  [a] Standardised difference = absolute difference in means or proportions divided by standard error; imbalance defined as value greater than 0.20.
  [b] South America including Brazil, Chile and Colombia.
  [c] Defined by scores 2–5 on the mRS.

regions reflects its simplicity, safety and low cost [24,41], whilst the similarly infrequent use of psychological therapy reflects its limited availability and high cost; even in the UK, only one-third of ASUs have access to clinical psychology services [42].

It is well recognised that the length of time stroke patients spend in hospital varies across regions, and tends to be longer in China with some variations by the level of hospitals (teaching/tertiary vs. rural/secondary) [43]. It is important to note that the variations in functional outcomes between patients in China and India does not appear to be explained entirely by the severity of stroke deficit [31], when the benefits of ASU care have been shown to apply equally across grades of neurological severity [44].

Some strengths of our study include the large number of patients with wide ranging characteristics who were managed in contrasting health care settings, where the pragmatic cluster crossover design minimised selection bias and facilitated recruitment and efficient application of the intervention as part of routine care. However, as these data were derived from a clinical trial, only a limited range of management variables were collected; and they lacked standardised definitions across hospitals. Since hospitals were purposefully selected to participate in the trial, these results might be more favourable than compared to other, less research active hospitals in these regions. Finally, our approach to clustering hospitals within regions was rather arbitrary, while post-hoc analyses and multiple testing introduces potential bias and chance findings. Further data on variation in ASU care would help design multinational research studies and strengthen the external validity of these findings [45].

In summary, further analysis of our large international study has shown considerable variation in the characteristics of patients, and the types of care and management they receive under the umbrella of ASU care, within and across different health care systems. The extent to which this is driven by policy, costs, skills, beliefs, and expectations, requires further investigation.

Funding

Author contributions

CSA and MO contributed to the concept and rationale for the study. MO undertook statistical analyses with assistance from LB and XW. MO wrote the first draft of manuscript with input from LS, XW, YZ and CSA. All authors commented upon and approved the final version of the manuscript for publication.

Disclosures

PML reports grants from The George Institute for Global Health and Clínica Alemana de Santiago, during the conduct of the study; and non-financial support from Boehringer Ingelheim, grants and personal fees from Bayer and AstraZeneca, and grants from CONICYT, outside the submitted work. MLH holds a National Health and Medical Research Council of Australia (NHMRC) Career Development Fellowship. VVO reports grants from The George Institute for Global Health and Clínica
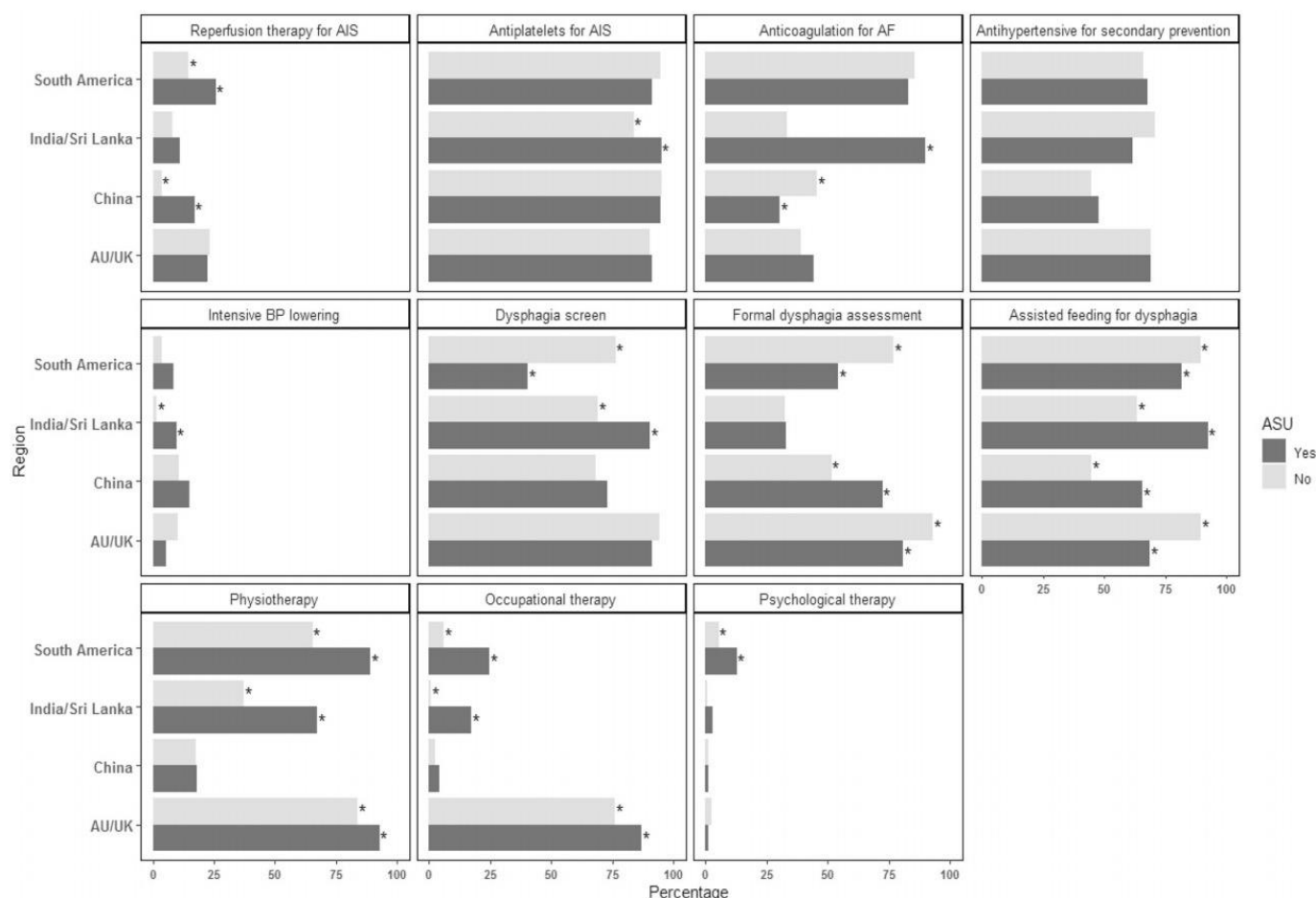
Fig. 1. Process of care according to acute stroke unit (ASU) admission by region.
AF denotes atrial fibrillation, AIS acute ischaemic stroke, ASU acute stroke unit, AU Australia, BP blood pressure, UK United Kingdom.
*Standardised difference (absolute difference between two groups in proportions divided by standard error) greater than 0.20.
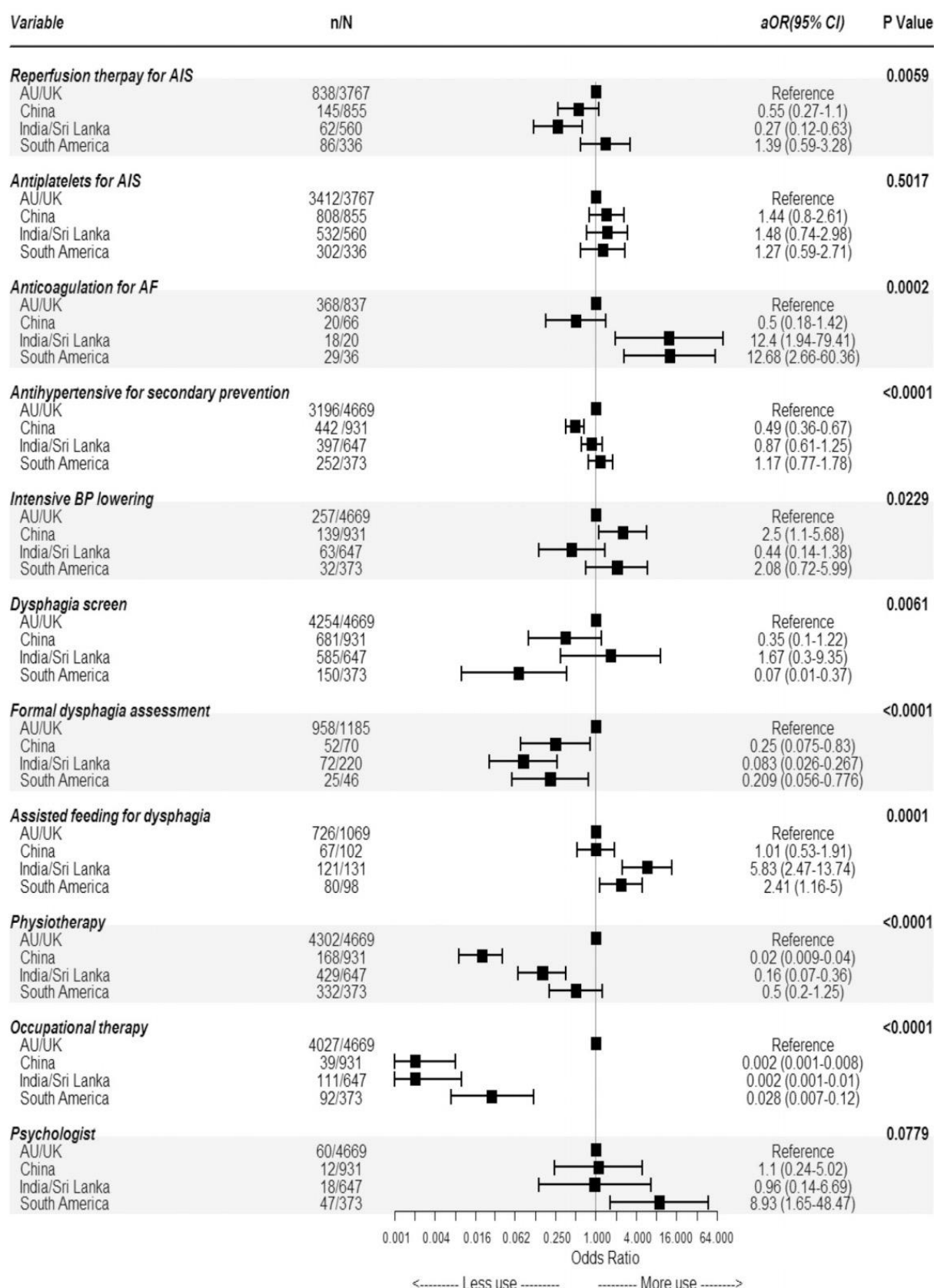
Fig. 2. Variations of acute stroke unit (ASU) process of care by region.

AF denotes atrial fibrillation, AIS acute ischaemic stroke, aOR adjusted odds ratio, ASU acute stroke unit, AU Australia, BP blood pressure, CI confidence interval, UK United Kingdom.

Square indicates point estimate and error bar indicates 95% CI.

Hierarchical mixed models adjusted study design (fixed effects of head position [lying-flat vs. sitting-up] and crossover period, and random effects of cluster and interaction between cluster and crossover period) and baseline variables related to the patients (age, sex, neurological severity [National Institutes of Health Stroke Scale score] and pathological stroke subtype) and hospital (academic status, size and geographical region).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2020.117187.

References

[1] Chinese Society of Neurology CSS, Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2018, Chin. J. Neurol. 51 (2018) 666–682.

[2] Stroke Foundation, (Australian) Clinical Guidelines for Stroke Management, Stroke Foundation, 2019.

[3] A.J.M. Bowen, G. Young, National clinical guideline for stroke prepared by the Intercollegiate Stroke Working Party, Royal College of Physicians, London, 2016.

[4] D Khurana, M.V. Padma, R. Bhatia, S. Kaul, J. Pandian, P.N. Sylaja, S Narayan, Recommendations for the early management of acute ischemic stroke: a consensus statement for healthcare professionals from the indian stroke association, J. Stroke Med. 1 (2018) 79–113.

[5] P. Langhorne, Organised inpatient (stroke unit) care for stroke, Stroke 45 (2014) e14–e15.

[6] L. Candelise, M. Gattinoni, A. Bersano, G. Micieli, R. Sterzi, A. Morabito, Stroke-unit care for acute stroke patients: an observational follow-up study, Lancet (London, England) 369 (2007) 299.

[7] P.M. Venturelli, X. Li, S. Middleton, C. Watkins, P.M. Lavados, V.V. Olavarría, et al., Impact of evidence-based stroke care on patient outcomes: a multilevel analysis of an international study, J. Am. Heart Assoc. 8 (2019).

[8] E.E. Smith, K.A. Hassan, J. Fang, D. Selchen, M.K. Kapral, G. Saposnik, Do all ischemic stroke subtypes benefit from organized inpatient stroke care? Neurology 75 (2010) 456–462.

[9] G. Saposnik, M.K. Kapral, S.B. Coutts, J. Fang, A.M. Demchuk, M.D. Hill, Do all age groups benefit from organized inpatient stroke care? Stroke 40 (2009) 3321–3327.

[10] M.N. Ungerer, P. Ringleb, B. Reuter, C. Stock, F. Ippen, S. Hyrenbach, et al., Stroke admission is associated with better outcome and lower mortality in patients with intracerebral hemorrhage, Eur. J. Neurol. 27 (2020) 825–832.

[11] J.D.W.A. Pandian, M.P. Kate, B. Norrving, G.A. Mensah, S. Davis, et al., Strategies to improve stroke care services in low- and middle-income countries: a systematic review, Neuroepidemiology 49 (2017) 45–61.

[12] P. Langhorne, L. de Villiers, J.D. Pandian, Applicability of stroke-unit care to low-income and middle-income countries, Lancet Neurol. 11 (2012) 341–348.

[13] L.V. Feigin, A.B. Norrving, A.G. Mensah, Global burden of stroke, Circ. Res. 120 (2017) 439–448.

[14] P. Muñoz Venturelli, T. Robinson, P.M. Lavados, V.V. Olavarría, H. Arima, L. Billot, et al., Regional variation in acute stroke care organisation, J. Neurol. Sci. 371 (2016) 126.

[15] S.A. Ayis, B. Coker, A. Bhalla, I. Wellwood, A.G. Rudd, A. Di Carlo, et al., Variations in acute stroke care and the impact of organised care on survival from a European perspective: the European registers of stroke (EROS) investigators, J. Neurol. Neurosurg. Psychiatry 84 (2013) 604–612.

[16] P. Seenan, M. Long, P. Langhorne, Stroke units in their natural habitat: systematic review of observational studies, Stroke 38 (2007) 1886–1892.

[17] C.S. Anderson, H. Arima, P. Lavados, L. Billot, M.L. Hackett, V.V. Olavarría, et al., Cluster-randomized, crossover trial of head positioning in acute stroke, N. Engl. J. Med. 376 (2017) 2437.

[18] J. Mainz, B.R. Krog, B. Bjrnshave, P. Bartels, Nationwide continuous quality improvement using clinical indicators: the Danish national indicator project, Int. J. Qual. Health Care 16 (2004) i45–i50.

[19] A. Ingeman, G. Andersen, H.H. Hundborg, M.L. Svendsen, S.P. Johnsen, Processes of care and medical complications in patients with stroke, Stroke 42 (2011) 167–172.

[20] R.E. Hall, F. Khan, M.T. Bayley, E. Asllani, P. Lindsay, M.D. Hill, et al., Benchmarks for acute stroke care delivery, Int. J. Quality Health Care 25 (2013) 710.

[21] National Institute of Neurological Disorders and Stroke, Stroke Scale, 2020.

[22] World Bank Country and Lending Groups.2020.

[23] P.J. Broderick, P.O. Adeoye, P.J. Elm, Evolution of the modified Rankin scale and its use in future stroke trials, Stroke 48 (2017) 2007–2012.

[24] P. Langhorne, M.J. O'Donnell, S.L. Chin, H. Zhang, D. Xavier, A. Avezum, et al., Practice patterns and outcomes after stroke across countries at different economic levels (INTERSTROKE): an international observational study, Lancet (London, England) 391 (2018) 2019.

[25] O.C. Pandos, A.G. Milton, A. Nagpal, T.J. Kleinig, J. Jannes, S.A. Koblar, et al., Stroke unit legislation—mandating a uniform standard of care? Int. J. Stroke 15 (2020) (174749302090351-NP174749302090357).

[26] W.J. Wang, J.J. Lu, Y.J. Wang, C.X. Wang, Y.L. Wang, K. Hoff, et al., Clinical characteristics, management, and functional outcomes in Chinese patients within the first year after intracerebral hemorrhage: analysis from China national stroke registry, CNS Neurosci. Ther. 18 (2012) 773–780.

[27] Z. Li, X. Ma, X. Zhao, L. Liu, H. Gu, C. Wang, et al., Achievement of guideline-concordant process of care and 1-year outcomes in patients with acute ischemic stroke in secondary and tertiary hospitals: results from China national stroke registry ii, Stroke 48 (2017).

[28] A.R. Massaro, Stroke in Brazil: a South America perspective, Int. J. Stroke 1 (2006) 113–115.

[29] S. Ouriques Martins, C. Sacks, W. Hacke, M. Brainin, Figueiredo F. de Assis, P. Lavados Germain, et al., Priorities to reduce the burden of stroke in Latin American countries, Lancet Neurol. 18 (2019) 674–683.

[30] W.-J. Wang, J.-J. Lu, Y.-J. Wang, C.-X. Wang, Y.-L. Wang, K. Hoff, et al., Clinical characteristics, management, and functional outcomes in chinese patients within the first year after intracerebral hemorrhage: analysis from China National Stroke Registry, CNS Neurosci. Ther. 18 (2012) 773.

[31] P.Z. Li, H.J. Pandian, B.P.N. Sylaja, B.Y. Wang, B.X. Zhao, B.L. Liu, et al., Quality of care for ischemic stroke in China vs India: findings from national clinical registries, Neurology 91 (2018) e1348–e1354.

[32] Z.Y. Wang, N.X. Liao, N.X. Zhao, N.D. Wang, N.C. Wang, N.M. Nguyen-Huynh, et al., Using recombinant tissue plasminogen activator to treat acute ischemic stroke in China: analysis of the results from the Chinese National Stroke Registry (CNSR), Stroke 42 (2011) 1658–1664.

[33] J.D. Pandian, P. Sudhan, Stroke epidemiology and stroke care services in India, J. Stroke 15 (2013) 128.

[34] Y. Wang, B. Hu, Chinese neurologists' perspective on intravenous thrombolysis for acute ischemic stroke, Brain Behav. 8 (2018).

[35] R.A.Y. Khatib, M.A. Berendsen, S. Prabhakaran, M.D. Huffman, Presentation, evaluation, management, and outcomes of acute stroke in low- and middle-income countries: a systematic review and meta-analysis, Neuroepidemiology 51 (2018) 104–112.

[36] T. Asakawa, L. Zong, L. Wang, Y. Xia, H. Namba, Unmet challenges for rehabilitation after stroke in China, Lancet (London, England) 390 (2017) 121.

[37] Y. Wang, Z. Li, Y. Xian, X. Zhao, H. Li, H. Shen, et al., Rationale and design of a cluster-randomized multifaceted intervention trial to improve stroke care quality in China: the golden bridge-acute ischemic stroke, Am. Heart J. 169 (2015) 767.

[38] M.D.J. Lou, B. Hu, Y. Zhang, Z. Li, Z. Tan, et al., 中国脑血管病临床管理指南(节选）——卒中组织化管理, Chin. J. Stroke 14 (2019) 692–699.

[39] India Go, Guidelines for Prevention and Management of Stroke, 2019.

[40] M. Miao, E. Power, R. O'Halloran, Factors affecting speech pathologists' implementation of stroke management guidelines: a thematic analysis, Disabil. Rehabil. 37 (2015) 674–685.

[41] F. Pan, L. Hernandez, A. Ward, Cost-effectiveness of stroke treatments and secondary preventions, Expert. Opin. Pharmacother. 13 (2012) 1751–1760.

[42] N.T. Boakye, R. Scott, A. Parsons, S. Betteridge, M.A. Smith, G. Cluckie, All change: a stroke inpatient service's experience of a new clinical neuropsychology delivery model, BMJ Open Quality 8 (2019).

[43] J.W. Wei, E.L. Heeley, S. Jan, Y. Huang, Q. Huang, J.-G. Wang, et al., Variations and determinants of hospital costs for acute stroke in China (cost of acute stroke in China), PLoS One 5 (2010), e13041.

[44] P. Langhorne, S. Ramachandra, Organised inpatient (stroke unit) care for stroke: network meta-analysis, Cochrane Database of Systematic Reviews (4) (2020), https://doi.org/10.1002/14651858.CD000197.pub4. Art. No.: CD000197.

[45] N.U. Weir, P.A.G. Sandercock, S.C. Lewis, D.F. Signorini, C.P. Warlow, Variations between countries in outcome after stroke in the International Stroke Trial (IST), Stroke 32 (2001) 1370–1377.

Chapter 5 Implement guideline-recommended care in routine practice

Clinical guidelines translate medical research and expert opinions into recommendations to support health professionals' daily practice. However, the delivery and implementation of clinical guidelines in routine practice are challenging. In this Chapter, my work aimed to determine the factors that impeded and facilitated a goal-directed intervention for ICH management in China. The INTERACT3 study aims to evaluate the effectiveness of a protocol based on guideline recommendations, as a novel intervention 'care bundle' package applied to patients with ICH as part of routine care. It involves the rapid correction of physiological parameters and their maintenance during hospitalisation. The process evaluation on INTERACT3 provides insights into how well the intervention was implemented and integrated into 'real-world' practice. The first part of this Chapter is the INTERACT3 process evaluation protocol (Section 5.1) which explicitly illustrates the study design. The second part (Section 5.2) reports the process evaluation findings, including barriers and enablers of implementation of the intervention in the clinical settings in China (Section 5.2).

The main findings from the process evaluation study informed constant training, cases review, good communication with patients, and optimising the procedures and workflow that fits available resources are the facilitators to promote guideline recommendations uptake and implementation.

I co-designed the study, analysed the data, wrote the first draft of the manuscript, coordinated and incorporated co-authors' edits, and prepared and submitted the manuscript for publication (currently under review).

5.1 Understanding implementation of the guideline-recommended care bundle in the INTERACT3 study: process evaluation protocol for an international cluster randomized control trial

Abstract

Background: The third, INTEnsive care bundle with blood pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3) is an ongoing, international, multicentre, stepped wedge cluster, prospective, randomised, open, blinded event assessed trial evaluating the effectiveness of a quality improvement 'care bundle' for the management of patients with acute spontaneous intracerebral haemorrhage (ICH) in low- and middle-income countries (LMICs). An embedded process evaluation is designed to explore the uptake and implementation of the intervention, as well as understand the context and stakeholder perspectives, in interpreting the trial outcomes.

Methods: Mixed methods are used to evaluate implementation outcomes of fidelity, reach, dose, acceptability, appropriateness, adoption and sustainability, as well as relevant contextual factors, affecting the delivery of the care bundle. Semi-structured interviews and non-participant observations will be conducted with the primary implementers (physicians and nurses) and patients/carers to explore how the care bundle was integrated into routine care. Focus group discussions will be conducted with investigators and project operational staff to understand challenges and possible solutions in the organisation of the trial. Data from observational records, surveys, routine monitoring data, field notes and case report forms, will be used to assess contextual factors and adoption of the intervention. Purposive sampling of selected sites according to pre-specified criteria will be used to achieve sample representativeness.

Results: Findings of implementation outcomes, and relevant barriers and facilitators of embeding the care bundle into the routine practice, will be reported after the process evaluation is completed.

Discussion: The process evaluation will provide timely insights necessary to optimize the implementation of the care bundle across diverse settings in LMICs. It will provide an aid to understanding the relationship between care bundle elements and clinical outcomes.

Introduction

Acute spontaneous intracerebral haemorrhage (ICH) is the most severe and least treatable type of stroke, which is a major cause of the global burden of disease[1] in low- and middle-income countries (LMICs).[2,3] Protocols to systematically monitor and control key physiological parameters, such as blood pressure (BP), may improve outcomes in patients with acute ICH.[4] The INTEnsive care bundle with blood pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3) is an international, multicentre, stepped wedge cluster, prospective, randomised, open, blinded event assessed trial aims to determine the effectiveness of a quality improvement 'care bundle', comprising early intensive BP lowering, glycaemic control, treatment of pyrexia, and reversal of anticoagulation, in patients with acute ICH in LMICs. As a complex intervention with multiple components and involving organisational change, there is a need to provide details of how the care bundle is delivered and what local contextual factors impact outcomes.[5-7] Insufficient details of how the complex intervention and its components are implemented may limit the transferability of the generated evidence into other contexts, which is a recognised barrier to the provision of optimal care and treatment.[8,9] Moreover, consideration of how implementation can address knowledge gaps in real-world settings can better inform potential sustainability and scale-up.[10] A process evaluation allows examination of the complexities of implementation strategies, and explanations for discrepancies between expected and observed outcomes, how context influences outcomes, and aids wider implementation.[11-13]

A process evaluation was embedded into INTERACT3 with three principle aims: (i) determine implementation outcomes of care bundle through fidelity (whether the care bundle was delivered as intended), dose (what quantity and quality was delivered), reach (whether all eligible ICH patients received all components), acceptability (whether the care bundle was agreeable and acceptable to participants), appropriateness (participant views on the perceived fit or relevance of the care bundle in their practice settings), and adoption and sustainability (whether the care bundle was integrated and incorporated within routine practice and local policies; (ii) provide information to explain the trial results regarding possible barriers and facilitators of implementation on each of the components of care bundle, their integration into routine practice, and possible context factors related to implement of care bundle; and (iii) determine transferability and sustainability of the care bundle in LMICs through provision of participant perspectives on how and why the care bundle can or cannot be implemented at national level and in other LMICs.

Methods

Study design

INTERACT3 is a cluster stepped-wedge design (Figure 1) that aims to evaluate the effectiveness of a care bundle in 8360 patients at 110 hospitals in ten LMICs (Brazil, Chile [identified as high-income country in 2020], China, India, Mexico, Nigeria, Pakistan, Peru, Sri Lanka and Vietnam) from December 2017 to October 2022. All sites started in a control 'usual care' phase; and are then transferred to the intervention phase where the care bundle protocol is to be implemented as part of the regular standard of care. The stepped-wedge cluster design allows implementation of the care bundle through one direction cluster switch (from control to treatment) at different time points, reduces contamination between control and intervention patients, and allows evaluation of implementing multi-faceted system-wide changes.[14] Details of the study design are described elsewhere.[15]

Figure 1. Stepped-wedge design of INTERACT3

Study sites

Randomisation

	Group 1	Group 2	Group 3
Phase 1	control	control	control
Phase	Goal-directed care bundle	control	control
Phase	Goal-directed care bundle	Goal-directed care bundle	control
Phase	Goal-directed care bundle	Goal-directed care bundle	Goal-directed care bundle

Standard Nursing and Medical Care (Local Guidelines)

Data collection by sites at 0, 1, 7 days

Blinded assessment of outcome at 6 months

142

Theoretical approach

The process evaluation of INTERACT3 is informed by the Medical Research Council (MRC)[11] process evaluation guidance and framework. The framework includes three components: implementation (e.g. fidelity, dose, reach, etc.), mechanisms of impact (e.g. how nurses and physicians perceived the appropriateness of the care bundle), and context (external factors that influenced the delivery of the care bundle). As recommended by the MRC guidance, a logic model was developed to describe how the care bundle and research activities result in short- and long-term outcomes, and to inform data collection of relevant process indicators (Figure 2). Normalization Process Theory (NPT) is used to understand the adoption and integration of the care bundle into routine health care practice.[16] NPT is an implementation science theory that provides a deeper understanding of embedding integration and sustainability of a new model of care or guidelines, and to enhance understandings of the outcome data.[17] The core components of NPT include coherence (meaning and sense-making by participants), cognitive participation (commitment and engagement by participants), collective action (the work participants do to make the trial function) and reflexive monitoring (participants reflect on or appraise the trial).[18]A logic model of contextual determinants and intervention components was developed to describe how the care bundle and research activities result in short- and long-term outcomes, and to inform data collection of relevant process indicators (Figure 2). Considering the different contexts of each country, a separate implementation research logic model for each country is being generated to guide the PE.[19]

Figure 2. Logic model of INTERACT3 process evaluation
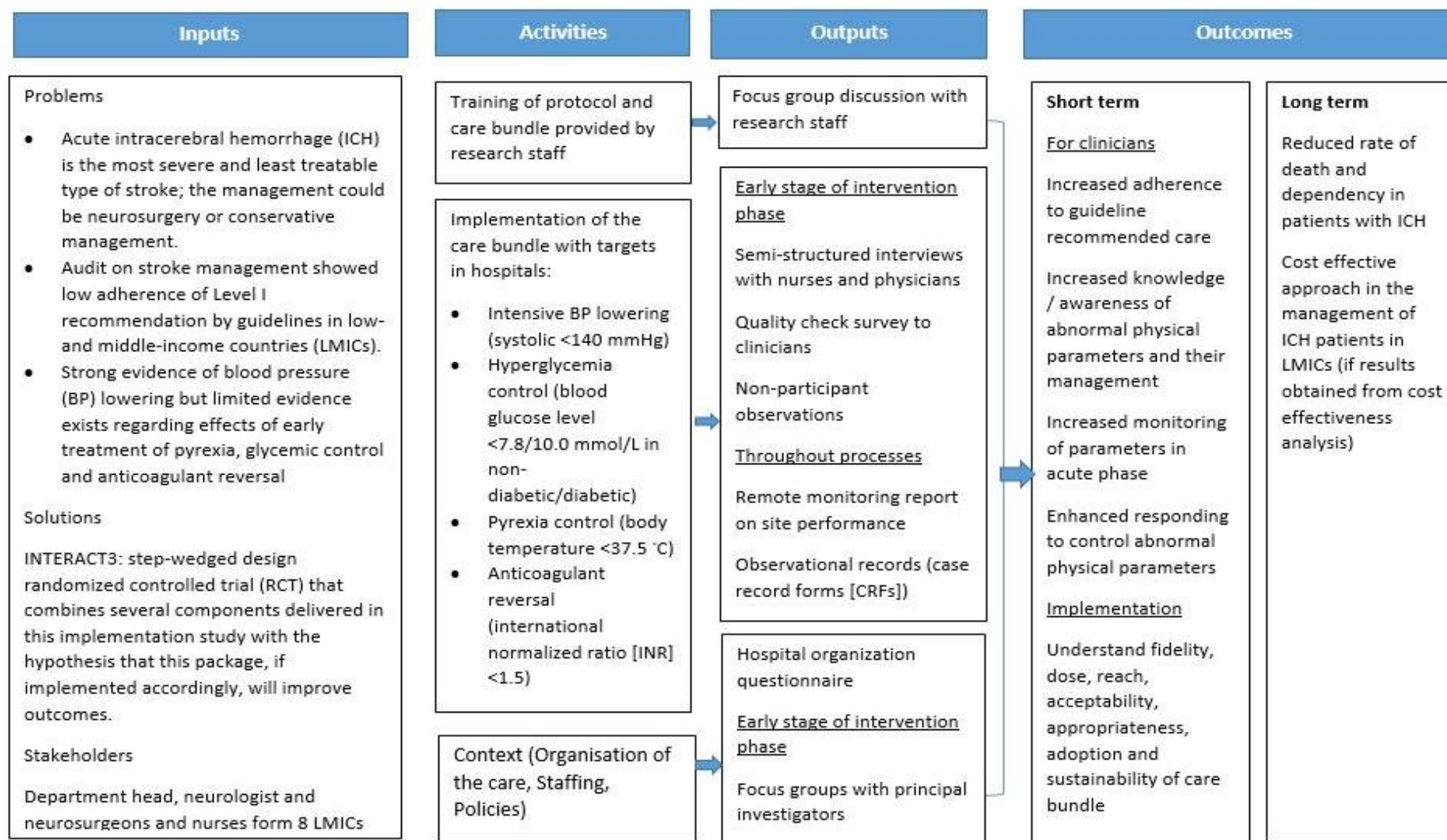
Setting and sampling

The study is being undertaken across different areas of hospitals including, emergency and intensive care departments and neurology and neurosurgery wards, where representative health professionals will be recruited through purposive sampling for qualitative data collection,[20] stratified by country. It is estimated that approximately 28-32 sites will be sampled using criteria of geographical location (across regions), level of the hospital (tertiary vs. secondary), and department (neurosurgical vs. neurology or emergency), and performance (e.g. recruitment speed, cooperation) although the final number will be determined by saturation of themes and available resources. Since most of the sites in INTERACT3 are in China (in the vanguard phase), it is estimated of 12 sites will be sampling in China and 18 sites in the other nine participating countries (average 2 sites per each country).

Participants

Participants for the process evaluation will be key stakeholders involved in implementing the INTERACT3 intervention, including study investigators, ward clinicians and nurses, patients (or carers) who have received the care bundle, and clinical research associates (CRAs) involved in training site staff in delivering the intervention. Only patients who are medically stable will be invited to participate in an interview. For patients who have communication issues, visual impairment or other conditions that might influence the information consent, their carers/family will be invited and informed for the interview. An information sheet and consent form will be sent to potential participants about the process evaluation and inviting them to an interview and/or focus group discussion with a member of the process evaluation team.

Data collection

A parallel mixed method with a convergent design approach is planned for data collection,[21,22] to provide different perspectives, validation and triangulation from multiple sources.[23] Table 1 and 2 outlines the mixed-methods approach being used, including both qualitative methods (semi-structured interviews, focused groups discussion, non-participant observation) and quantitative methods (observational records, surveys and questionnaires) to explore the implementation outcomes. Other data sources include observational records and a hospital organisation questionnaire to provide additional context for the participating sites and inform the sampling frame. The time point for data collection will be at an early phase of

intervention, ideally after at 2-5 patients have been enrolled, in order to obtain feedback from site staff about implementation challenges and allow the operations team to better support sites to optimise implementation of the care bundle. The interview and focus group discussion guides have been piloted with the physicians from the central site prior to the formal conduct of process evaluation.

Table 1. Summary of data collection methods

Item	Data collection method	Participants	Participant number	Time point of data collection
1	Semi-structured interviews	Doctors s and nurses from selected sites who implemented the intervention	3-4 per sampled sites	At early stage of intervention phase (e.g. enrolled 5-10 intervention patients)
2	Semi-structured interviews	Stable patients/carers (if patient is unable to inform consent or participate the interview) from selected sites	2-3 per sampled sites	Patient with condition stable (before discharge) in the intervention group
3	Non-participant observations	Selected sites	Purposive sampling sites (assume 28-32)	Onsite monitoring visit
4	Focus group discussions	PI invited from the sampled sites	Purposive sampling sites (assume 28-32)	Investigator meetings and quality control meeting
5	Focus group discussions	All CRAs from the regional coordinating center	Purposive sampling sites (assume 28-32)	At the early phase of intervention phase
6	Hospital Organisation Questionnaires	PI or Sub-Is	All sites	Collected prior to the recruitment
7	Survey	Doctors and nurses who implemented the intervention	All sites	Intervention phase: quality control meetings (in China) and throughout the intervention phase

	8	Monitoring records, including routine monitoring data, field notes, recruitment logs, and case report forms	N/A	All sites	Throughout the study

Table 2. Implementation outcomes summary

Implementation outcomes	Aims	Measurements	Participants to inform outcomes
Fidelity	Whether the care bundle under investigation in INTERACT3 was delivered as intended	Semi-structured interviews Non-participant observations Surveys Routine monitoring data, field notes and case report forms	Clinicians and patients/carers
Dose	What were the quantity and quality the care bundle was delivered	Semi-structured interviews Surveys Routine monitoring data, field notes and case report forms	Clinicians
Reach	Whether all eligible patients received all components of the care bundle	Semi-structured interviews Non-participant observations Recruitment logs	Clinicians and patients/carers
Acceptability	Whether the care bundle was agreeable and acceptable by participants	Semi-structured interviews Focus group discussions Survey	Clinicians, CRAs and patient/carers
Appropriateness	Participant views on the perceived fit or	Semi-structured	Clinicians

	relevance of the care bundle in their practice settings	interviews Focus group discussions	
Adoption and sustainability	Whether the care bundle was integrated and incorporated into routine practice and local policies	Semi-structured interviews Non-participant observations Focus group discussions Routine monitoring data, field notes and case report forms	Clinicians
Barriers and facilitators	What are the barriers and facilitators for the care bundle implementation in the clinical practice?	Semi-structured interviews Focus group discussions Survey	Clinicians. CRAs and patients/carers

Semi-structured interviews Semi-structured interviews are conducted with both primary implementers (physicians and nurses) and patients/carers from purposively sampled sites at an early phase of the intervention. At each sampled site, 3-4 implementers and 1-2 patients/carers will be invited to interview. For the implementers, the evaluation will explore options on challenges to implement the intervention, facilitating factors, context, progress on implementation, and perspectives of the intervention. For patients/carers, the interview will focus on their perspectives of receiving the goal-directed care bundle, and thoughts and concerns over participating in the study. The timing of the patient interview will be at hospital discharge (face to face) or during their follow up (via telephone) according to the patient's conditions and request. The semi-structured interview guide (see Appendix 1) has been developed based on the objectives of the process evaluation and after pilot testing. Early findings from interviews will be discussed with the project operation team and to allow minor modifications to procedures. Trained interviewers collect the qualitative data under the supervision of an experienced qualitative researcher by face-to-face or teleconference interview.

Focus group discussion

Focus group discussions are conducted to explore implementation barriers and facilitators of the care bundle as part of an international collaboration. Two sets of focus group discussions (see Appendix 2) will be conducted, involving the clinical trial coordinating team and principal investigators (PIs) or sub-principal investigators (Sub-Is) from selected sites. For the former, the group discussion will mainly involve CRAs to evaluate how well the training sessions to site implementers were delivered and received. These training sessions included presentations, hands-on exercises on using the database, onsite monitoring visits, and interactions with implementers. In the other group discussion involving 6-8 PIs/Sub-Is, the aim is to identify barriers at coordinating the site, including roles and responsibilities, leadership, training staff, and providing daily support. These discussions are facilitated by PE team from the International Coordinating Center via teleconference.

Non-participant observation

Non-participant observation aims to understand contextual factors, recruitment processes, and delivery of the care bundle. An observation template (see Appendix 3) was adapted from a process evaluation of another stroke trial[24] to allow the collection of information on implementer behaviour of operational staff alongside an onsite monitoring visit. Trained observers from the Regional Coordinating Center conduct the observation at the purposively sampled site.

The time point of data collection will be at an early phase of the intervention, to obtain feedback from site staff about implementation challenges and allow the operation team to better support sites to optimize implementation of the care bundle. Interviews with site staff will occur after at least 2 patients have been enrolled, and ideally as face-to-face interviews.

Survey

A quality check survey informed by NPT is used to collect perceptions of the intervention and other relevant information from clinicians (see Appendix 4) during the intervention phase. The quality check survey has been piloted at meetings with investigators from 20 sites who had completed at initial vanguard phase in China. All sites outside of China are invited to complete the survey at an early phase of intervention as a part of the PE.

Contextual information of health services will be collected through a Hospital Organization Questionnaire (HOQ) sent to all sites prior to patient recruitment (see Appendix 5). Monitoring records, field notes and case report forms, will be obtained to evaluate whether the intervention has been delivered as intended. These quantitative data will be reviewed

monthly as part of the routine monitoring of patient recruitment, data quality, and adherence to the protocol. Monthly performance reports highlighting recruitment targets and details of protocol adherence and intervention implementation will also be retrieved to assist sampling of the participating sites.

Data management

Data will be saved electronically in a secure password-protected system only accessible to specified members of the research team. Interview transcripts will be uploaded into the software program NVivo V.9 for data analysis.

Analysis and report

Qualitative data from focus groups, semi-structured interviews, non-participant observations and free text of answers to sections of the survey, will be thematically analysed.[25, 265] Inductive findings of the interviews involving the first three sites will be discussed by the process evaluation team to explore emerging themes to guide subsequent interviews. Interim-analysis will be performed after 5-10 interviews to further adapt the interview format and to generate themes for subsequent interviews. The data will be independently double coded by two trained researchers using a coding framework developed through iterative input from investigators to reveal consistency in patterns of data. Descriptive statistics will be undertaken on the quantitative data, with frequencies and percentages used to summarise categorical variables and means or median reported for continuous variables. The analysis will be initially stratified by the country to understand the local context, and to co-design implementation strategies for that context. The integration of quantitative and qualitative data will be done through merging methods and comparison across the numerical and textual data, addressing similar research questions.[22] Reporting of the integrated data will be done through a mixed methods joint display[22, 27] that synthesises data with a visual display and summary meta-inference of the findings.

The qualitative findings will be reported in accordance with the consolidated criteria for reporting qualitative research (COREQ),[28] with the implementation outcomes used to monitor and document fidelity to the project plan.

Discussion

PE is crucial to understanding contextual factors that may impact intervention implementation, especially as to whether the intervention can be adapted and implemented

effectively across other contexts.[13] Implementation outcomes will also be useful to explain what can actually be done in real-world settings and better understand any potential variation proposed treatment effect under investigation in the trial. Contextual factors (COVID-19 impact, current policies, settings resources, etc.) that could influence delivery of the intervention can be identified through interviews, focus group discussions, observations and survey, to enable a better understanding of the results, and the opportunity for future scale-up of the intervention to other LMICs. The INTERACT3 PE aims to inform a broader implementation plan that can be tailored to local contextual factors to improve the quality of care for patients with ICH, the most severe type of stroke. Relevant data pertaining to local stroke protocols and care pathways will provide a useful assessment of health systems for planning further studies that incorporate process evaluations to strengthen the implementation and assessment of complex health service interventions in multicentre clinical trials involving LMICs.

A systematic review of the use of PE in translational research indicates that most involve data collection at the post-intervention phase, but which has limited value in optimising implementation of the trial in complex health systems.[29] In INTERACT3, I have taken the opportunity to conduct a PE at the early phase of the intervention, to assist in the timely identification of barriers and facilitators, and to allow the coordinating team to address any issues that arise and to foster clinician confidence through support and training.[17] Moreover, implementation outcomes will also be useful in explaining what was actually done in real-world settings and allow a better unpacking of any potential variation in the proposed treatment effect under investigation in the trial. The causal relationship between intervention and trial outcome in real-life implementation might be affected by adaptability/unpredictable actors, and of a wide range of influencing elements at geographical and organisational levels (e.g. the impact of the COVID-19 pandemic on workforce capacity and patient engagement with health services).

Strength and weakness

Key strengths of this study include the use of multiple methods and diverse sources of data to obtain a comprehensive picture of the implementation of a goal-directed care bundle. The process evaluation will be conducted across different health care systems in multiple countries to document variable care pathways and health system factors (e.g. workforce, medication availability), and assist in understanding the value of implementation research and

its generalizability. However, there are limitations that include selection and information bias due to voluntary participation in interviews, further influenced by the COVID-19 pandemic restricting on-site visits and need to conduct many interviews by teleconference/video conference. Data provided through remote monitoring and regional coordinating data can go some way in mitigating these issues. In addition, the survey focuses on barriers in embedding care bundle into routine care can result in biased answers without the opportunity for positive feedback, which we aim to amend in future trials. Even flexible time points were offered for patient interviews, this may have introduced recall bias in relation to the patient reported experience of the care bundle.

Timeline of the process evaluation

The process evaluation is undertaken in stages and intended to be completed within 6 months of sites being activated in participating countries. However, due to the emergence of the COVID-19 pandemic from early 2020, the timelines of process evaluation in China have to be extended since patient recruitment, transfer to intervention phase and project staffing resources were affected. The process evaluation in other countries commenced in 2021, but again progress depends on the trial progress and COVID-19impact in each country.

Trial and process evaluation status

Up to May 2020, there are 5986 patients recruited into INTERACT3, including 261 enrolled outside of China. In China, focus group discussions involved 14 investigators from 9 sites, and 24 interviews with doctors/nurses at 9 sites, during January to December 2020. Preliminary analysis of transcripts has been reported to the project team to enhance operation and monitoring in the investigator meetings.

Reflections

The PE in a large multicenter international clinical stroke trial has improved capacity and built qualitative research skills at regional coordinating centres for conducting interviews and observations. However, the involvement of multiple countries in a common protocol requires significant ongoing efforts to address local language and cultural barriers. Although this study has been time and resource intensive, and crucial to the quality control component of the PE, it has also led to a strengthening of international collaborations through shared experience. I recommend the collection of preliminary data prior to proceeding with the delivery of an intervention across countries in order to better understand local health systems and inform focus group discussions. This could be facilitated by co-developing an

implementation logic model and implementation strategies to overcome anticipated local barriers with the local PIs and the trial coordinating team.

Ethics and Dissemination

Ethical approval for this study has been obtained from central and site-specific ethic committees in each country. The information sheet will be provided to the participants prior to individual interviews and focus group discussions. Written consent will be obtained prior to interviews, and verbal consent will also be taken prior to any participation in a focus group discussion.

Conclusions

The process evaluation of the INTERACT3 study will not only provide insights necessary to optimize implementation of the care bundle intervention across diverse settings, but also lead to better understandings of the relationship between elements of the care bundle and outcomes. The embedded PE should advance future conduct of international pragmatic stroke clinical trials to optimise implementing complex interventions within different health system contexts.

References

1.   van Asch C, Luitse M, Rinkel G, van Der Tweel I, Algra A, Klijn C. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: A systematic review and meta-analysis. *The Lancet Neurology*. 2010;9:167-176

2.   Feigin V, Lawes C, Bennett D, Barker-Collo S, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: A systematic review. *Lancet Neurol.* 2009;8:355-369

3.   Krishnamurthi RV, Ikeda T, Feigin VL. Global, regional and country-specific burden of ischaemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage: A systematic analysis of the global burden of disease study 2017. *Neuroepidemiology*. 2020;54:171-179

4.   Parry-Jones AR, Sammut-Powell C, Paroutoglou K, Birleson E, Rowland J, Lee S, et al. An intracerebral hemorrhage care bundle is associated with lower case fatality. *Annals of neurology*. 2019;86:495-503

5.   Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D, et al. Framework for design and evaluation of complex interventions to improve health. *BMJ*. 2000;321:694

6.   Campbell M, Katikireddi SV, Hoffmann T, Armstrong R, Waters E, Craig P. Tidier-PHP: A reporting guideline for population health and policy interventions. *BMJ*. 2018;361

7.   Hoffmann TC, Walker MF. 'Tidier-ing up' the reporting of interventions in stroke research: The importance of knowing what is in the 'black box'. *International Journal of Stroke*. 2015;10:657-658

8.   Scott SD, Rotter T, Hartling L, Chambers T, Bannar-Martin KH. A protocol for a systematic review of the use of process evaluations in knowledge translation research. *Systematic reviews*. 2014;3:149

9.   Wallin L. Knowledge translation and implementation research in nursing. *Int. J. Nurs. Stud.* 2009;46:576-587

10.   Peters DH, Adam T, Alonge O, Agyepong IA, Tran N. Implementation research: What it is and how to do it. *BMJ (Clinical research ed.)*. 2013;347:f6753

11.   Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical research council guidance. *BMJ: British Medical Journal*. 2015;350:h1258

12.   Grant A, Treweek S, Dreischulte T, Foy R, Guthrie B. Process evaluations for cluster-randomised trials of complex interventions: A proposed framework for design and reporting. *Trials*. 2013;14:15

13. Limbani F, Goudge J, Joshi R, Maar MA, Miranda JJ, Oldenburg B, et al. Process evaluation in the field: Global learnings from seven implementation research hypertension projects in low-and middle-income countries. *BMC public health*. 2019;19:953

14. Fayers PM, Jordhoy MS, Kaasa S. Cluster-randomized trials. *Palliat Med*. 2002;16:69-70

15. Song L, Hu X, Ma L, Chen X, Ouyang M, Billot L, et al. Intensive care bundle with blood pressure reduction in acute cerebral hemorrhage trial (INTERACT3): Study protocol for a pragmatic stepped-wedge cluster-randomized controlled trial. *Trials (forthcoming)*. 2021

16. May C, Finch T. Implementing, embedding, and integrating practices: An outline of normalization process theory. *Sociology*. 2009;43:535-554

17. May C, Cummings A, Girling M, Bracher M, Mair F, May C, et al. Using normalization process theory in feasibility studies and process evaluations of complex healthcare interventions: A systematic review. *Implementation Science*. 2018;13: 80

18. Murray E, Treweek S, Pope C, Macfarlane A, Ballini L, Dowrick C, et al. Normalisation process theory: A framework for developing, evaluating and implementing complex interventions. *BMC Medicine*. 2010;8:63

19. Smith JD, Li DH, Rafferty MR. The implementation research logic model: A method for planning, executing, reporting, and synthesizing implementation projects. *Implementation Science*. 2020;15:84

20. Suri H. Purposeful sampling in qualitative research synthesis. *Qualitative Research Journal*. 2011;11:63-75

21. Shorten A, Smith J. Mixed methods research: Expanding the evidence base. *Evid Based Nurs*. 2017;20:74-75

22. Fetters MD, Curry LA, Creswell JW. Achieving integration in mixed methods designs-principles and practices. *Health Serv Res*. 2013;48:2134-2156

23. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical research council guidance. *BMJ*. 2015;350:h1258-h1258

24. Liu H, Lindley R, Alim M, Felix C, Gandhi DBC, Verma SJ, et al. Protocol for process evaluation of a randomised controlled trial of family-led rehabilitation post stroke (ATTEND) in India. *BMJ Open*. 2016;6: e012027

25. Nowell LS, Norris JM, White DE, Moules NJ. Thematic analysis: Striving to meet the trustworthiness criteria. *International Journal of Qualitative Methods*. 2017;16(1)

26. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology*. 2006;3:77-101

27. Johnson RE, Grove AL, Clarke A. Pillar integration process: A joint display technique to integrate data in mixed methods research. *Journal of mixed methods research*. 2019;13:301-320

28.	Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): A 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007;19:349-357

29.	Scott SD, Rotter T, Flynn R, et al. Systematic review of the use of process evaluations in knowledge translation research. *Syst Rev*. 2019;8:266

5.2 Implementation of a goal-directed care bundle for intracerebral haemorrhage management in China: process evaluation in the INTERACT3 trial

Paper submitted to Cerebrovascular Diseases as

Implementation of a goal-directed care bundle for intracerebral haemorrhage management in China: process evaluation in the INTERACT3 trial

Menglu Ouyang, Craig S. Anderson, Lili Song, Stephen Jan, Lingli Sun, Guojuan Cheng, Honglin Chu, Xin Hu, Lu Ma, Xiaoying Chen, Chao You, Hueiming Liu

Refer to the following 25 pages

∗ ∗ ∗

Abstract

Background: The third INTEnsive care bundle with blood pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3) is an ongoing international, multicentre, stepped-wedge, cluster randomised trial to determine the effectiveness of a goal-directed care bundle (early intensive blood pressure [BP] lowering, glycaemic control, treatment of pyrexia, and reversal of anticoagulation), as compared to standard of care, on patient-centred outcomes after acute intracerebral haemorrhage (ICH). An embedded process evaluation aims to identify factors related to the uptake and implementation of the intervention. Herein, we present the results of the process evaluation for hospital sites in China.

Methods/design: A mixed methods approach, including surveys, focused group staff discussions and interviews with implementers, routine monitoring and recruitment logs were used to collect data across purposively sampled hospitals. Medical Research Council guidance and Normalisation Process Theory were used as theoretical frameworks for design, data analysis and synthesis.

Results: Twenty quantitative surveys were completed with implementers, and 26 interviews and two focus group discussions, were conducted during 2019-2020. The care bundle was generally delivered as planned and acceptable by doctors and nurses, but difficulties were reported in achieving the protocol-defined target levels of BP and glycaemic control. Resistance to implementing the care bundle occurred for patients perceived to be at high risk of adverse effects. Common organisational contextual factors that impeded implementation included delayed processes and limited medication supply, while established background care procedures, expertise and capacity influenced its integration into routine practice. Areas to facilitate implementation included optimising workflow within available resources, having a dedicated team, and recognising the potential benefits of the intervention.

Conclusions: Varied established care protocols across sites, different levels of background expertise, and lack of staff capacity impeded the integration of goal-directed care bundle into routine practice for ICH patients in China. Ready identification, and efforts to address, these barriers could facilitate uptake of future guideline-recommended interventions for the management of patients with ICH.

Trial registration: ClinicalTrials.gov NCT03209258, registered on 1 July 2017. Chinese Trial Registry ChiCTR-IOC-17011787, registered on 28 June 2017.

Background

Spontaneous intracerebral haemorrhage (ICH) is the most severe and least treatable type of stroke, generally related to rupture of blood vessels from elevated blood pressure (BP), with approximately two-thirds of patients either dying or left disabled.[1] Several physiological parameters, such as elevated BP, hyperglycaemia and pyrexia, predict poor outcomes after ICH,[2-4] while the rapid reversal of systematic anticoagulation in those with associated use of anticoagulants may reduce haematoma enlargement and improve recovery.[5] A before-and-after study showed that the implementation of a care bundle, involving rapid anticoagulant reversal, intensive BP lowering and access to criticial care with immediate neurosurgical referral, significantly decreased 30-day case fatality after ICH.[6]

The third INTEnsive care bundle with blood pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3) is an ongoing international, multicentre, stepped wedge, cluster randomised clinical trial that aims to determine the effectiveness of a multifaceted interventional package of care in 8000+ patients with acute ICH and a broad range of characteristics who are managed at 110 hospitals across eight LMICs (China, India, Nigeria, Pakistan, Peru, Sri Lanka and Vietnam), and one high-income country (Chile) during 2017-2022. The intervention is a goal-directed care bundle that involves the rapid correction (<1 hour) of several variables as soon as an abnormality is recognised, and to maintain this control in patients over seven days (or prior to hospital discharge or death, if these occur earlier). These variables include (i) intensive BP lowering to the systolic target of <140 mmHg; (ii) control of elevated blood glucose level (BGL) to targets of 6.1-7.8 and 7.8-10.0 mmol/L in those without and with diabetes mellitus, respectively; (iii) treatment of pyrexia to a target body temperature ≤37.5 °C; and (iv) reversal of anticoagulation to target international normalised ratio (INR) of <1.5 using vitamin K and prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP).

The care bundle in INTERACT3 is a complex intervention that contains multiple interacting components requiring changes in behaviour for delivering or receiving the intervention, within existing structures and processes of the local health care systems.[7] As implementation of a complex intervention is often challenging, it is critical to examine the experiences of healthcare professionals to understand how the intervention was interpreted, perceived and implemented.[8] This informs further implementation strategies to ensure broader fidelity and consistency of use. A process evaluation (PE) examines the implementation of such complex

interventions with regards to adoption, implementation barriers, facilitators, and contextual factors that influence outcomes. A lack of appreciation of the contextual factors in particular, may limit the transferability of evidence-based practice by policymakers and practitioners into routine practice, and challenge intervention scale-up and sustainability.[9] Several constraints on healthcare services can impede the delivery of care in LIMCs. These include a shortage and poor distribution of qualified staff, low pay and lack of motivation, weak technical guidance, program management and supervision, limited medical supplies, and inadequate drug policies and supply systems.[10] Previous studies have focused on barriers of evidence-based care implementation in acute ischaemic stroke, for example, in the uptake of thrombolysis treatment, but there are limited studies on the management of acute ICH, especially in LMICs.[11]

INTERACT3 was initiated as a vanguard phase in 28 hospitals in China in 2017, before expansion to 110 hospitals in late 2019. An embedded PE in the vanguard phase, aims to explore the feasibility and identify any implementation barriers that can inform subsequent implementation in other sites. Herein, we outline how the goal-directed care bundle was implemented and explore clinician perspectives and contextual conditions that influence the quality of the implementation in China.

Methods

Theoretical framework

The PE was informed by the Medical Research Council (MRC)[12] guidance and framework, with three components: implementation, mechanisms of impact and context (The domains to evaluate for implementation include fidelity, dose, reach, acceptability, appropriateness, adoption and sustainability (definitions are in Figure 1). Mechanisms of impact are explored by how the clinicians perceived the appropriateness of the care bundle. The external factors that influenced the delivery of the care bundle were investigated to understand the context (Supplemental Figure S1).

Normalisation process theory (NPT)[13] was used to understand the adoption and integration of the care bundle into routine health care practice. Core components of NPT include coherence (meaning and sense-making by participants), cognitive participation (commitment and engagement by participants), collective action (the work participants do to make trial function) and reflexive monitoring (participants reflect on or appraise the trial).[13] NPT is a valuable theory to aid a comprehensive understanding of implementation as a dynamic

process, to identify and explain the fundamental mechanisms that promote or impede implementation, and the embedding of a complex intervention into everyday practice .[13, 14] The theoretical approach to the PE design is displayed in Figure 1.

Figure 1. Theoretical approach of the INTERACT3 Process Evaluation
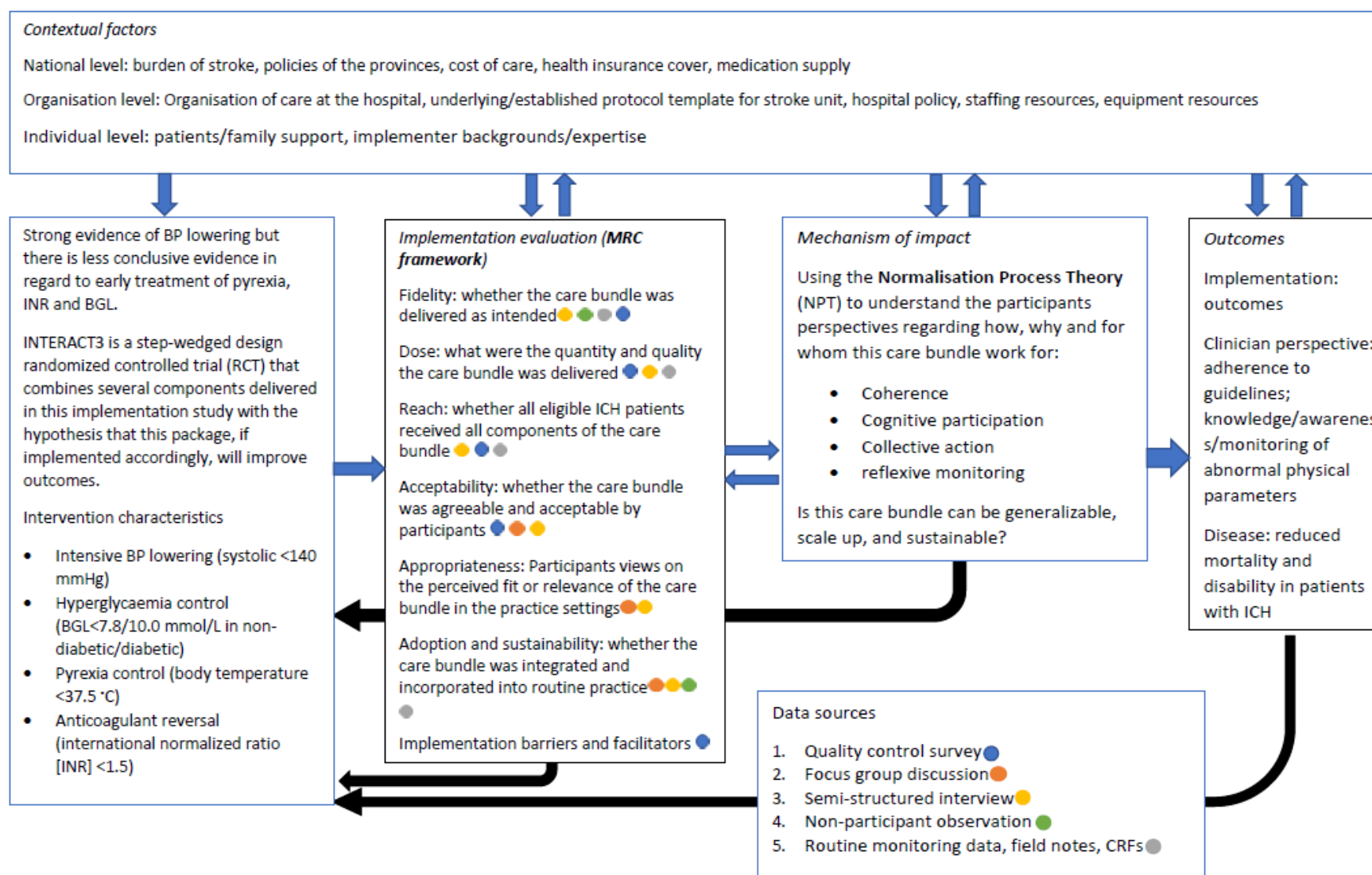
Sample, participant and setting

We used purposive sampling to select representative sites for semi-structured interviews.[15] Sampling was based upon pre-specified criteria to achieve representativeness and stratified by: geographical location; hospital level (tertiary vs. secondary); department (neurosurgery vs. neurology or emergency); rate of recruitment (actual enrolment number divided by expected weekly enrolment) using routine monitoring chart and data entry quality assessed according to case report forms (CRFs) completion (see Supplementary Table S1). We invited at least three clinicians at each sampled site to obtain information from the perspective of different roles, including a co-investigator (a member of the research team designated and supervised by the principal investigator [PI] to perform critical study-related processes and make important decisions), study coordinator, attending physicians, and research nurses that were designated by the department head. Twelve sampled sites were invited to participate during the early intervention phase, and nine sites agreed to participate, which included 26 doctors, nurses, and other ward staff. All the participating sites received training on the INTERACT3 protocol provided by the central coordinating centre via onsite visits and ongoing remote monitoring. The nominated 'local champion' from the designated research team at each site is responsible to champion the study at the hospital, and to provide refresher training for existing and new staff on the intervention at regular intervals.

Data sources and collection

A mixed-methods approach with convergent design[16] was used to collect data, with data sources and flow work presented in Supplemental Figure S2.

Quantitative data

An initial quality control survey to understand the concepts and project operational barriers to implementing the intervention, and inform the approach to interviews, was conducted among 20 clinicians from seven hospitals transferred into the intervention phase at a regional investigator meeting in June 2019. A hospital organisation questionnaire (HOQ) was used at the beginning of the trial to capture different health system contexts, such as the characteristics of hospitals (region, level, participating department). The rate of recruitment speed obtained from monitoring logs and data entry quality assessed from CRFs were used to inform sampling for the interviews.

Qualitative data

A focus group discussion was conducted with site Principal Investigators (PIs) who attended a national investigator meeting facilitated by PE research team, prior to the in-depth interviews in January 2020. There was discussion over role responsibilities and assignment, their experience in trial conduction, how the intervention was being implemented, and factors that might impede or facilitate the intervention components. Another focus group was conducted with project clinical research associates (CRAs) when all the sites transferred from control to intervention phases to gain further perceptions of the implementation challenges from an operational perspective. Semi-structured interviews were conducted by two trained researchers (MO, LLS) between January and October 2020 and audio recordings were collected for analysis. Interviewees were crucial stakeholders involved in the implementation of intervention, and included study coordinators, ward clinicians and nurses. Interview guide questions were informed by the NPT domains to enable an in-depth understanding of the integration of the care bundle into routine practice. During the process of conducting the interviews, questions were iteratively modified to allow the exploration of emergent themes identified by the research team. All interviews were conducted in Chinese, with interviews undertaken in person at the first three hospitals, while the rest were conducted online due to restricted health services access during the COVID-19 pandemic.

Ethical approval and participants consent

De-identification data were collected through the processes, with ethical approval obtained by the participating sites. The information sheet and consent form were sent to the participants prior to the interview, and verbal consent was obtained prior to the focus group discussions.

Data analysis and report

Quantitative data were analysed using descriptive statistics and reported in numbers and percentages. Qualitative data were analysed independently by two trained coders to ensure the credibility of the findings. Transcripts in Chinese were coded, and the themes and illustrative quotes were translated into English by the two coders (MO and LLS) who are bilingual (native speakers of Chinese and proficient with English). The two coders have intensive experience in academic research and clinical background, with a higher degree of education (master/doctoral degree). An initial thematic codebook was developed from the first four sites (12 interviews) by two independent coders to examine the key variations of context, intervention acceptability, adoption, and fidelity, at each site. Thematic saturation was reached after interviews were completed from nine sites (26 interviews), with no new

codes being created and agreement reached between two coders. Preliminary findings were discussed with the research team over interpretation and the need to explore the significance of the results. Nvivo 11.0 was used to manage the data and COREQ checklist[17] was used to report the qualitative findings (Appendix 1).

The merging method was used to integrate both quantitative and qualitative datasets for analysis and comparison across the numerical and textual data that were derived from similar questions.[16] Joint display technique, a helpful approach to visualise data integration to enhance insights into the findings in mixed methods research,[18] was used to display integrated findings through a merging of percentages obtained from the quality survey and themes from qualitative data.

Results

Characteristics of participants

There were 20 participants from seven hospitals who completed the initial qualitative survey, and 14 PIs/sub-PIs from eight hospitals who underwent focus group discussions after their site had transferred over to the intervention phase. Semi-structured in-depth interviews were conducted in eight tertiary and one secondary hospital (4, 3, and 1 each, in Eastern, Western, and Northern and Middle regions of China, respectively). Interviews occurred with 26 implementers, who were mostly (76%) doctors from Neurosurgery Departments with different professional grades. Among the sampled hospitals, four had a low recruitment rate, while six had moderate to good data entry quality (Supplemental Table S1).

Fidelity, reach, dose, acceptability and appropriateness, adoption and sustainability

Table 1 summarises the implementation outcomes of the care bundle. Participants were in agreement over the perceived importance of the care bundle for ICH management, and they reported that it had been delivered as planned. However, many expressed a reluctance to provide the care bundle to patients where there were concerns over the potential to cause harm from hypotension or hypoglycaemia. Clinicians concerns of compensatory physiological responses (e.g. stress hyperglycaemia), and underlying similar established care procedures but with a broader range of target values also compromised delivery of care bundle, especially over glycaemic control. Participants also reported difficulties in reaching and maintaining the protocol-defined target levels of BP and blood glucose level (BGL). Moreover, the low recruitment rate was due to a shortage of staff and beds, particularly in

secondary or rural hospitals. This factor was highlighted by participants as relevant to the potential scale out of the intervention at a national level.

Table 1. Implementation outcomes of the guideline-recommended care bundle in INTEREACT3

Implementation outcomes	Definition	Coded theme	Quote
Fidelity	Whether the care bundle under investigation in INTERACT3 was delivered as intended	• The care bundle was delivered as planned • Concerns of delivery in high-risk patients • Culture beliefs and underlying established management impede the delivery	*"Patients with comorbidity of heart disease felt uncomfortable and agitated after lowering blood pressure to 140; then we feared to control"* (No.4, neurosurgeon) *"We did not take specific control of pyrexia according to the protocol because the procedure is similar to the routine care and the doctors thought it is not meaningful to do so…"* (No.3, neurologist)
Dose	What were the quantity and quality of the care bundle was delivered	• Adherence to BP/BGL/body temperature monitoring as planed • Hard to achieve and maintain the target level for BP and BGL	*"We tried (to achieve<140mmHg)but half of the patients can achieve the target level, but some patients had very high blood pressure and became aggressive in the acute phase, make it difficult to reduce the blood pressure to target level within one hour"* (No.5, neurosurgeon) *"The glucose level control also involves the patient's diet intake, so sometimes it is not easy to control…there is a delay in the insulin adjustment after food intake and after adjusted a higher dose of insulin the level decreased…then introduce a big fluctuation "* (No.3, neurologist)
Reach	Whether all eligible ICH patients received all components of the care bundle	• Care bundle was delivered for all recruited patients except self-discharged patients due to economic burden	*"Some very severe patients self-discharged because the economic burden and stopped the treatment"* (No.9, neurosurgeon) *"Some patients would like to be recruited but not enrolled because considered lack of economic support for the medications for BP lowering…"* (No.5, nurse)

		• Insufficient consecutive recruitment due to contextual factors such asshort of medications and resources	*"Not all the eligible patients were included in the study, some were related to an unwillingness to participate from the family, others might because the doctors were too busy and missed to recruit…" (No.5, neurosurgeon)*
Acceptability and appropriateness	Whether the care bundle was acceptable and perceived fit in practice settings	• The implementers accepted the care bundle • Implementers perceived the benefit of care bundle to ICH management	*"The trial has clinical practice guidance instruction because it is a bundle concentrates on the key treatments for the ICH acute phase and have better effects than single treatment…This kind of treatment strategy and standard quality certainly meaningful for clinical practice" (No.3, neurologist)* *"Because the care bundle is taken consider for the patients, they usually not reject to (receive) it. We have successfully implemented this intervention…" (No.9, nurse)*
Adoption and sustainability	Whether the care bundle was integrated and incorporated into routine practice and local policies	• Recognised the importance of adopted into routine care and widely used • Factors such as resources, knowledge and admit of the benefits on the care bundle need to be solved to ensure the sustainability	*"I think it is not easy to implement the care bundle for the hospitals at our level (tertiary hospital). The care bundle needs sufficient staffing…BP intervention is fine since we have electric monitors but BGL monitoring will be a heavy workload" (No.6, neurosurgeon)* *"The cooperation between multiple departments and medication supply might have issues for generalizability…" (No.2, neurosurgeon)*

Footnote: BGL denotes blood glucose level, BP blood pressure, ICH intracerebral haemorrhage;

Data sources are from semi-structured interview.

From the survey, 45% and 40% of participants reported that BP and BGL control, respectively, were challenging to implement, but only 20% stated difficulties with the treatment of pyrexia. Regarding anticoagulation reversal, 45% of the participants claimed that very few patients were eligible for this intervention. From interviews and focus group discussions, BGL control was highlighted as the most complex intervention to implement, where there were concerns about treating simple stress hyperglycaemia, the need for frequent finger prick or venepuncture tests, difficulties in regulating BGL in fasting patients, and increased out-of-pocket payments with greater monitoring. Conversely, interventions for BP lowering and treatment of pyrexia were simpler to implement as it was part of routine management outlined in national guidelines. Given the infrequent use, few reflections were expressed over barriers to pyrexia treatment and reversal of anticoagulation in the context of the small number of patients already taking anticoagulants prior to admission or being admitted with pyrexia.

Implementation barriers

From the in-depth interviews with doctors and nurses, further insightful barriers of each component of care bundle implementation were identified at implementer, patient and organisational levels (Table 2). From the clinician's level, lack of guidelines for specific conditions (e.g. more severe patients or for those with comorbidities) and concerns over harms from adverse events were the most frequently cited factors that challenged them in care bundle delivery. Patient level included cardiac or renal disease comorbidities, and lack of cooperation from the patient/families related to non-adherence of diet advice and complaints about increased frequency of BGL testing, impacted upon clinician's decision to deliver the care bundle. Contextual factors at an organisational level, such as lack of staff and equipment, underlying similar established procedures, shortage of medication supply, and local policy on restrictions related to health insurance, were reported as common barriers to the delivery of intervention components.

Table 2. Barriers and facilitators of the intervention implementation by each component

Components	Barriers			Facilitators & Suggested solutions
	Implementer level	**Patient level**	**Organisational level**	
Intensive BP lowering	• Concerns of adverse effects of ischemia or hypotension, especially in elder, heart disease or surgery patients • New or changed staffs lack communication or training to deliver intensive care • No specific guidelines for patients under surgery when BP lowering is not the priority • Similar procedure of hypertension control but not intensive	• Difficult to achieve target in patients with severe, agitated, very high BP, renal hypertension, with pain, incontinence or medication-resistant • Patients did not accept the intervention due to increased medication expenses for hypertensive agents	• Local policy or restriction of medication supply • Difficult to achieve the target level within 1 hour due to assessment delay, pre-operation preparation	• Constant training, especially for new or rotated clinicians • Delegated nurse to ensure the process • Case review to summarize the reasons of BP elevation and find out a solution • Start BP lowering at the ED with a smooth pathway • Deep communication between multiple departments • Standardized BP procedure leading by residency doctors • Ensure medication supply and appropriate administration

| Blood sugar control | • Concerns of hypoglycaemia, especially in non-diabetic
• No specific guidelines for random BGL, e.g. after dinner and stressed hyperglycaemia
• High frequent monitoring-not feasible outside NICU
• BGL fluctuation: difficult to adjust insulin to achieve narrow target range | • Challenging to achieve target BGL in patients with comorbidities
• Not adhere to diet advice
• Complain and in-cooperation because high frequent finger point tests | • Lack of insulin pump and staff to do monitoring
• Hospital policy restricted frequently monitoring-related to expense for BGL check
• Underlying established protocol | • Communication with patients/family of the frequent BGL testing
• Constant training
• Use additional pumps to control glucose and consider the nasogastric nutrition
• Consider patients disabled side to do BGL check can reduce pain
• Consultation with endocrine expertise of insulin treatment case by case
• Non-diabetic patients should set routine prescriptions of glucose level monitoring to assure adequate monitoring |
| Body temperature control | • Similar procedures and monitoring in routine care
• Not strict control if temperature not over 38.5 from routine care | • Difficult to achieve the target in patients with pneumonia
• Small number of patients with pyrexia after admission | N/A | N/A |

| Anticoagulant reversal | • Limited supply of fresh blood plasmin | • Small number of patients using anticoagulation
• Patients very severe and family did not accept treatment | • Restriction policy of using fresh plasmin | N/A |

Footnote: BP denotes blood pressure, BGL blood glucose level, ED emergency department, N/A not applicable, NICU neuro-intensive care unit; data sources are from semi-structured interviews and focus group discussions.

Since achieving the effective BP and BGL control were reported as the most challenging aspects of the protocol in both the survey and interviews, the findings were integrated as a joint display. From the survey, nearly half of respondents reported medication limitation as the main barrier to reaching the BP control target; this was related to hospital policy and insufficient supply (probed interview, Supplemental Figure S3). For BGL control, barriers in correcting abnormal glycaemia levels were reported by 50% of the survey respondents, as the target BGL range was narrow, glucose solutions were often used. Moreover, as many neurosurgeons lacked expertise in internal medicine, they found it difficult to control BGL in patients with high levels of hyperglycaemia (Supplemental Figure S4).

Implementation facilitators and suggested solutions

Constant training during regular trial operational meetings, especially for new or rotated clinicians, was the main facilitator reported. Other facilitators/solutions included case reviews, specific procedures for timely initiation of the intervention, and good communication with patients (Table 2). Interviewees also identified solutions that could improve implementation: such as designating particular personnel for ensuring quality processes for BP lowering, early initiation of the intervention in the ED through effective communication and collaboration, obtaining additional insulin pumps to allow effective BGL control, and establishing routine prescriptions for BGL monitoring, particularly in non-diabetic patients with elevated BGL.

Preliminary findings from this section were reported to the project operations team and discussed in trial meetings involving lead investigators to address the barriers in June 2020. Additional training was provided to staff at participating sites to enhance the delivery of the intervention and improve implementation quality. After these meetings and training, there were improvements in BP reduction and glycaemic control: the average time to achieve the BP target was reduced by 0.5 hours (comparison provided in Supplemental Figure S5), and the rate achieving the BSL target was increased by 9% in sites in the intervention phase (38% in May 2020 vs. 47% in July 2020).

Mechanism of embedding the care bundle into routine practice

The themes to understand the mechanisms of normalising the care bundle into routine practice were coded according to the domains of NPT in Table 3 and Supplemental Table S2. These themes include an appreciation of the interventions as standardised guidelines (coherence), 'champions' in the view of constraints (cognitive participation), streamlining the

workflow across departments (collective action), recognition of the care bundle advantages and case reviews to improve implementation quality (reflexive monitoring). From the reflexive monitoring, nurses were more focused and motivated to make efforts to reach the intervention target by reviewing details of each individual case, self-directed group discussions and consulting specialist; whereas doctors who considered patients with severe ICH to be more prone to adverse effects or those with comorbidities showed resistance to following the guideline-directed care bundle. Neurosurgeons recognised improvement in regular monitoring and increased awareness of abnormal physical parameters while ED doctors who have already established similar practice and knowledge reported non-adherence to the care bundle.

Table 3. Mechanism of embedding the care bundle into routine care by NPT domains

NPT domains and theme	Explanation	Quote
Coherence: established procedures and knowledge challenging the integration	• Implementers appreciated the care bundle standardised usual care, and perceived a benefit of how participating in the trial provided them with a chance to learn and enhance their knowledge on the primary care of ICH patients.	*"I knew doctors from secondary hospitals did not apply standard ICH management. I think this intervention is very standardised management for ICH, and that participating in this trial can learn more on how to monitor and manage hypertension-related ICH…especially for guidance in secondary hospitals." (No.7, neurosurgeon)*
	• Resistance in embedding the care bundle into routine practice mainly due to established procedures and different levels of background expertise that did not agree with the suggested cut-off parameters of the care bundle	*"Some of the doctors did not adhere intervention protocol because they thought it is not meaningful. Actually, everyone controls body temperature in the routine care, but we usually treat pyrexia when body temperature over 38ºC or 39ºC, so we are not following your standard (37.5ºC)" (No.3, neurologist)* *"The BGL ranges for both diabetic and non-diabetic patients have no special meanings to our Emergency Department doctors. To control blood glucose between 7-10 mmol/L is similar to our usual care and we did not intervene too much if it is between 6~12 mmol/L." (No.8, ED doctor)*
Cognitive participation: responsibility, capacity and incentives	• Participation of the site staff was reportedly reliant on whether there were designated 'champions' with clear responsibility and supervision from the PI. This was in the	*"Without the supervision of the director and me, everyone is not particularly interested (to participate). Because they are uncertain as to whether it can be done or not, and the workload is increasing. This may be a problem in every research centre" (No.5, neurosurgeon)*

	context of the trial imposing greater workload, thereby affecting site staff's commitment to take part in the research.	
	• Incentives (such as opportunities to have academic outputs) could be a motivation to promote participation:	*"If the PI appointed delegated staffs to be responsible for the implementation and they have a clear division of work with individual responsibility, then the implementation is better in this site. Incentives and opportunity to have academic outputs also can be motivations for the doctors" (project research coordinator)*
Collective action: Optimising workflow at the organisational level with a dedicated team	• It was important to adapt and streamline workflows through standardised procedures while ensuring that there was a specific group of clinicians to support the implementation of the intervention in routine care.	*"Because the ED is very busy, and it is difficult to rely on them to operate. Therefore, we have a nurse team to the ED and ensure the diagnosis immediately after CT, then inform the responsible doctors for enrolment and activate intervention…We are cooperating well with ED and familiar with each other, so the intervention implementation could be relatively better." (No.3, nurse)*
		"The patients admitted ED had done most investigations in ED so that no delays or disrupts in the ward then the intervention can initiate immediately. This is the improvement we did for the procedures after transfer to intervention" (No. 7, neurosurgeon)
	• Involving multiple departments was seen as difficult to coordinate from an administrative perspective	*"Regarding the quality of implementation, because the neurosurgical department is paralleled to our department (neurology), I cannot supervise them and ensure they have achieved the target level timely" (No.4, neurologist)*
Reflexive monitoring:	• Recognition of improvement in regular monitoring and	*"Probably the internal medicine doctors might be more aware of it (BGL) since we (neurosurgeons) more focused on surgeries…but I found the doctors*

176

acknowledged benefits and reflections on contextual factors for broad implementation	increased awareness of abnormal physical parameters, especially among the neurosurgeons.	*in our department have more awareness of the BGL than before also in the nurses. Usually, the internal medicine doctors were more likely to reach the target ranges while neurosurgeons more focus on extreme variabilities and pay less awareness of the range." (No.1, neurosurgeon)*
	• Organising case reviews to solve delayed processes and difficulties to reach the target levels of parameters within the timeframe, consultation with experts, and efficient communication.	*"To find the underlying reason of increased BP before reducing BP helps. We constantly started learning from the intervention phase and reviewing cases of different patients to analyse and practice. For blood glucose control, we usually collaborate with the Endocrine Department…" (No.6, nurse)*
	• Elements relating to settings, staffing resources, equipment, medication supply, patient insurance and hospital policy are important for integration and sustainability of the care bundle.	*"I don't think it will be an issue to generalise this care bundle into the national level, but I'm not sure in other general wards. Nurses will have increased workload, and if the ward has adequate monitoring equipment and the hospital has the policy for performance-related payment as a commission, then that should not be an issue…" (No.2, nurse)*

Footnote: BGL denotes blood glucose level, BP blood pressure, ED emergency department, ICH intracerebral haemorrhage, PI principal investigator; data sources are from semi-structured interview.

Discussion

The guideline-directed complex intervention of INTERACT3 has been found to be feasible and acceptable in clinical practice. However, the target parameter levels of the intervention were difficult to achieve due to the critical illness and pathophysiology nature of ICH in China and severe comorbid conditions, and contextual factors at an organisational level such as delayed processes, limited supply of medication and lack of staff capacity. The embedding of care bundle into routine care required the clinicians to optimise workflow at the organisational level with a dedicated team, accept the care bundle and reflect on contextual factors for broad implementation. Strategies such as generating a streamlined workflow within available resources, having a dedicated team, and processes that fed back the benefits of the care bundle, assisted the implementation of the care bundle in routine clinical practice.

Our findings are consistent with other studies that have identified common barriers to implementing guideline recommendations, such as lack of time, concerns over adverse effects, financial constraints, and personal preferences or values.[19] We found contextual factors at an organisational level, such as lack of staffing and equipment, inconsistent procedures and limited medication supply, were the most often mentioned barriers for intervention delivery. These factors were also recognised as potential barriers to scale-up the care bundle into a national level, especially at secondary hospitals located in regional areas with limited sources yet bear the major burden of diagnosis and treatment for the populations.[20] Significant heavy workload on healthcare professionals in China compromised their capacity to do additional work, which challenges their ability to adhere to new clinical guidelines and participate in research.[20]

Establishing protocols and procedures at local sites might go some way to address the heavy workload and responsibilities but appear to impede the implementation of guideline-based care bundle. Although the Chinese Stroke Association recommends there are no contraindications to reduce SBP<140mmHg in ICH patients with elevated BP (SBP>150mmHg), there is no explicit time interval provided around such targets being achieved.[22] For BGL management, the recommendation is for close monitoring to avoid both hyperglycaemia and hypoglycaemia, but without any specific goals being recommended.[21] Compared to usual care based on national guidelines, the care bundle of INTERACT3 provides more details, but this requires more time and effort to embed into routine care. Clinicians reported that they did not explicitly adhere to the recommended level of pyrexia

control (<37.5 ºC) as it was set similar to the target level (<38ºC) in the national guideline.[22] Given the low rate of warfarin use (6%-14%) in Chinese patients,[23] it is not too surprising that the clinicians claimed that very few patients required anticoagulation reversal.

We found that the decision-making and management processes underlying implementation of the care bundle varied according to the different background expertise of clinicians. This is consistent with another study where nurses had a tendency towards problem-solving and for their management to be influenced by individuals while the decision of doctors was generally based on experience and autonomy.[24] Guidelines may be most influential in physicians who are less experienced or lack of a dominant practice style,[25] which could explain the attitude change on physiological parameters monitoring in neurosurgeons who were used to focusing on surgical interventions and lack of regular monitoring of BGL in their general practice.

Formal leadership and behaviour regulation are essential ingredients for ensuring that stroke care is of high quality and evidence-based.[26] Although most participants recognised the importance and appropriateness of the care bundle, they also highlighted the PI's role in motivating its delivery, and the value of generating a specialised procedure/workflow within available hospital resources to optimise the integration of the care bundle into routine practice. Dissemination of clinical guidelines alone was ineffective at changing the behaviour of healthcare professionals; involving all staff in establishing new routines and procedures around guidelines is necessary to implement evidence-based care in practice.[24] In China, however, establishing standardised therapies and protocols are challenging due to variation and discrepancies between services. Thus, there is a need to consider the availability of resources and systems before introducing workflows around implementing guidelines.

Implications

Careful consideration of potential barriers and facilitators, in collaboration with health services providers should be done prior to the start of the trial and in an ongoing iterative process to identify and deliver implementation strategies relevant to local sites. These strategies include: having a lead physician to evaluate the available resources and involve all staffs in changing management to optimise standardised workflow to allow timely initiation of interventions to achieve required targets; having a designated team of experienced nurses and doctors that can facilitate processes in collaboration with ED; encouraging constant training and regular case reviews, to improve the quality of implementation.

In regards to other LMICs implementing guideline-recommended interventions for ICH

management, it is crucial to identify and solve relevant issues at an organisational level, such as medication supply, necessary equipment and personnel resourcing.

Strengths and limitations

This is the first study using mixed methods to explore the implementation and integration of guideline-directed ICH management in China in conjunction during a vanguard phase of a stepped wedged international trial, which provided timely opportunity to optimise implementation. The sample size for the initial survey was small due to the limited number of sites had transferred into intervention phase at that time point. Moreover, we were limited in the number of people available for interview, and these were not balanced for region or level of hospitals. Despite our efforts at purposive sampling, most of the participating hospitals were academic tertiary-referral level hospitals with the capacity and interest to participate in research. Due to the pause of recruitment and restrictions to access the hospitals during the COVID-19 pandemic, we were unable to expand the survey and conduct non-participant observations to obtain more objective data on the care bundle implementation. We acknowledge limitations that introduced by deviations to the protocol and timeline. Lack of perceptions from patients is another limitation, which was due to the severity and unstable nature of ICH in the acute phase, and it was difficult to engage with patients/family in an efficient manner, especially as the COVID-19 pandemic evolved. However, we did include questions regarding the patient journey to the clinician interviews to understand patient's attitude and experience towards the care bundle. We intend to undertake similar PE studies as the study rolls out in the other LMICs, including a series of patient interviews when the patient's condition has stabilised, to enable a deeper understanding of the patient's journey and the impact of the intervention and patient outcomes of the trial.

Conclusion

Varied local established care procedures across sites, different levels of background expertise, and lack of staff capacity impeded the integration of goal-directed care bundle into routine practice for ICH management in China. Identifying and addressing these barriers is likely to facilitate implementation of the protocol in other LMICs with similar limited resources and settings, and more broadly if the trial results prove positive. For future study designs, explicit consideration at organizational and care-delivery levels should be given at the trial set up to develop strategies for intervention implementation.

Statement of Ethics

All written informed consent to participate in the study were obtained. The Biomedical Ethics Committee of West China Hospital approved the INTERACT3 study before the commencement of any patient recruitment (Ethics Reference No. 2017 Review [217]). According to funding request from Medical Research Council, additional approval (Ethic Reference: 26596-tgr2-ls: cardiovascular sciences, dept of) had been obtained from Research Ethics Committee of the University of Leicester, United Kingdom. Ethics approval was obtained in each site before site activation. Cluster Guardian consent (signed by General Manager or Chief Executive of hospital, or Head of Neurology/Neurosurgery/Stroke Department) for patients to receive the randomised care bundle to be implemented for acute intracerebral haemorrhage patients in Emergency Department, Stroke Unit, Intensive Care Unit or Neurology/Neurosurgery Wards. Written individual standard consent for the collection of data through in-person assessment and data extraction from medical records during the hospital stay and follow-up, and for release of personalised information for research purposes to allow centralised follow-up at 6 months following admission will be obtained from all patient participants or their person responsible.

Reference

1.   Donkor ES. Stroke in the 21st century: A snapshot of the burden, epidemiology, and quality of life. *Stroke research and treatment*. 2018;2018:3238165-3238165

2.   Willmot M, Leonardi-Bee J, Bath PMW. High blood pressure in acute stroke and subsequent outcome: A systematic review. *Hypertension*. 2004;43:18-24

3.   Kimura K, Iguchi Y, Inoue T, Shibazaki K, Matsumoto N, Kobayashi K, et al. Hyperglycemia independently increases the risk of early death in acute spontaneous intracerebral hemorrhage. *J Neurol Sci*. 2007;255:90-94

4.   Schwarz S, HÄFner K, Aschoff A, Schwab S. Incidence and prognostic significance of fever following intracerebral hemorrhage. *Neurology*. 2000;54:354-361

5.   Goldstein JN, Thomas SH, Frontiero V, Joseph A, Engel C, Snider R, et al. Timing of fresh frozen plasma administration and rapid correction of coagulopathy in warfarin-related intracerebral hemorrhage. *Stroke*. 2006;37:151-155

6.   Parry-Jones AR S-PC, Paroutoglou K, Birleson E, Rowland J, Lee S, Cecchini L, Massyn M, Emsley R, Bray B, Patel H. An intracerebral hemorrhage care bundle is associated with lower case fatality. *Ann Neurol*. 2019;86:495-503

7.   Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: The new medical research council guidance. *BMJ*. 2008;337:29-983

8.   Hoffmann TC, Walker MF. Tidier-ing up' the reporting of interventions in stroke research: The importance of knowing what is in the 'black box. *Int J Stroke*. 2015;10:657-658

9.   Wallin L. Knowledge translation and implementation research in nursing. *Int J Nurs Stud*. 2009;46:576-587

10.   Mills A. Health care systems in low- and middle-income countries. *N Engl J Med*. 2014;370:552-557

11.   Feigin LV, Norrving AB, Mensah AG. Global burden of stroke. *Circulation Research*. 2017;120:439-448

12.   Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical research council guidance. *BMJ: British Medical Journal*. 2015;350:h1258

13.   Murray E, Treweek S, Pope C, Macfarlane A, Ballini L, Dowrick C, et al. Normalisation process theory: A framework for developing, evaluating and implementing complex interventions. *BMC Medicine*. 2010;8:63

14.   May C, Cummings A, Girling M, Bracher M, Mair F, May C, et al. Using normalization process theory in feasibility studies and process evaluations of complex healthcare interventions: A systematic review. *Implementation Science*. 2018;13:80

15.   Suri H. Purposeful sampling in qualitative research synthesis. *Qualitative Research Journal*. 2011;11:63-75

16.   Fetters MD, Curry LA, Creswell JW. Achieving integration in mixed methods designs-principles and practices. *Health Serv Res*. 2013;48:2134-2156

17.   Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): A 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007;19:349-357

18.   Johnson RE, Grove AL, Clarke A. Pillar integration process: A joint display technique to integrate data in mixed methods research. *Journal of mixed methods research*. 2019;13:301-320

19.   Baatiema L, Otim ME, Mnatzaganian G, de-Graft Aikins A, Coombes J, Somerset S. Health professionals' views on the barriers and enablers to evidence-based practice for acute stroke care: A systematic review. *Implement Sci*. 2017;12:74-74

20.   Jiang K, Tian L, Yan C, Li Y, Fang H, Peihang S, et al. A cross-sectional survey on patient safety culture in secondary hospitals of northeast china. *PLoS One*. 2019;14:e0213055-e0213055

21.   Liping L, David W, Wong KSL, Yongjun W. Stroke and stroke care in china: Huge burden, significant workload, and a national priority. *Stroke*. 2011;42:3651-3654

22.   Lou M, Ding J, Hu B, Zhang Y, Li H, Tan Z, et al. Chinese stroke association guidelines for clinical management of cerebrovascular disorders: Executive summary and 2019 update on organizational stroke management. *Stroke and vascular neurology*. 2020;5:260-269

23.   Guo Y, Wang H, Tian Y, Wang Y, Lip GYH. Time trends of aspirin and warfarin use on stroke and bleeding events in Chinese patients with new-onset atrial fibrillation. *Chest*. 2015;148:62-72

24.   Kristensen N, Nymann C, Konradsen H. Implementing research results in clinical practice-the experiences of healthcare professionals. *BMC Health Serv Res*. 2016;16:48-48

25.   Halm EA, Atlas SJ, Borowsky LH, Benzer TI, Metlay JP, Chang Y, et al. Understanding physician adherence with a pneumonia practice guideline: Effects of patient, system, and physician factors. *Arch Intern Med*. 2000;160:98-104

26.   Stecksén A, Lundman B, Eriksson M, Glader E-L, Asplund K. Implementing thrombolytic guidelines in stroke care: Perceived facilitators and barriers. *Qual Health Res*. 2014;24:412-419

Chapter 6 Discussion and future research direction

Nurses, as integral members of the interdisciplinary team who work across the whole stroke care continuum, are responsible for the rapid assessment of patients with suspected stroke and in processes to facilitate the appropriate use of interventions. The various nursing care processes include timely screening and/or assessment of dysphagia, nutrition and hydration status, mood and rehabilitation needs; monitor and respond to abnormalities in physiological parameters; and identify and manage common complications. This body of work is primarily based on the data derived from two large-scale, international, multicentre, cluster-randomised controlled trials focusing on aspects of acute stroke care: HeadPoST and INTERACT3. With a background in nursing, I am proud to have been given the opportunity to work on these projects and conduct specific research on care processes that are relevant to nursing care, including dysphagia screening, indwelling urinary catheterisation (IUC), early detection and management of low presenting BP and SaO_2 levels. My work also involves exploring the variations of the components of stroke unit care across regions, and defining the enablers to improve the care implementation in clinical practice. I believe these nursing care processes are crucial to ensuring optimum recovery for patients, and future studies are needed to enhance the development, uptake and delivery of the clinical guidelines for stroke care. Within this context, I will summarise the key findings of this thesis, explain their implications for clinical practice, and make several recommendations for future research.

6.1 Summary of the key findings

In Chapter 2, I found patients who failed a dysphagia screen or used an IUC were vulnerable to post-stroke infections and had a significantly increased risk of adverse outcomes. The frequency and timing for care processes for dysphagia screening varied widely across regions, with it being high in Australia/UK (91.4%) and low in China (69.2%) and South America (61.5%). I found patients who failed a simple dysphagia screen had an increased risk of both pneumonia and death or dependency (aOR 3.00, 95%CI 2.18-4.10, and aOR 1.66, 95%CI 1.41-1.95, respectively) compared to those who passed. Failed a formal dysphagia assessment was also associated with greater odds of pneumonia and poor outcome (aOR 3.04, 95% CI 2.11-4.39, and aOR 2.22, 95% CI 1.76-2.80, respectively). Moreover, subsequent use of feeding restrictions in patients who failed either of the dysphagia evaluations was related to a higher risk of pneumonia (aOR 4.06, 95% CI 1.72-9.54). I also found there is a significant association between early IUC and death or dependency (aOR

1.40, 95%CI 1.13-1.74) but not in urinary tract infection (UTI, aOR 1.13; 95% CI 0.59-2.18), after adjusting for a range of key prognostic and management factors. In the stratified analysis, a similar magnitude of association was identified in patients without UTI (aOR 1.43, 95%CI 1.15-1.78), suggesting that UTI was not a mediator between the relationship of early IUC and poor outcome. Again, significant regional variation was also identified in the frequency and duration of early IUC, with the highest utilisation in India/Sri Lanka (33.8%) and lowest in China (5.7%). The longest duration of insertion was in Australia/UK and China (6 days) compared to the shortest in India/Sri Lanka (4 days).

In Chapter 3, my findings suggest that patients with a low BP or SaO_2 were at increased risk of adverse outcomes. I found a 'J-shaped' relationship between BP and poor outcomes. The odds of death or dependency increased when SBP <130mmHg, especially in patients with a final diagnosis of AIS. Patients with a low presenting SBP (<120 mmHg) were younger, more likely to have comorbid heart disease and functional impairment, and greater neurological impairment at the time of stroke onset. Compared to those presenting with moderate SBP (120-139 mmHg), patients with low SBP had an increased risk of death or dependency (aOR 1.27, 95% CI 1.02-1.58) and SAEs (aOR 2.31, 95% CI 1.16-4.60), after adjusting for potential confounders of pre-existing cardiac/cerebral comorbidity, dependency/frailty, and severity of the neurological deficit. Similar results applied to diastolic blood pressure (DBP) and were consistent in the sensitivity analyses. The significant association between low BP and adverse outcomes was not explained by reverse causality from pre-existing cardiac comorbidities, and the findings support the hypothesis that low BP exacerbates cardiac and cerebral ischaemia after acute stroke. Regarding SaO_2 in the first 24 hours after acute stroke, I found a reverse 'J-shaped' relationship between the lowest SaO_2 and death or dependency, with a nadir at 96-97%. Patients with oxygen desaturation (SaO_2 <93%) were older, and more likely to have a severe neurological impairment, premorbid disability and cardio-respiratory disease. Oxygen desaturation was not clearly associated with death or dependency (aOR 1.19, 95%CI 0.95-1.48) but with increased odds of any SAEs (aOR 1.34, 95%CI 1.07-1.68) within 90 days. No heterogeneity was found across the prespecified subgroups by head position or cardio-respiratory comorbidity.

In Chapter 4, I found patients in low- and middle-income countries (LMICs), compared to those in high-income countries, were less likely to receive established optimal treatments that are beneficial to better functional recovery, particularly of admission to an ASU and multidisciplinary allied health care. I identified significant variations in the components of

care processes according to ASU admission across four economically-defined regional groups of the world (Australia/UK, China, India/Sri Lanka and South America). ASU admission was highest in Australia/UK (98.2%), followed by India/Sri Lanka (84.0%), South America (41.3%) and China (20.0%). I also showed considerable regional variation in the characteristics of the patients admitted to ASU, and the types of care and management they received under the umbrella of ASU care, within and across different health care systems. Consistent with previous findings, the data confirmed that admission to ASU differed by age, neurological severity, and presence of comorbidities. Patients admitted to ASU having a better functional outcome, and this was consistent across all regions. Clinical outcomes by ASU admission also varied across regions, with the highest case fatality in India/Sri Lanka (12.3%). Compared to patients in Australia/UK, those in lower-income regions were less likely to receive reperfusion therapy as a care process in ASU, especially in India/Sri Lanka (aOR 0.27, 95%CI 0.12-0.63). The probability of receiving allied health care, including formal dysphagia assessment, physiotherapy, and occupational therapy, was significantly lower in all LMICs than in Australia/UK.

In Chapter 5, my findings outlined the key factors that influence the implementation of a quality-improvement intervention for ICH management in a middle-income country, China. Clinician knowledge, preferences, and values around the intervention, and level of patient acceptance, all complicate a healthcare professional decision over the provision of evidence-based care. Moreover, contextual factors at the organisational level, such as lack of staff and equipment, underlying established care procedures, limited medication supply, local policy and restrictions related to health insurance, impede stroke care delivery. Conversely, constant training, cases review, good communication with patients, and optimising the procedures were all the areas that were identified as facilitators for care implementation. Generating workflow that fits into available resources, having a dedicated team, and recognising the benefits of the intervention, were elements that assisted the embedding of the new system of care into everyday clinical practice.

6.2 Implication of findings for researchers and clinicians

Standardise care process to improve quality of care

It is crucial to standardise local protocols to deliver high-quality stroke care to prevent post-stroke complications. Simple dysphagia screening alone or combined with a formal assessment (e.g. video-fluoroscopy) is cost-effective for patients with acute stroke.[1] Although

dysphagia screening is recommended by the World Stroke Organisation (WSO) and widely used as a stroke care quality indicator,[2] the frequency of performing this procedure is often low (46.1% in Germany, 74.4% in the US).[3, 4] There is an urgent need to standardise protocols for dysphagia evaluations and incorporate them in clinical pathways with regular audits to ensure local competence. Early IUC was independently associated with death or dependency at 90 days after stroke (Chapter 2.2), highlighting the need for appropriate use to decrease potential risks and promote recovery in vulnerable patients. Although guidelines recommend avoiding the routine placement of a urinary catheter, studies have shown that improper use of IUC is high (43.9% to 52.8%).[5] Explicit clinical policy at national and hospital levels, and regulation of documentation and specific education for healthcare professionals, could ensure high quality of care for patients with acute stroke.[6]

Closely monitoring and appropriate management on vulnerable patients

Clinicians should closely monitor patients with low BP and SaO_2 levels and take appropriate corrective management as needed. Potential causes of low BP including volume depletion, acute myocardial infarction, cardiac arrhythmia, blood loss and aortic dissection.[7] Treatment should be rapid and tailored to underlying diagnoses, but at the same time being cautious in vulnerable patients, such as those with pre-existing cardiac comorbidities, who are prone to the complications of volume overload. In Chapter 3.2, I showed that patients with the lowest SaO_2 (96-97%) in the first 24 hours of admission had a better outcome compared to those with full concentration (SaO_2 100%). Together with other evidence that liberal oxygen therapy is associated with increased mortality and no improvement in other outcomes,[8] supplemental oxygen therapy should be used cautiously in clinical practice. As such, guidelines recommend avoiding routine use of supplemental oxygen, but instead restricted to patients with evidence of desaturation and to reach a reasonable treatment SaO_2 target of 94-96%.[9] However, excessive use of supplemental oxygen is often reported in patients with acute stroke without hypoxia, partly because healthcare professionals believe oxygen has little or no harm.[10] Thus, as well as regular monitoring of vulnerable patients, clinicians should be cautious with their actions that may contribute to adverse outcomes.

Improve accessibility and availability of acute stroke care in low- and middle-income countries

An organised ASU, with a coordinated multidisciplinary team and special expertise in stroke, has been proven effective in improving patient outcomes after stroke.[11] Although guidelines

recommend all stroke patients be admitted to ASU,[12-14] the admission rates are low in LMICs, suggested in Chapter 4. There were few or no ASU in any of the settings within LMICs due to limited resources, fragmentation of care, and lack of standardised health policies.[15-17] Moreover, findings from Chapter 2 and 4 indicate the timely dysphagia assessment, probability of receiving essential care processes, such as reperfusion therapy and allied health care, were lower in LMICs compared to HICs. As rtPA has been shown highly cost-effective for AIS, it is recommended as a priority treatment across the world.[18, 19] However, only 3-19% of the cases of AIS receive the treatment, and the use is particularly low in LMICs because of limited accessibility, availability and affordability.[17, 20] Multidisciplinary stroke care is also an effective management strategy, improving outcomes and length of hospital stay particularly in those with mild to moderate neurological impairment.[21] However, in many LMICs, there is limited multidisciplinary care and formal rehabilitation, with less than 10 skilled allied health practitioners per 1 million people.[17, 22] Health ministry and other government departments need to establish policies to improve accessibility and availability of organised acute stroke care.[17, 23, 24] Furthermore, there is a need to develop opportunities for career advancement, upskilling and training, and actions to promote and retain healthcare professionals where there are gaps in specialists.[17]

Strategies to improve implementation of guideline recommendations

I have shown that the implementation of guideline-recommended care could be improved by enhancing the knowledge and awareness of clinicians, and by systematically identifying and addressing barriers related to necessary resources. I recognise that embedding evidence into clinical practice is challenging, and many obstacles have to be overcome with various strategies.[25] Such implementation strategies need to be based on sound evidence (knowledge) of benefits and risks to improve clinician's awareness and agreement with self-efficacy, skills and motivation over implementing guidelines recommendations, and that with all potential implementation barriers are identified and addressed.[26-28] The embedding of constant training/education and regular case reviews are two approaches to improving knowledge and motivation among health professionals within a broad strategy of integrating evidence-based care in routine practice. Stroke services vary across regions according to the availability of skills and resources: human resources, healthcare facilities, diagnostic and laboratory services, medications, and transport.[16] Contextual factors impeding the delivery of the various components of a complex intervention should be readily identified at the early stages of an implementation strategy. Generating a workflow that suits available resources for

a particular setting and having a dedicated and committed team are two solutions to minimise contextual barriers and promote the use of procedures to facilitate implementation, as outlined in Chapter 5.

6.3 Strength and limitations of studies

The studies involved in this thesis included a very large number of patients with a broad range of characteristics who were managed across a variety of health settings. This enhances the generalisability of the findings. Selection bias was minimised through the use of broad inclusion criteria and the consecutive enrolment of participants, particularly so in the HeadPoST trial which used cluster recruitment with guardian consent.

However, there are several limitations.

1. Much of my work involved post-hoc analysis in the trial population, which increases the potential for chance findings, and incomplete adjustment of unknown confounding that is common in observational studies.
2. The subgroup analysis might be complicated by random associations due to the low power introduced by small sample sizes.
3. The inability to pre-specify or standardise the various care under investigation, such as procedures of dysphagia screening and assessment, feeding restrictions, IUC, and recordings of BP and SaO_2, prohibits a greater detail and potentially introduces indication bias, whereby sicker patients received particular interventions.
4. In this large pragmatic HeadPoST study, there was a limited range of variables with simple criteria, and no data were collected on other variables that may influence the recovery from stroke, such as depression, pain, caregiver support, financial resources. Moreover, the analyses pertained to associations and are therefore complicated by indication bias (i.e. the more severe cases received an intervention and have a worse outcome than others) and incomplete adjustment for severity.
5. Another factor relevant to this design was the high proportion of missing values in the primary outcome. Although multiple imputation approach was used to solve this problem, missingness does not always occur at random as assumed in statistical programs.
6. For the mixed methods study in Chapter 5, the lack of participation from consumers (patients/families) is an acknowledged limitation. Moreover, this aspect of the thesis was interrupted during the course of the COVID-19 pandemic, which introduced deviations of the data collection from the protocol. There was an inability to undertake interviews with

patients/carers, and non-participant observation on ward due, to restricted access to the hospitals.

6.4 Recommendation for future research

This body of work provides sound evidence and foundation for future research in acute stroke care that can inform the development of guideline recommendations and their implementation into clinical practice.

A particular area for further research is the prevention and management of post-stroke infections. AHA/ASA guidelines recommend the early use of nasogastric tube feeding in patients with dysphagia,[14] but the Australian Stroke Foundation suggests a broader 'early consideration of alternative non-oral routes' without explicit guidance on the choice of feeding method.[9] It is unclear how patients will benefit from different timing and approaches to assisted feeding after stroke.[29] Further studies are required to evaluate indications and effects of feeding actions to improve outcomes in those with dysphagia. Another topic is the management of urinary incontinence, which is common after stroke.[30] Considering the prognostic significance of early IUC, studies are needed to guide the appropriate use of urinary catheters in these vulnerable patients.

Abnormal physiological responses, such as low BP and oxygen desaturation after acute stroke, require rapid treatment to minimise adverse outcomes. However, few studies have examined the best approach to manage low BP, and the few small trials have produced inconclusive results.[31] Moreover, guideline recommendations lack explicit guidance on volume and duration of parenteral fluid replacement to treat hypotension and/or hypovolemia due to insufficient data.[4] Future research should focus on identifying the mechanisms of low BP and test different appropriate managements to improve clinical guidelines.

The extent to which variations in acute stroke care are driven by policy, system, costs, healthcare professional skills and beliefs, needs further investigation. Future studies are needed on how to effectively increase the uptake and delivery of stroke care, especially in other LMICs. This could include a comprehensive scoping study of the guideline recommendations in LMICs, as a foundation to a broad implementation strategy based on local contextual factors to improve the quality of care for patients (and families) affected by stroke.

Chapter References

1.   Wilson RD, Howe EC. A cost-effectiveness analysis of screening methods for dysphagia after stroke. *PM R*. 2012;4:273-282

2.   Lindsay P, Furie KL, Davis SM, Donnan GA, Norrving B. World Stroke Organization global stroke services guidelines and action plan. *Int J Stroke*. 2014;9:4-13

3.   Heuschmann PU, Biegler MK, Lowitzsch K, Misselwitz B, Nabavi DG, Otten K, et al. Development and implementation of evidence-based indicators for measuring quality of acute stroke care: the quality indicator board of the German stroke registers study group (ADSR). *Stroke*. 2006;37:2573-2578

4.   Cumbler E, Murphy P, Jones WJ, Wald HL, Kutner JS, Smith DB. Quality of care for in-hospital stroke: analysis of a statewide registry. *Stroke*. 2011;42:207-210

5.   Hu F-W, Yang D-C, Huang C-C, Chen C-H, Chang C-M. Inappropriate use of urinary catheters among hospitalized elderly patients: clinician awareness is key. *Geriatrics & Gerontology International*. 2015;15:1235-1241

6.   Krumholz H, Brass, LM, Every, NR, Spertus, JA, Bazzarre, T, Cohen, DJ, Hlatky, MA, Peterson, ED, Radford, MJ, Weintraub, WS. Measuring and improving quality of care: a report from the American Heart Association/American College of Cardiology first scientific forum on assessment of healthcare quality in cardiovascular disease and stroke. *Stroke*. 2000;31:1002-1012

7.   Mullen MT, McKinney JS, Kasner SE. Blood pressure management in acute stroke. *J Hum Hypertens*. 2009;23:559-569

8.   Chu DK KL, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, Szczeklik W, Schünemann HJ, Neary JD, Alhazzani W. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet*. 2018;391:1693-1705

9.   Stroke Foundation. Clinical guidelines for stroke management. 2019. https://informme.org.au/en/Guidelines/Clinical-Guidelines-for-Stroke-Management.

10.   Siemieniuk RAC, Chu DK, Kim LH-Y, Güell-Rous M-R, Alhazzani W, Soccal PM, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. *BMJ*. 2018;363:k4169-k4169

11.   Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database of Systematic Reviews*. 2013; 2013(9):CD000197

12. Bowen A JM, Young, G. National clinical guideline for stroke prepared by the Intercollegiate Stroke Working Party. *Royal College of Physicians*; 2016.

13. Chinese Society of Neurology, Chinese Stroke Society. Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2018. *Chinese Journal of Neurology*. 2018;51:666-682

14. Powers JW, Rabinstein AA, Ackerson MT, Adeoye CO, Bambakidis MN, Becker CK, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50:e344-e418

15. Langhorne P, O'Donnell MJ, Chin SL, Zhang H, Xavier D, Avezum A, et al. Practice patterns and outcomes after stroke across countries at different economic levels (INTERSTROKE): an international observational study. *Lancet (London, England)*. 2018;391:2019

16. Pandos OC, Milton AG, Nagpal A, Kleinig TJ, Jannes J, Koblar SA, et al. Stroke unit legislation—mandating a uniform standard of care? *Int J Stroke*. 2020;15:174749302090351-NP174749302090357

17. Chimatiro GL, Rhoda AJ. Scoping review of acute stroke care management and rehabilitation in low and middle-income countries. *BMC Health Serv Res*. 2019;19:789-789

18. Boudreau DM, Guzauskas G, Villa KF, Fagan SC, Veenstra DL. Cost-effectiveness of recombinant tissue plasminogen activator 3–4.5 hours after onset of acute ischemic stroke in patient subgroups. *Annals of emergency medicine*. 2013;61:46-55

19. Boudreau DM, Guzauskas GF, Chen E, Lalla D, Tayama D, Fagan SC, et al. Cost-effectiveness of recombinant tissue-type plasminogen activator within 3 hours of acute ischemic stroke: current evidence. *Stroke*. 2014;45:3032-3039

20. Berkowitz AL MM, McLane HC, Shen GC, Muralidharan R, Lyons JL, Shinohara, RT, Shuaib A, Mateen FJ. Worldwide reported use of IV tissue plasminogen activator for acute ischemic stroke. *Journal of Stroke*. 2014;9:349-355

21. Langhorne P, Baylan S, Early Supported Discharge Trialists. Early supported discharge services for people with acute stroke. *Cochrane Database Syst Rev*. 2017;7:CD000443.

22.   Prvu Bettger J, Liu C, Gandhi DBC, Sylaja PN, Jayaram N, Pandian JD. Emerging areas of stroke rehabilitation research in low- and middle-income countries: a scoping review. *Stroke*. 2019;50:3307-3313

23.   Langhorne P, de Villiers L, Pandian JD. Applicability of stroke-unit care to low-income and middle-income countries. *Lancet Neurol.* 2012;11:341-348

24.   Baatiema L, Otim M, Mnatzaganian G, Aikins AD-G, Coombes J, Somerset S. Towards best practice in acute stroke care in Ghana: a survey of hospital services. *BMC Health Serv Res*. 2017;17:108-108

25.   Curtis K, Fry M, Shaban RZ, Considine J. Translating research findings to clinical nursing practice. *J Clin Nurs*. 2017;26:862-872

26.   Gagliardi AR, Alhabib, S. & and the members of the Guidelines International Network Implementation Working Group. Trends in guideline implementation: a scoping systematic review. *Implementation Science*. 2015;10:54

27.   Lugtenberg M Z-vSJ, Westert GP, Burgers JS. Why don't physicians adhere to guideline recommendations in practice? An analysis of barriers among Dutch general practitioners. *Implement Sci*. 2009;4:54

28.   Fischer F, Lange K, Klose K, Greiner W, Kraemer A. Barriers and strategies in guideline implementation-a scoping review. *Healthcare (Basel)*. 2016;4:36

29.   Wirth R, Smoliner C, Jäger M, Warnecke T, Leischker AH, Dziewas R. Guideline clinical nutrition in patients with stroke. *Exp Transl Stroke Med*. 2013;5:14-14

30.   Dumoulin C, Komer-Bitensky N, Tannenbaum C. Urinary incontinence after stroke: identification, assessment, and intervention by rehabilitation professionals in Canada. *Stroke*. 2007;38:2745-2751

31.   Mistri AK, Robinson TG, Potter JF. Pressor therapy in acute ischemic stroke: systematic review. *Stroke*. 2006;37:1565-1571

Appendices

Supplementary Appendix of Chapter 1

Appendix 1. National Institute of Health Stroke scale

Assessment	Response	Score
1a. Level of Consciousness: The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert; keenly responsive. 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, areflexic.	
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.	
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to them (pantomime) and score the result (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.	
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI) score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eye contact	0 = Normal. 1 = Partial gaze palsy. This score is given when gaze is abnormal in one or both eyes, but where forced deviation or total gaze paresis are not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.	

Assessment	Response	Score
and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.		
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate. Patient must be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia is found. If patient is blind from any cause score 3. Double simultaneous stimulation is performed at this point. If there is extinction patient receives a 1 and the results are used to answer question 11.	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).	
4. Facial Palsy: Ask, or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barrier obscures the face, these should be removed to the extent possible.	0 = Normal symmetrical movement. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).	
5 & 6. Motor Arm and Leg: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be "9" and the examiner must clearly write the explanation for scoring as a "9".	0 = No drift, limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift, Limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity, limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity, limb falls. 4 = No movement 9 = Amputation, joint fusion explain:	-
	5a. Left Arm	
	5b. Right Arm	
	0 = No drift, leg holds 30 degrees position for full 5 seconds. 1 = Drift, leg falls by the end of the 5 second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity, leg falls to bed immediately. 4 = No movement. 9 = Amputation, joint fusion explain:	-
	6a. Left Leg	
	6b. Right Leg	
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, insure testing is done in intact visual field. The	0 = Absent . 1 = Present in one limb . 2 = Present in two limbs If present, is ataxia in?	

Assessment	Response	Score
finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion may the item be scored "9", and the examiner must clearly write the explanation for not scoring. In case of blindness test by touching nose from extended arm position.	**Right arm** 1 = Yes 2 = No 9 = amputation or joint fusion, explain: _____	-
	Left arm 1 = Yes 2 = No 9 = amputation or joint fusion, explain : _____	-
	Right leg 1 = Yes 2 = No 9 = amputation or joint fusion, explain: _____	-
	Left leg 1 = Yes 2 = No 9 = amputation or joint fusion, explain: _____	-

8. Sensory:

Sensation or grimace to pin prick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas [arms (not hands), legs, trunk, face] as needed to accurately check for hemisensory loss. A score of 2, "severe or total," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will therefore probably score 1 or 0. The patient with brain stem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic score 2. Patients in coma (item 1a=3) are arbitrarily given a 2 on this item.	0 = Normal; no sensory loss. 1 = Mild to moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick but patient is aware he/she is being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.	

9. Best Language:

A great deal of information about comprehension will be obtained during the preceding sections of the examination. The patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in coma (question 1a=3) will arbitrarily score 3 on this item. The examiner must choose a score in the patient with stupor or limited cooperation but a score of 3 should be used only if the patient is mute and follows no one step commands.	0 = No aphasia, normal. 1 = Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided material difficult or impossible. For example in conversation about provided materials examiner can identify picture or naming card from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.	

10. Dysarthria:

If patient is thought to be normal an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or	0 = Normal. 1 = Mild to moderate; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe; patient's speech is so slurred as to be unintelligible in the absence of or out	

Assessment	Response	Score
has other physical barrier to producing speech, may the item be scored "9", and the examiner must clearly write an explanation for not scoring. Do not tell the patient why he/she is being tested.	of proportion to any dysphasia, or is mute/anarthric. 9 = Intubated or other physical barrier, explain: _____	
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space.	
TOTAL		**/42**
Additional item, not a part of the NIH Stroke Scale score.		-
A. Distal Motor Function: The patient's hand is held up at the forearm by the examiner and patient is asked to extend his/her fingers as much as possible. If the patient can't or doesn't extend the fingers the examiner places the fingers in full extension and observes for any flexion movement for 5 seconds. The patient's first attempts only are graded. Repetition of the instructions or of the testing is prohibited.	0 = Normal (No flexion after 5 seconds). 1 = At least some extension after 5 seconds, but not fully extended. Any movement of the fingers which is not command is not scored. 2 = No voluntary extension after 5 seconds. Movements of the fingers at another time are not scored.	-
	a. Left Arm	
	b. Right Arm	

Reference: National Institutes of Health, National Institute of Neurological Disorders and Stroke. Stroke Scale. https://www.ninds.nih.gov/sites/default/files/NIH_Stroke_Scale_Booklet.pdf.

Appendix 2. modified Rankin Scale

	Score

0 = No symptoms at all.	
1 = No significant disability despite symptoms, able to carry out all usual duties and activities	
2 = Slight disability, unable to carry out all previous activities but able to look after own affairs without assistance.	
3 = Moderate disability requiring some help, but able to walk without Assistance.	
4 = Moderate severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance.	
5 = Severe disability, bedridden incontinent, and requiring constant nursing care and attention.	
6 = Dead.	

Simplified mRS
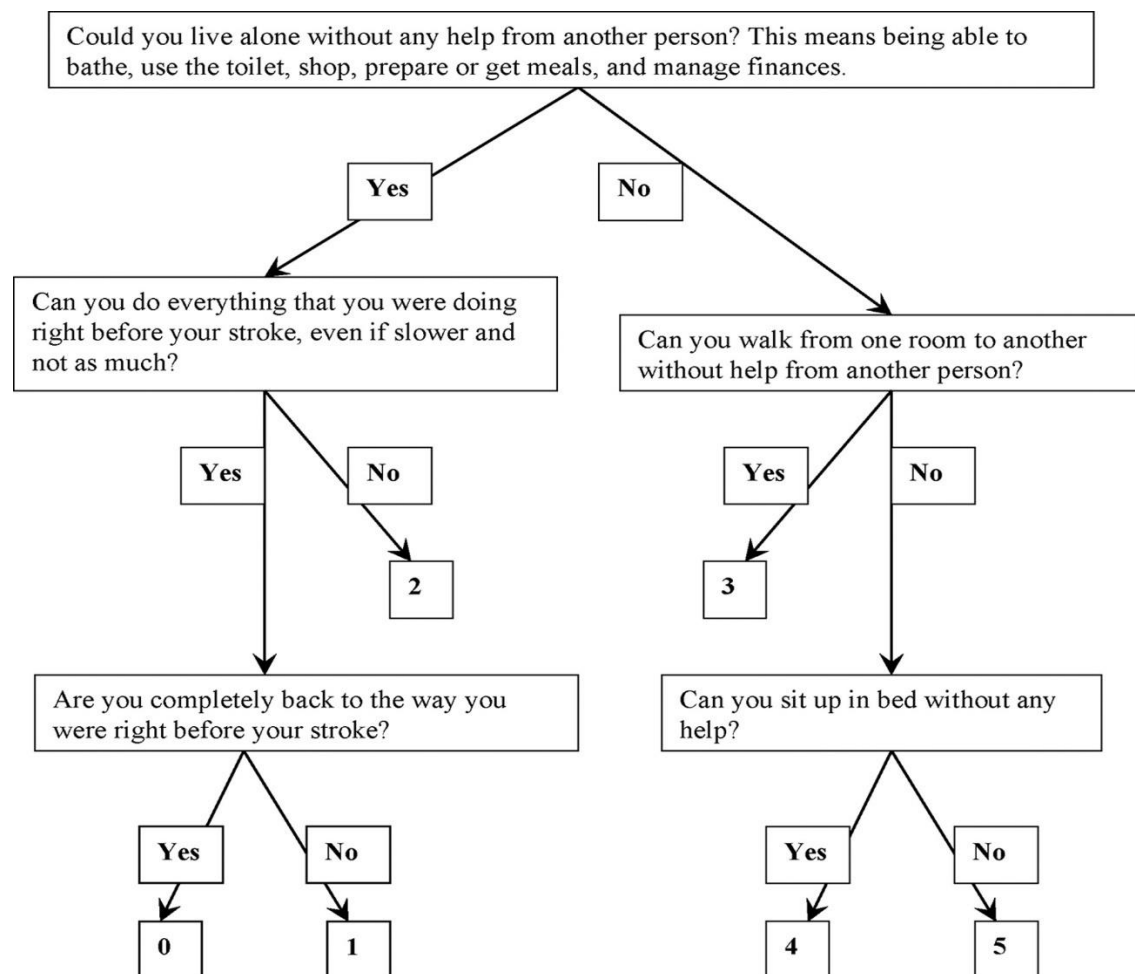
Appendix 3. Barthel Index

FEEDING

0 = unable

5 = needs help cutting, spreading butter, etc., or requires modified diet

10 = independent _____

BATHING

0 = dependent

5 = independent (or in shower) _____

GROOMING

0 = needs to help with personal care

5 = independent face/hair/teeth/shaving (implements provided) _____

DRESSING

0 = dependent

5 = needs help but can do about half unaided

10 = independent (including buttons, zips, laces, etc.) _____

BOWELS

0 = incontinent (or needs to be given enemas)

5 = occasional accident

10 = continent _____

BLADDER

0 = incontinent, or catheterized and unable to manage alone

5 = occasional accident

10 = continent _____

TOILET USE

0 = dependent

5 = needs some help, but can do something alone

10 = independent (on and off, dressing, wiping) _____

TRANSFERS (BED TO CHAIR AND BACK)

0 = unable, no sitting balance

5 = major help (one or two people, physical), can sit

10 = minor help (verbal or physical)

15 = independent _____

MOBILITY (ON LEVEL SURFACES)

0 = immobile or < 50 yards

5 = wheelchair independent, including corners, > 50 yards

10 = walks with help of one person (verbal or physical) > 50 yards

15 = independent (but may use any aid; for example, stick) > 50 yards _____

STAIRS

0 = unable

5 = needs help (verbal, physical, carrying aid)

10 = independent _____

TOTAL (0–100): _____

Guidelines

1. The index should be used as a record of what a patient does, not as a record of what a patient could do.

2. The main aim is to establish degree of independence from any help, physical or verbal, however minor

and for whatever reason.

3. The need for supervision renders the patient not independent.

4. A patient's performance should be established using the best available evidence. Asking the patient,

friends/relatives and nurses are the usual sources, but direct observation and common sense are also

important. However direct testing is not needed.

5. Usually the patient's performance over the preceding 24-48 hours is important, but occasionally longer

periods will be relevant.

6. Middle categories imply that the patient supplies over 50 per cent of the effort.

7. Use of aids to be independent is allowed.

Appendix 4. EQ5D

1.   Mobility

Thinking about your health today, which of the following statements best describes your mobility?

☐   I have no problems walking about

☐   I have some problems in walking about

☐   I am confined to bed

2.   Self-care

Thinking about your health today, which of the following statements best describes your self-care?

☐   I have no problems with self-care

☐   I have some problems washing or dressing myself

☐   I am unable to wash or dress myself

3.   Usual activity

Thinking about your health today, which of the following statements best describes your usual activities such as work, study, housework, family or leisure activities?

☐   I have no problems with performing my usual activities

☐   I have some problems performing my usual activities

☐   I am unable to perform my usual activities.

4.   Pain/discomfort

Thinking about your health today, which of the following statements best describes any pain or discomfort you may be experiencing?

☐   I have no pain or discomfort

☐   I have moderate pain or discomfort

☐   I have extreme pain or discomfort

5.   Anxiety/depression

Thinking about your health today, which of the following statements best describes any anxiety and depression you may be experiencing?

☐   I am not anxious or depressed

☐   I am moderately anxious or depressed

☐   I am extremely anxious or depressed

Appendix 5. Data flowchart for Chapter 2-3

11093 patients assigned to randomized head position
(5295 to lying-flat; 5798 to sitting-up)

Chapter 2

Chapter 3

Chapter 2.1

Chapter 2.2

Chapter 3.1

Chapter 3.2

Figure 1 (a).
Pneumonia outcome
analysis: N=10579;
(b). Poor outcome
analysis: N=9310

Figure 2 (a).
Pneumonia outcome
analysis: N=8390;
(b). Poor outcome
analysis: N=7341

Table 2. Death or
dependency analysis:
Complete case
N=9192; Multiple
imputation N=10996

Table 3. UTI
complete case
analysis: N=10419;
multiple imputation
N=10996

Figure 1 (a). death or
dependency: N=9375;
(b). SAE: N=10633

Figure 2 (a). AIS:
N=8080; (b). ICH:
N=775

Figure 3. original
dataset: Trial population
N=9375, confirmed
stroke N=8855, AIS
N=8080, ICH N=775

Figure 1 (a). death or
dependency: N=6476
(b). SAE: N=7488

Appendix 6. Data availability of the variables in HeadPoST study

Variable	Missing in full dataset (N=11093)	Missing in dataset for functional outcome analysis* (N=9748)
Baseline variable		
Age	2/11093 (0.02)	0/9784 (0.00)
Sex	0/11093 (0.00)	0/9784 (0.00)
Region group	0/11093 (0.00)	0/9784 (0.00)
Baseline assessment		
SBP in mmHg	10/11093 (0.09)	9/9784 (0.09)
DBP in mmHg	10/11093 (0.09)	9/9784 (0.09)
Blood glucose level	2990/11093 (26.95)	2650/9784 (27.19)
NIHSS at admission	162/11093 (1.46)	127/9784 (1.30)
GCS score at admission	19/11093 (0.17)	16/9784 (0.16)
Pre-morbid according to mRS	22/11093 (0.20)	19/9784 (0.19)
Lowest SaO_2 during the first 24 hours	3026/11093 (27.3)	2799/9784 (28.71)
Prior medical history		
Hypertension	32/11093 (0.29)	25/9784 (0.26)
Previous stroke	35/11093 (0.32)	32/9784 (0.33)
Coronary artery disease	70/11093 (0.63)	58/9784 (0.59)
Atrial fibrillation	71/11093 (0.64)	57/9784 (0.58)
Heart failure	96/11093 (0.87)	83/9784 (0.85)
Diabetes mellitus	35/11093 (0.32)	32/9784 (0.33)
COPD/emphysema	92/11093 (0.83)	76/9784 (0.78)
Current smoker	118/11093 (1.06)	100/9784 (1.3)
Hypercholesterolaemia	60/11093 (0.54)	52/9784 (0.53)
Other major health conditions	154/11093 (1.39)	129/9784 (1.3)
Dysphagia	94/11093 (0.85)	87/9784 (0.89)
Medications at admission		
Aspirin/other antiplatelet	12/11093 (0.11)	12/9784 (0.12)
Anticoagulation	18/11093 (0.16)	18/9784 (0.18)
Time from stroke onset to hospital arrival	7/11093 (0.06)	5/9784 (0.05)
Pathology subtype of stroke	33/11093 (0.30)	10/9784 (0.10)
Assessment at day 7		
NIHSS at 7 days/before discharge	377/11093 (3.40)	300/9784 (3.08)
mRS at 7 days/before discharge	121/11093 (1.09)	95/9784 (0.97)
Hospital management variable (during 7 days/before discharge)		
ICU admission	69/11093 (0.62)	6/97840 (0.62)
ASU admission	7/11093 (0.63)	7/9784 (0.07)
IUC insertion	87/11093 (0.78)	83/9784 (0.85)
Length of IUC insertion	62/1167 (5.31)	51/1035 (4.93)
Antibiotic treatment	63/11093 (0.57)	54/9784 (0.55)

Variable	Missing in full dataset (N=11093)	Missing in dataset for functional outcome analysis* (N=9748)
Reperfusion therapy for AIS	28/9485 (0.25)	22/8383 (0.23)
Antiplatelets for AIS	27/9485 (0.24)	23/8383 (0.23)
Anticoagulation for atrial fibrillation	10/1189 (0.84)	10/1036 (0.97)
Intensive blood pressure lowering	10/11093 (0.09)	8/9784 (0.08)
Dysphagia screening performed	17/11093 (0.15)	13/9784 (0.13)
Time from hospital arrival to dysphagia screening	6/8784 (0.07)	5/7670 (0.07)
Dysphagia screening results	2/8784 (0.02)	2/7670 (0.03)
Formal dysphagia assessment performed	19/11093 (0.17)	14/9784 (0.14)
Time from hospital arrival to dysphagia assessment	0/3917 (0.00)	0/3495 (0.00)
Dysphagia assessment results	4/3917 (0.10)	4/3495 (0.11)
Assisted feeding for dysphagia	15/2045 (0.73)	14/1793 (0.78)
Physiotherapy	60/11093 (0.54)	50/9784 (0.51)
Occupational therapy	64/11093 0.58)	55/9784 (0.56)
Psychologist therapy	86/11093 (0.78)	72/9784 (0.74)
Surgical procedures for ICH	9/931 (0.97)	8/819 (0.99)
Withdrawal active care	73/11093 (0.66)	65/9784 (0.67)
Endotracheal intubation	56/11093 (0.50)	46/9784 (0.47)
Time from hospital arrival to discharge	6172/11093 (55.63)	5553/9784 (56.97)

Footnote: AIS denotes acute ischaemic stroke, ASU acute stroke unit, COPD chronic obstructive pulmonary disease, DBP diastolic blood pressure, GCS Glasgow Coma Scale, ICH intracerebral haemorrhage, ICU intensive care unit, IUC indwelling urinary catheter, mRS modified Rankin scale, NIHSS National Institute of Health stroke scale, SBP systolic blood pressure, UK United Kingdom
*There were 12% missing data for the mRS at 90 days due to loss of follow-up

Appendix 7. Multiple imputation methods

Multiple imputation was used to impute missing outcome data, using PROC MI and PROC MIANALYZE in SAS version 9.2 (or later) software. Multiple imputation is generally considered the least biased method, since it incorporates uncertainty to the imputed value, and a non-monotone missing pattern is assumed modified Rankin scale (mRS) score at 90 days. A distribution for the outcome was derived from a regression model that accounts for covariates (listed in the hierarchical mixed model) and a random sample from this distribution was used to impute values for missing outcomes. Ten multiple sample data sets with complete outcome data were generated through PROC MI, and the results (regression parameter and covariance matrix estimates) for each sample combined and analysed with PROC MIANALYZE to derive a valid statistical inference about the association with outcomes.

Appendix 8. Glossary of stroke care process terms

Care indicators	Definition
Reperfusion therapy for AIS	Intravenous or intra-arterial rtPA/other thrombolytic therapy for acute ischaemic stroke patients within the first 7 days of hospitalisation/before discharge if earlier
Antiplatelets for AIS	Antiplatelet therapy for acute ischaemic stroke patients initiated within the first 7 days of hospitalisation/before discharge if earlier
Anticoagulation for AF	Anticoagulant therapy for acute stroke patients with AF initiated within the first 7 days of hospitalisation/before discharge if earlier
Antihypertensive for secondary prevention	Oral antihypertensive agents for secondary prevention initiated within the first 7 days of hospitalisation/before discharge if earlier
Intensive BP lowering	Multidrug antihypertensive therapy with a BP target less than 140/90mmHg initiated within the first 7 days of hospitalisation/before discharge if earlier
Dysphagia screen	Initial screening for swallowing function within 24 hours of hospital arrival
Formal dysphagia assessment	Formal assessment for swallowing function by speech pathologist/allied health professionals if screening failed
Assisted feeding for dysphagia	Assisted feeding included modified diet (liquid, puree, soft food), nasogastric tube or percutaneous gastrostomy provided to acute stroke patients with diagnosed dysphagia within the first 7 days of hospitalisation/before discharge if earlier
Physiotherapy	Formal assessment by physiotherapist within the first 7 days of hospitalisation/before discharge if earlier
Occupational therapy	Formal assessment by occupational therapist within the first 7 days of hospitalisation/before discharge if earlier
Psychological therapy	Formal assessment by psychologist within the first 7 days of hospitalisation/before discharge if earlier

AF denotes atrial fibrillation, AIS acute ischaemic stroke, BP blood pressure, rtPA recombinant tissue plasminogen activator

Table S1. National guideline recommendations for dysphagia screening/assessment, feeding restrictions and urinary catheterisation after stroke

Care process	AHA/ASA Guidelines[1,2]	ESO[3]	Australia Stroke Foundation[4]	UK NICE Guideline[5]
Dysphagia screening/assessment	AIS: Dysphagia screening before begins eating, drinking, or receiving oral medications (Level C); It is reasonable for dysphagia screening to be performed by a speech pathologist or trained healthcare provider (Level C). ICH: A formal screening procedure for dysphagia should be performed in all patients before the initiation of oral intake to reduce the risk of pneumonia (Level C).	All patients with acute stroke, recommend a formal dysphagia screening test to prevent post-stroke pneumonia and decrease risk of early mortality. Screen the patients as fast as possible after admission (Moderate Level); A dysphagia assessment in all stroke patients failing a dysphagia screen and/or showing other clinical predictors of post-stroke dysphagia, in particular a severe facial palsy, severe dysarthria, severe aphasia or an overall severe neurological deficit (NIH-SS $\geq$ 10 points). Dysphagia assessment should be done as soon as possible. In addition to the clinical swallow examination, VFSS or,	Acute stroke should have swallowing screened, using a validated screening tool by a trained healthcare professional (Weak); Screening should be within four hours of arrival at hospital and before being given any oral food, fluid or medication (Consensus-based); All stroke who failed swallow screening or who deteriorate should have a comprehensive swallowing assessment performed by a speech pathologist (Weak).	Ensure acute stroke have swallow screening by an appropriate trained healthcare professional before given any oral food, fluid or medication; If admission screen indicates problems with swallowing, ensure that the person has a specialist assessment of swallowing, within 24 hours of admission and not more than 72 hours.

	preferentially, FEES should be available (Low level); In acute stroke patients swallowing of tablets should routinely be evaluated as part of dysphagia assessment in addition to assessing the swallowing of liquid and different food consistencies and quantities (Low level).		
Feeding in dysphagia	AIS: Enteral diet should be started within 7 days of admission after acute stroke (Level B); For patients with dysphagia, it is reasonable to initially use nasogastric tubes for feeding in the first 7 days and place PEG tube in patients with persistent inability to swallow (>2-3 weeks) (Level C). ICH: No specific advice.	In patients with acute stroke, we recommend no administration of any food or liquid items, including oral medication, until a dysphagia screening has been done and swallowing was judged to be safe (Moderate Level).	Patients with dysphagia on texture-modified diets and/or fluids should have their intake and tolerate to the modified diet monitored regularly due to the increased risk of malnutrition and dehydration (Consensus-based).	Acute stroke who are unable to take adequate nutrition, fluids and medication orally should: received tube feeding with a nasogastric tube within 24 hours of admission unless had thrombolysis; be considered for a nasal bridle tube or gastrostomy not tolerate to nasogastric tube
Urinary	AIS: Routinely placement of	No specific recommendation.	The routine use of indwelling	No specific recommendation.

| catheterisation | indwelling bladder catheters should not be performed because of the associated risk of catheter-associated urinary tract infections (Level C). ICH: No specific advice. | catheters is not recommended (Consensus-based). |

AIS denotes acute ischaemic stroke, ICH intracerebral haemorrhage, AHA American Heart Association, ASA American Stroke Association, ESO European Stroke Organisation, UK United Kingdom, NICE National Institute for Health and Care Excellence, PEG Percutaneous Endoscopic Gastrostomy

Reference:

1. Powers JW, Rabinstein AA, Ackerson MT, Adeoye CO, Bambakidis MN, Becker CK, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50:e344-e418

2. Hemphill CJ, Greenberg MS, Anderson SC, Becker RK, Bendok LB, Cushman NM, et al. Guidelines for the management of spontaneous intracerebral haemorrhage: A guideline for healthcare professionals from the Association/American Stroke Association. *Stroke*. 2015;46:2032-2060

3. Dziewas R, Michou E, Trapl-Grundschober M, et al. European Stroke Organisation and European Society for Swallowing Disorders guideline for the diagnosis and treatment of post-stroke dysphagia. *European Stroke Journal*. 2021;6(3):LXXXIX-CXV. doi:10.1177/23969873211039721.

4. Australian Stroke Foundation. Clinical guidelines for stroke management. 2017. https://informme.org.au/en/Guidelines/Clinical-Guidelines-for-Stroke-Management

5. National Institute for Health and Care Excellence. Stroke and transient ischaemic attack in over 16s: diagnosis and initial management. *NICE Guideline*. 2019.

Table S2. Services required for optimal acute stroke care at each stage of care[1] and barriers at each level in low- and middle-income countries[2]

Level	1. Early diagnosis and monitoring	2. Acute management	3. Discharge planning
Minimal	• Standard clinical history and examination	• Basic risk factor assessment and management (BP, HR, BGL, temperature) • Ongoing neurological assessments • Swallow screening and management of dysphagia	• Early assessment of discharge needs • Early rehabilitation planning Secondary prevention
Essential	• Neurological assessments • Electrocardiography, CT scanning etc. • Acute thrombolysis treatment	• Admission to an organized stroke unit • Depression assessment and management • Cognition assessment and management	• Referral to rehabilitation and lifestyle medication specialists
Advanced	• Magnetic resonance imaging, CT perfusion scans, prolonged electrocardiographic monitoring devices • Endovascular thrombectomy, neurosurgery, hemicraniectomy, anticoagulant reversal products	• Multidisciplinary team of stroke experts • Coordinated stroke care provided across geographically discrete regions	• Referral to rehabilitation and lifestyle medication specialists
Barriers of implementation in LMICs	• Delays in patient arrival • Lack or malfunction of diagnostics • Unavailability of standardised stroke protocols • Cost, especially for advanced care	• Staff shortages and lack of stroke experts • Lack of medications • Shortages in bed capacity Cost, especially for advanced care	• Lack of research on effectiveness and applicability • Insufficient training in rehabilitation and primary care for secondary prevention • Cost, especially for advanced care

BGL denotes blood glucose level, BP blood pressure, CT computerised tomography, HR heart rate, LMICs low- and middle-income countries

Reference:

1. Lindsay P, Furie KL, Davis SM, Donnan GA, Norrving B, et al. World Stroke Organization global stroke services guidelines and action plan. Int J Stroke. 2014;9(Suppl A100):4–13

2. Khatib R, Jawaada AM, Arevalo YA, Hamed HK, Mohammed SH, Huffman MD. Implementing evidence-based Practices for acute stroke care in Low- and Middle-Income Countries. Current Atherosclerosis Reports. 2017; 19(12): 61.

Supplementary Appendix of Chapter 2.1

Dysphagia screening and risks of pneumonia and adverse outcomes after acute stroke: an international multicentre study

Ouyang M, Bowden L, Arima H, Lavados PM, Billot L, et al.

Supplemental Tables: 16

Supplemental Figures: 13

Table S1 1: Baseline characteristics by clinical outcomes at 90 days of follow up

	Outcomes of interests					
	Pneumonia			Modified Rankin Scale		
	Yes	No		Poor outcome	Favourable outcome	
Baseline characteristics	(N=362)	(N=10731)	P-value	(N=3826)	(N=5922)	P-value
Age, yr	77.0$\pm$12.7	67.7$\pm$13.7	<.0001	72.8$\pm$13.2	65.1$\pm$13.0	<.0001
Male	202 (55.8%)	6462 (60.2%)	0.092	2023 (52.9%)	3866 (65.3%)	<.0001
Region			<.0001			<.0001
Australia and UK	228 (63.0%)	4533 (42.2%)		1687 (44.1%)	2165 (36.6%)	
China and Taiwan	49 (13.5%)	4603 (42.9%)		1284 (33.6%)	3063 (51.7%)	
India and Sri Lanka	26 (7.2%)	744 (6.9%)		411 (10.7%)	283 (4.8%)	
South America	59 (16.3%)	851 (7.9%)		444 (11.6%)	411 (6.9%)	
Pathological subtype			<.0001			<.0001
Uncertain	13 (3.6%)	650 (6.1%)		146 (3.8%)	387 (6.6%)	
Ischaemic stroke	295 (82.2%)	9172 (85.7%)		3266 (85.6%)	5103 (86.4%)	
Intracerebral haemorrhage	51 (14.2%)	879 (8.2%)		404 (10.6%)	414 (7.0%)	
NIHSS at admission‡	13.0 (6.5, 19.0)	4.0 (2.0, 8.0)	<.0001	8.0 (4.0, 14.0)	3.0 (2.0, 5.0)	<.0001
GCS score at admission	14.0 (11.0, 15.0)	15.0 (14.0, 15.0)	<.0001	15.0 (12.0, 15.0)	15.0 (15.0, 15.0)	<.0001

	Outcomes of interests					
	Pneumonia			Modified Rankin Scale		
	Yes	No		Poor outcome	Favourable outcome	
Baseline characteristics	(N=362)	(N=10731)	P-value	(N=3826)	(N=5922)	P-value
Pre-morbid mRS score*			<.0001			<.0001
0-1	214(59.2)	8521(79.6)		2580(67.6)	5134(86.8)	
2	50(13.9)	1099(10.3)		488(12.8)	517(8.7)	
3-5	97(26.9)	1090(10.1)		747(19.6)	263(4.5)	
Past medical history†	218 (60.2%)	5478 (51.0%)	0.0006	2315 (60.5%)	2715 (45.8%)	<.0001
History of COPD	27 (7.6%)	379 (3.6%)	<.0001	191 (5.0%)	157 (2.7%)	<.0001
Smoker	37 (10.5%)	2088 (19.7%)	<.0001	527 (14.0%)	1342 (22.9%)	<.0001

Data are n (%), mean±SD, or median (interquartile range)

GCS denotes Glasgow coma scale, mRS modified Rankin scale, NIHSS National Institute of Health Stroke Scale, COPD donates Chronic Obstructive Pulmonary Disease

*Pre-stroke grade function according to mRS scores (0=no symptoms, 1=symptoms, 2=disability but independence, 3-5= increasing grades of disability requiring assistance)

†includes history of heart disease, stroke or diabetes mellitus

‡NIHSS at admission: Pneumonia (missing value N=6), non-pneumonia (missing value N=156); Poor outcome (missing value N=64), favourable outcome (N=63).

Table S22: Hospital characteristics according to clinical outcomes at 90 days of follow up

	Outcomes of interests					
	Pneumonia			Modified Rankin Scale		
	Yes	No		Poor outcome	Favourable outcome	
Hospital characteristics	(N=362)	(N=10731)	P-value	(N=3828)	(N=5922)	P-value
Number of stroke patients admitted annually			<0.0001			<0.0001
<500	103 (28.5%)	2582 (24.4%)		1053 (27.9%)	1346 (23.1%)	
500-1000	175 (48.3%)	4115 (38.9%)		1578 (41.8%)	2090 (35.9%)	
>1000	84 (23.2%)	3880 (36.7%)		1146 (30.3%)	2386 (41.0%)	
Academic hospital	297 (82.0%)	9287 (86.5%)	0.014	3243 (84.8%)	5244 (88.6%)	<0.0001
Location of hospital			0.0004			0.22
Metropolitan or urban	263 (72.7%)	8553 (79.7%)		3010 (78.7%)	4740 (80.0%)	
Semi-metropolitan or semi-urban	84 (23.2%)	1975 (18.4%)		750 (19.6%)	1077 (18.2%)	
Rural or countryside	15 (4.1%)	203 (1.9%)		66 (1.7%)	105 (1.8%)	
Present of stroke unit	330 (91.2%)	9647 (91.1%)	0.96	3468 (91.6%)	5261 (90.3%)	0.039
Guidelines for acute treatment of stroke	341 (94.2%)	10080 (95.2%)	0.40	3612 (95.4%)	5520 (94.8%)	0.18

	Outcomes of interests					
	Pneumonia			Modified Rankin Scale		
	Yes	No		Poor outcome	Favourable outcome	
Hospital characteristics	(N=362)	(N=10731)	P-value	(N=3828)	(N=5922)	P-value
Local special pathway or service organisation for stroke care	332 (91.7%)	9641 (91.0%)	0.65	3496 (92.3%)	5203 (89.3%)	<0.0001
Local protocols for swallow dysfunction	338 (93.4%)	9780 (91.1%)	0.14	3454 (90.3%)	5384 (90.9%)	0.29
Available of neurologist	234 (64.6%)	7556 (70.4%)	0.018	2677 (70.0%)	4271 (72.1%)	0.022
Dysphagia specialist nurse	138 (38.1%)	3311 (30.9%)	0.0033	1225 (32.0%)	1810 (30.6%)	0.13
Speech language pathologist	308 (85.1%)	6250 (58.2%)	<0.0001	2429 (63.5%)	3114 (52.6%)	<0.0001

Data are n (%), Chi-square for P-value

Table S3. Baseline characteristics of 11,076 stroke patients according to use of dysphagia screen

Characteristic	Screened (N=8784)	Not screened (N=2292)	P Value
Age, yr	68±14	67±13	<0.0001
Male	5278 (60.1)	1379 (60.2)	0.95
Pathological subtype			
Ischaemic stroke	7466 (85.2)	1989 (87.1)	<0.0001
Intracerebral haemorrhage	703 (8.0)	226 (9.9)	
Uncertain	592 (6.8)	70 (3.1)	
GCS score	15 (14-15)	15 (13-15)	
Severe (3-8)	184 (2.1)	196 (8.6)	<0.0001
NIHSS score	4 (2-9)	4 (2-8)	
Severe ≥15	963 (11.1)	243 (10.9)	<0.0001
Pre-morbid mRS score*			
0-1	6980 (79.6)	1749 (76.3)	<0.0001
2	882 (10.1)	267 (11.7)	
3-5	907 (10.3)	276 (12.0)	
Prior cardiovascular disease risk†	4510 (51.3)	1182 (51.6)	0.85
Past history of COPD	329 (3.8)	76 (3.4)	0.38
Smoker	1736 (20.0)	387 (17.0)	0.0011

Data are n (%), mean±SD, or median (interquartile range); GCS denotes Glasgow coma scale, mRS modified Rankin scale, NIHSS National Institute of Health Stroke Scale, COPD donates Chronic Obstructive Pulmonary Disease; *Pre-morbid function according to mRS scores (0=no symptoms, 1=symptoms, 2=disability but independence, 3-5 increasing grades of disability requiring assistance); †includes history of heart disease, stroke or diabetes mellitus

Table S4 Error! Bookmark not defined.**: Admitted hospital characteristics of 11076 patients according to use of dysphagia screen**

Hospital characteristics	Screened (N=8784)	Not screened (N=2292)	P-value
More than 1000 stroke patients admitted annually	2944 (34.1%)	1015 (44.5%)	<.0001
Academic hospital	7545 (85.9%)	2028 (88.5%)	0.0013
Location of hospital			
Metropolitan or urban	6995 (79.6%)	1807 (78.8%)	0.042
Semi-metropolitan or semi-urban	1631 (18.6%)	425 (18.5%)	
Rural or countryside	158 (1.8%)	60 (2.6%)	
Present of stroke unit	8133 (94.0%)	1827 (79.9%)	<.0001
Guidelines for acute treatment of stroke	8262 (95.5%)	2142 (93.7%)	0.0002
Local special pathway or service organisation for stroke care	7895 (91.3%)	2061 (90.1%)	0.083
Local protocols for swallow dysfunction	8052 (91.7%)	2049 (89.4%)	0.0006
Available of neurologist	5897 (67.1%)	1890 (82.5%)	<.0001
Dysphagia specialist nurse	2565 (29.2%)	879 (38.4%)	<.0001
Speech language pathologist	5591 (63.6%)	950 (41.4%)	<.0001

Data are n (%), Chi-Square Test for p-value

Table S5 Error! Bookmark not defined.**: Admitted hospital characteristics of 11067 patients according to use of dysphagia assessment**

Hospital characteristics	Assessment N=3914	No assessment N=7153	P-value
More than 10000 stroke patients admitted annually	1250 (32.0%)	2708 (38.6%)	<.0001
Academic hospital	3342 (85.3%)	6230 (87.0%)	0.011
Location of hospital			
Metropolitan or urban	3057 (78.0%)	5743 (80.2%)	<.0001
Semi-metropolitan or semi-urban	717 (18.3%)	1339 (18.7%)	
Rural or countryside	143 (3.7%)	75 (1.0%)	
Present of stroke unit	3557 (90.9%)	6401 (91.1%)	0.73
Guidelines for acute treatment of stroke	3785 (96.8%)	6617 (94.2%)	<.0001
Local special pathway or service organisation for stroke care	3569 (91.3%)	6385 (90.9%)	0.55
Local protocols for swallow dysfunction	3797 (96.9%)	6302 (88.1%)	<.0001
Available of neurologist	2936 (75.0%)	4851 (67.8%)	<.0001
Dysphagia specialist nurse	1450 (37.0%)	1995 (27.9%)	<.0001
Speech language pathologist	2643 (67.5%)	3897 (54.5%)	<.0001

Data are n (%), Chi-Square Test for p-value

Table S6. Distribution of baseline characteristics by dysphagia assessment in 2,292 patients who did not have a dysphagia screen

Characteristic	Assessment N=739	No assessment N=1553	P Value
Age, yr	71±14	65±12	<0.0001
Male	406 (54.9)	973 (62.7)	<0.001
Pathological subtype			
Acute ischaemic stroke	635 (86.5)	1354 (87.3)	0.23
Intracerebral haemorrhage	70 (9.5)	156 (10.1)	
Uncertain	29 (4.0)	41 (2.6)	
GCS score	15 (14-15)	15 (13-15)	<0.0001
Severe (3-8)	20 (2.7)	176 (11.3)	
NIHSS score	6 (3-11)	3 (2-7)	<0.0001
Severe (≥15)	125 (17.1)	118 (7.9)	
Pre-morbid mRS score*			
0-1	504 (68.2)	1245 (80.2)	<0.0001
2	81 (11.0)	186 (12.0)	
3-5	154 (20.8)	122 (7.9)	
Feeding restriction	343 (46.4)	233 (15.0)	<0.0001

Data are n (%), mean±SD, or median (interquartile range); GCS denotes Glasgow coma scale, mRS modified Rankin scale, NIHSS National Institute of Health Stroke Scale; *Pre-morbid function according to mRS scores (0=no symptoms, 1=symptoms, 2=disability but independence, 3-5 increasing grades of disability requiring assistance)

Table S7. Distribution of baseline characteristics by dysphagia assessment in 2003 patients who failed a dysphagia screen

Characteristic	Assessment N=1402	No assessment N=601	*P* value
Age, yr	73.4±13.5	70.3±15.0	<0.0001
Male	721 (51.4)	341 (56.7)	0.03
Pathological subtype			
Acute ischaemic stroke	1213 (87.0)	501 (83.6)	0.01
Intracerebral haemorrhage	130 (9.3)	81 (13.5)	
Uncertain	52 (3.7)	17 (2.8)	
GCS score	15 (12-15)	14 (10-15)	
Severe (3-8)	49 (3.5)	68 (11.3)	<0.0001
NIHSS score	17 (10-22)	12 (7-19)	<0.0001
Severe (≥15)	461 (33.4)	244 (41.3)	<0.0001
Pre-morbid mRS score*			0.07
0-1	1028 (73.6)	445 (74.3)	
2	157 (11.2)	49 (8.2)	
3-5	212 (15.2)	105 (17.5)	
Feeding restrictions	1174 (83.7)	507 (84.4)	0.58

Data are n (%), mean±SD, or median (interquartile range); GCS denotes Glasgow coma scale, mRS modified Rankin scale, NIHSS National Institute of Health Stroke Scale; *Pre-morbid function according to mRS scores (0=no symptoms, 1=symptoms, 2=disability but independence, 3-5 increasing grades of disability requiring assistance)

Table S83. Baseline characteristics by neither screen nor assessment compared to undertake screened

Baseline characteristics	Neither screen nor assessed N=1553	Dysphagia screened N=8784	P-value
Age, yr	65.4±12.4	68.2±13.9	0.0014
Male	973 (62.7%)	5278 (60.1%)	0.06
Region			<.0001
Australia and UK	149 (9.6%)	4338 (49.4%)	
China and Taiwan	1275 (82.1%)	3218 (36.6%)	
India and Sri Lanka	99 (6.4%)	670 (7.6%)	
South America	30 (1.9%)	558 (6.4%)	
Past medical history	777 (50.0%)	4510 (51.3%)	0.3407
Stroke category			<.0001
Acute ischaemic stroke	1354 (87.3%)	7466 (85.2%)	
Intracerebral haemorrhage	156 (10.1%)	703 (8.0%)	
Uncertain	41 (2.6%)	592 (6.8%)	
NIHSS at admission	3.0 (2.0, 7.0)	4.0 (2.0, 9.0)	<0.0001
Severe ($\geq$15)	118(7.9)	963 (11.1)	0.0002
GCS score at admission	15.0 (13.0, 15.0)	15.0 (14.0, 15.0)	<0.0001
Severe (3-8)	176 (11.3)	184 (2.1)	<0.0001
Pre-morbid function*			0.0016
0-1	1245 (80.2)	6980 (79.6)	
2	186 (12.0)	882 (10.1)	
3-5	122 (7.8)	907 (10.3)	
History of COPD	36 (2.3%)	329 (3.8%)	0.0049
Smoker	292 (18.9%)	1736 (20.0%)	0.3061
Feeding restrictions	233 (15.1%)	2431 (27.9%)	<.0001

Data are n (%), mean±SD, or median (interquartile range); GCS denotes Glasgow coma scale, mRS modified Rankin scale, NIHSS National Institute of Health Stroke Scale; *Pre-morbid function according to mRS scores (0=no symptoms, 1=symptoms, 2=disability but independence, 3-5 increasing grades of disability requiring assistance)

Table S9. Outcomes, by region of recruitment, according to use of dysphagia screen, dysphagia assessment, and feeding restriction

Variable	Pneumonia			Poor outcome*		
	n/N (%)		P Value	n/N (%)		P Value
Overall	362/11093 (3.3)			3826/9748 (39.3)		
Region of recruitment						
Australia/UK	228/4761 (4.8)		<0.0001	1687/3852 (43.8)		<0.0001
China†	49/4652 (1.1)			1284/4347 (29.5)		
India/Sri Lanka	26/770 (3.4)			411/694 (59.2)		
South America	59/910 (6.5)			444/855 (51.9)		
Dysphagia screen performed						
Yes	304/8784 (3.5)		0.03	3018/7675 (39.3)		0.72
No	58/2292 (2.5)			801/2060 (38.9)		
Dysphagia screen						
Pass	103/6778 (1.5)		<0.0001	1820/5913 (30.8)		<0.0001
Fail	201/2004 (10.0)			1198/1760 (68.1)		
Dysphagia assessment performed						
Yes	206/3917 (5.3)		<0.0001	1661/3495 (47.5)		<0.0001
No	156/7157 (2.2)			2157/6239 (34.6)		
Dysphagia assessment results						
Pass	72/2895 (2.5)		<0.0001	988/2605 (37.9)		<0.0001
Fail	134/1018 (13.2)			671/886 (40.5)		
Feeding restriction						
Yes	286/3007 (9.5)		<0.0001	1775/2627 (67.6)		<0.0001
No	73/8000 (0.9)			2022/7044 (28.7)		
Time to dysphagia screen, hrs						
<4	244/5258 (3.0)		0.001	1629/4602 (35.4)		<0.0001
4-24	80/2195 (3.6)			813/1894 (42.9)		
>24	38/667 (5.7)			345/609 (56.7)		

*defined by scores 3-6 on the modified Rankin scale at 90 days

†includes Taiwan

Table S10. Frequency and timing of dysphagia screen and assessment in stroke patients by outcomes

Outcome	Dysphagia screen performed			Dysphagia assessment performed		
		Time from hospital arrival			Time from hospital arrival	
	N (%)	Median (IQR), hr	P Value*	N (%)	Median (IQR), hr	P Value*
Pneumonia						
Yes (N=362)	304 (84.0)	3.0 (1.0-11.4)	<0.0001	206 (56.9)	25.3 (15.1-51.6)	<0.0001
No (N=10714)	8480 (79.2)	2.2 (0.8-6.3)		3711 (34.6)	11.0 (1.7-26.9)	
Clinical outcome						
Favourable (N=5922)†	4657 (78.6)	1.9 (0.8-5.2)	<0.0001	1834 (31.0)	4.6 (1.2-22.3)	<0.0001
Poor (N=3826)‡	3018 (79.0)	2.7 (1.0-10.3)		1661 (43.5)	19.3 (4.2-40.9)	

*P value for time from hospital arrival, obtained from Mann Whitney Test (Wilcoxon rank sum test); †Favourable outcome refers to modified Rankin Scores (mRS) 0 to 2 at 90-day; ‡Poor outcome refers to mRS 3-6 at 90-day

Table S11. Distribution of baseline characteristics, by 90-day outcome data

Characteristic	mRS Available N=9748 (88%)	Outcome at 90-day Missing N=1345 (12%)	P Value
Age, yr	69±14	67±15	<0.01
Male	5889 (60.4)	775 (57.6)	0.05
Pathological subtype			
Ischaemic stroke	8369 (86.1)	1098 (81.9)	<0.0001
Intracerebral haemorrhage	818 (8.4)	112 (8.4)	
Uncertain stroke	533 (5.5)	130 (9.7)	
GCS score	15 (14-15)	15 (14-15)	0.15
Severe (3-8)	335 (3.4)	45 (3.4)	0.86
NIHSS score	4 (2-8)	4 (2-9)	<0.01
Severe≥15	1057 (11.0)	150 (11.5)	0.71
Pre-morbid mRS score*			
0-1	7714 (79.3)	1021 (76.1)	<0.0001
2	1005 (10.3)	144 (12.5)	
3-5	1010 (10.4)	177 (13.2)	
Prior cardiovascular disease risk†	5030 (51.6)	666 (49.5)	0.15
Prior COPD	348 (3.6)	58 (4.4)	0.16
Feeding restrictions	2627 (27.2)	380 (28.4)	0.33
Time to screen, hrs	2.1 (0.8-6.5)	2.4 (0.9-5.8)	0.81
>24	609 (8.6)	58 (5.7)	<0.01
Outcome of pneumonia	325 (3.3)	37 (2.8)	0.26

Data are n (%), mean±SD, or median (interquartile range); GCS denotes Glasgow coma scale, mRS modified Rankin scale, NIHSS National Institute of Health Stroke Scale; *Pre-morbid function according to mRS scores (0=no symptoms, 1=symptoms, 2=disability but

independence, 3-5 increasing grades of disability requiring assistance); †includes history of heart disease, stroke or diabetes mellitus

Table S12: Clinical outcomes by feeding restrictions in 2253 patients failed screen or assessment

Clinical outcomes	No feeding (N=339)	Feeding restriction (N=1910)	P-value
Pneumonia	6 (1.8)	227 (11.9)	<0.0001
Poor outcome	126 (41.9)	1238 (74.0)	<0.0001

Data are n (%), Chi-square P-value

Table S13. Feeding practices by region of recruitment in 2000 stroke patients who failed dysphagia screen

Region of recruitment	Use of feeding restriction N (%)		Feeding practice N (%)			
	No	Yes	Nil by mouth	IV fluids	Soft/puree diet	NG tube
Overall (N=2000)	319 (16.0)	1681 (84.0)	633 (37.7)	352 (20.9)	539 (32.1)	829 (49.3)
Region						
Australia/UK (N=1212)	219 (18.1)	993 (81.9)	537 (54.1)	300 (30.2)	442 (44.5)	322 (32.4)
China*(N=319)	75 (23.5)	244 (76.5)	1 (0.4)	7 (2.9)	21 (8.6)	143 (58.6)
India / Sri Lanka (N=257)	7 (2.7)	250 (97.3)	72 (28.8)	36 (14.4)	13 (5.2)	235 (94.0)
South America (N=212)	18 (8.5)	194 (91.5)	23 (11.9)	9 (4.6)	63 (32.5)	129 (66.5)

IV denotes intravenous, NG nasogastric tube

*includes Taiwan

Table S14 Error! Bookmark not defined.**: Baseline characteristics by use of dysphagia assessment in patients passed screen**

Baseline characteristics	Assessment (N=1775)	No assessment (N=5000)	P-value
Age (years)	66.8±13.2	66.9±13.8	0.63
Male	1124 (63.3%)	3089 (61.8%)	0.25
Country group			<0.0001
Australia and UK	438 (24.7%)	2679 (53.6%)	
China and Taiwan	1149 (64.7%)	1750 (35.0%)	
India and Sri Lanka	94 (5.3%)	319 (6.4%)	
South America	94 (5.3%)	252 (5.0%)	
Pathological subtype			<.0001
Acute ischaemic stroke	1552 (87.4%)	4195 (84.1%)	
Intracerebral haemorrhage	141 (7.9%)	350 (7.0%)	
Uncertain	82 (4.6%)	441 (8.8%)	
Prior cardiovascular disease risk	904 (50.9%)	2467 (49.3%)	0.25
NIHSS score	3 (2-6)	4 (2-6)	0.15
Severe ($\geq$15)	78(4.4)	180(3.6)	0.13
GCS score	15(14-15)	15(15-15)	<0.0001
Severe (3-8)	23(1.3)	44(0.9)	0.13
Pre-morbid mRS score*			0.11
0-1	1112(63.0)	3043(61.6)	
2	574(32.5)	1721(34.8)	
3-5	78(4.4)	180(3.6)	
History of COPD	40 (2.3%)	198 (4.0%)	0.0008
Smoker	420 (23.8%)	1020 (20.6%)	0.0054
Feeding restriction	234 (13.2%)	515 (10.4%)	0.0013

Data are n (%), mean±SD, or median (interquartile range); GCS denotes Glasgow coma scale, mRS modified Rankin scale, NIHSS National Institute of Health Stroke Scale; *Pre-morbid score according to mRS scores (0=no symptoms, 1=symptoms, 2=disability but independence, 3-5 increasing grades of disability requiring assistance).

Table S15. Distribution of baseline characteristics of 3913 stroke patients, according to results of dysphagia assessment

| Characteristic | Dysphagia assessment | | P Value |
	Pass N=2895	Fail N=1018	
Age, yr	69±13.7	74±13.3	<0.0001
Male	1732(59.8)	517(50.8)	
Pathological subtype			
Ischaemic stroke	2499(86.5)	898(88.7)	<0.0001
Intracerebral haemorrhage	241(8.3)	100(9.9)	
Uncertain	148(5.1)	15(1.5)	
GCS score	15(14-15)	14(11-15)	<0.0001
Severe (3-8)	33(1.1)	59(5.8)	<0.0001
NIHSS score	4(2-8)	12(7-19)	<0.0001
Severe ≥15	240(8.3)	425(41.8)	<0.0001
Pre-morbid mRS score*			
0-1	2297(79.3)	712(69.9)	<0.0001
2	272(9.4)	124(12.2)	
3-5	319(11.0)	181(17.8)	
Prior cardiovascular disease risk†	1527(52.8)	567(55.7)	0.10
Feeding restrictions	792(27.4)	1017(94.1)	<0.0001

Data are n (%), mean±SD, or median (interquartile range); GCS denotes Glasgow coma scale, mRS modified Rankin scale, NIHSS National Institute of Health Stroke Scale; *Pre-morbid function according to mRS scores (0=no symptoms, 1=symptoms, 2=disability but independence, 3-5 increasing grades of disability requiring assistance); †includes history of cardiac disease, stroke or diabetes mellitus

Table S16: Baseline characteristics of patients in 5290 lying-flat head position by dysphagia screen

Characteristic	No screen (N=1072)	Screen (N=4218)	*P* value
Age, yr	67±13.1	69±14.1	0.02
Male	644(60.1)	2508(59.5)	0.71
Pathological subtype			
Ischaemic stroke	944(88.3)	3577(85.1)	<0.001
Intracerebral haemorrhage	92(8.6)	327(7.8)	
Uncertain	33(3.1)	303(7.2)	
GCS score	15(13-15)	15(14-15)	<0.0001
Severe (3-8)	99(9.2)	86(2.0)	<0.0001
NIHSS score	4(2-9)	4(2-9)	0.40
Severe≥15	126(11.5)	468(11.2)	0.17
Pre-morbid mRS score*			
0-1	839(78.3)	3365(80.0)	0.46
2	116(10.8)	417(9.9)	
3-5	117(10.9)	426(10.1)	
History of cardiovascular disease risk†	567(52.9)	2107(50.0)	0.09

Data are n (%), mean±SD, or median (interquartile range).

GCS denotes Glasgow coma scale, mRS modified Rankin scale, NIHSS National Institute of Health Stroke Scale.

*mRS modified Rankin scale (0=no symptoms, 1=symptoms, 2=disability but independence, 3-5 increasing grades of disability requiring assistance)

†includes history of cardiac disease, stroke or diabetes mellitus

Figure S1. Patient Flow

Patients flow of receiving dysphagia screening and assessment in the HeadPoST study
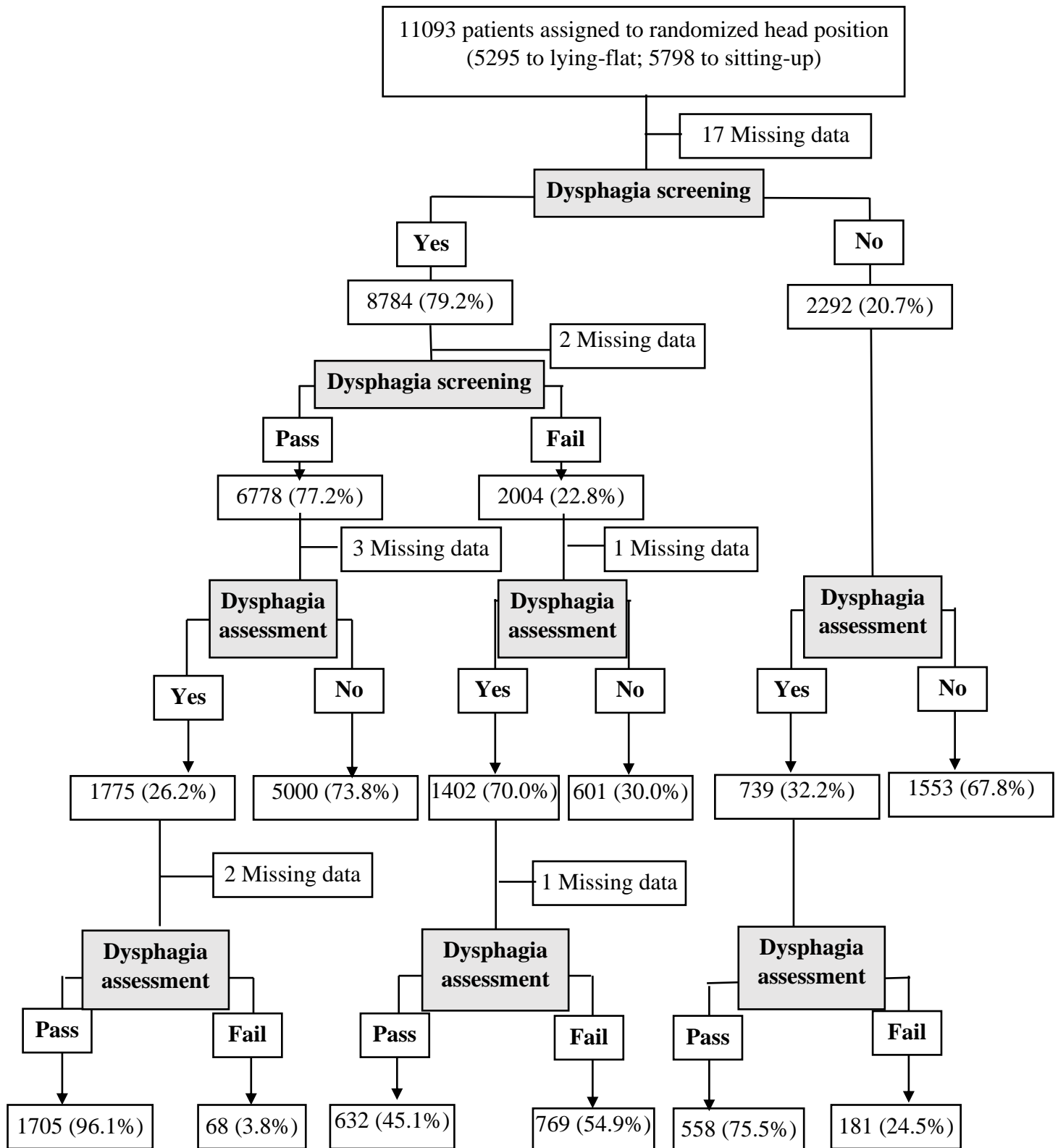
Figure S2. Effect of use of dysphagia assessment on clinical outcomes, by utility and results of dysphagia screen
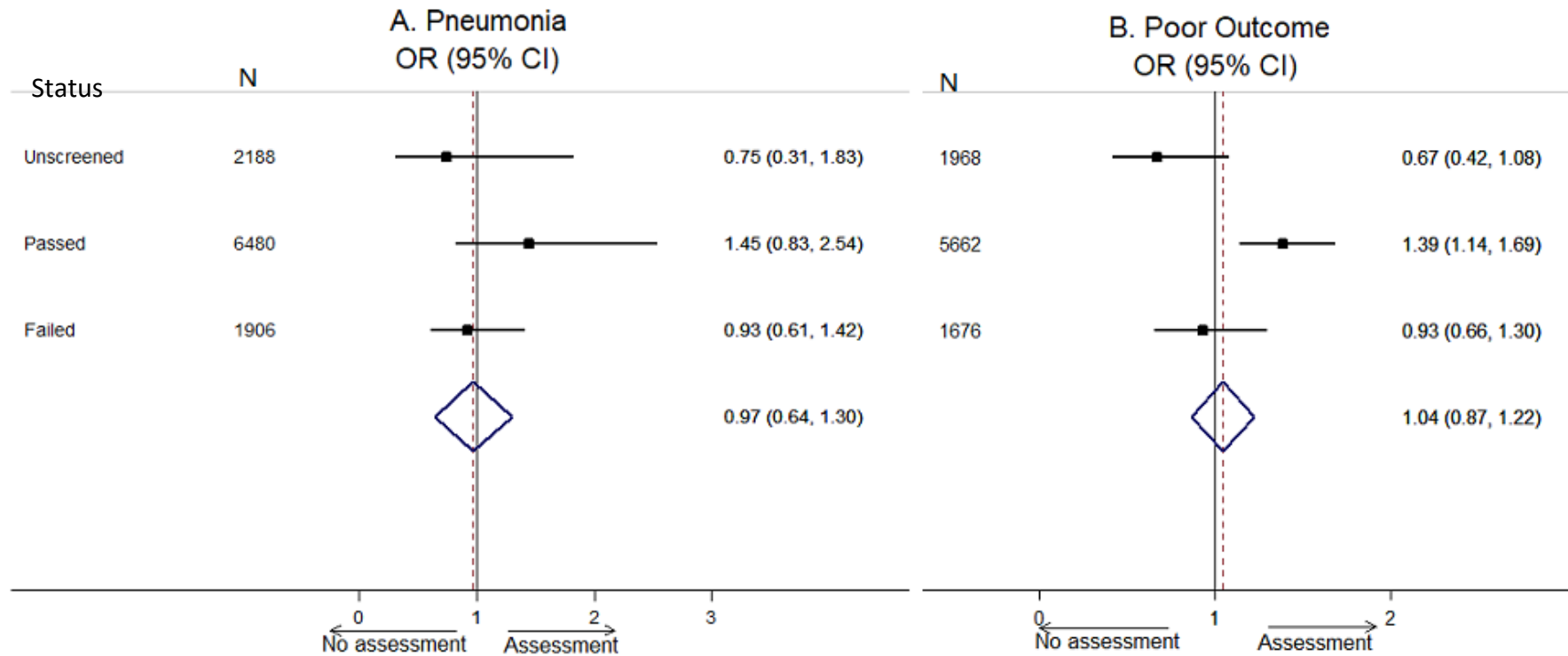
Status donates the utility of dysphagia screen; N donates the number of patients in each status

Poor outcome is death or disability at 90-day according to scores 3-6 on the modified Rankin scale

Hierarchical mixed models used in analyses

Figure S3. Effects of dysphagia assessment results on poor outcome stratified by country groups in 5662 patients passed screen
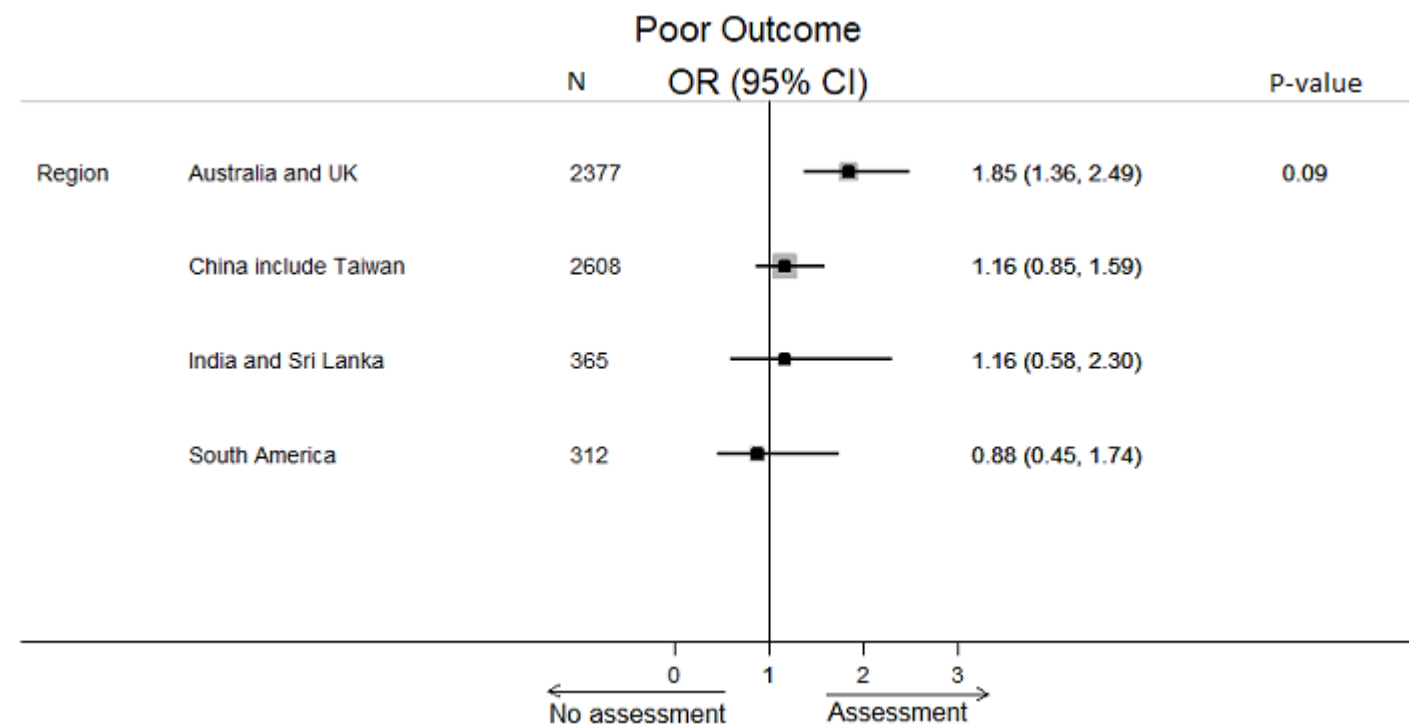
N donates the number of patients in each status

Poor outcome is death or disability at 90-day according to scores 3-6 on the modified Rankin scale

Hierarchical mixed models used in analyses

Figure S4. Effects of dysphagia assessment results on clinical outcomes
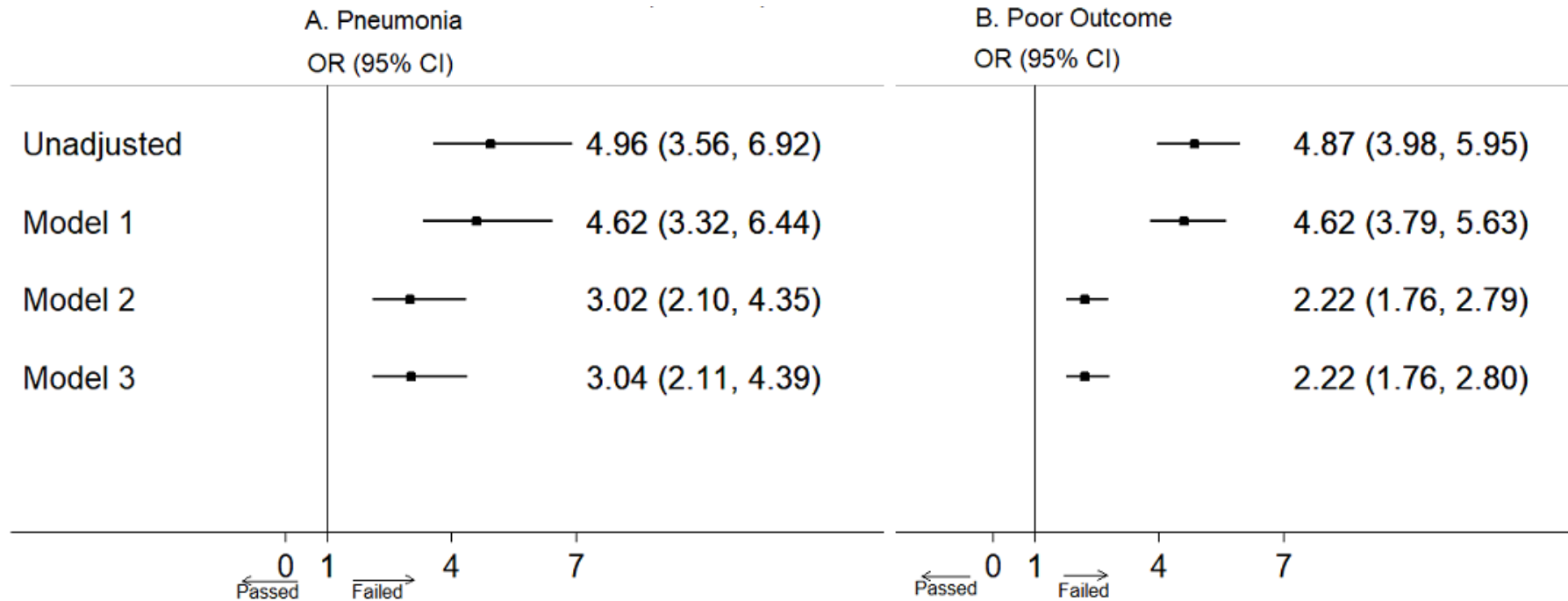
N donates the number of patients in each subgroup, Passed donates passed assessment, Failed donates failed assessment

Poor outcome is death or disability at 90-day according to scores 3-6 on the modified Rankin scale

Passed donates passed dysphagia assessment, Failed donates failed dysphagia assessment

Hierarchical mixed models used in analyses

Figure S5. Effects of use of dysphagia screen on pneumonia in 10579 patients by pre-defined subgroups
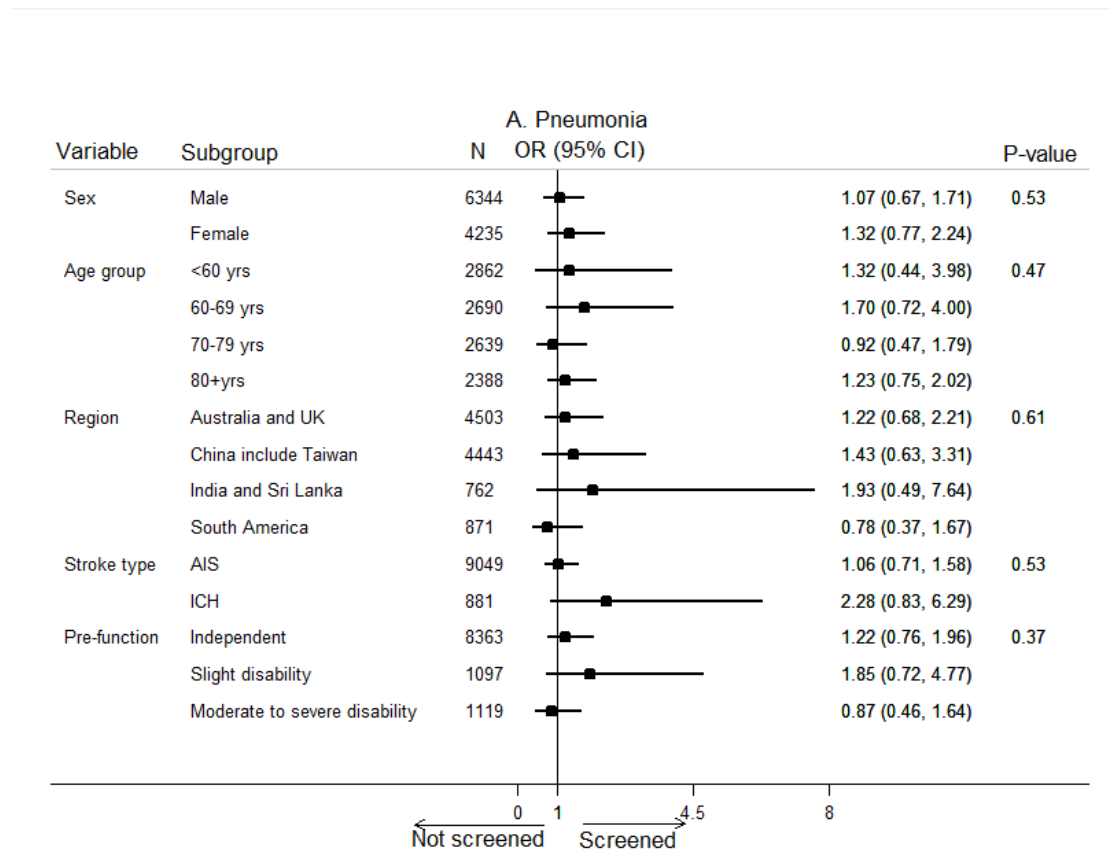
Variable	Subgroup	N	A. Pneumonia OR (95% CI)	P-value
Sex	Male	6344	1.07 (0.67, 1.71)	0.53
	Female	4235	1.32 (0.77, 2.24)	
Age group	<60 yrs	2862	1.32 (0.44, 3.98)	0.47
	60-69 yrs	2690	1.70 (0.72, 4.00)	
	70-79 yrs	2639	0.92 (0.47, 1.79)	
	80+yrs	2388	1.23 (0.75, 2.02)	
Region	Australia and UK	4503	1.22 (0.68, 2.21)	0.61
	China include Taiwan	4443	1.43 (0.63, 3.31)	
	India and Sri Lanka	762	1.93 (0.49, 7.64)	
	South America	871	0.78 (0.37, 1.67)	
Stroke type	AIS	9049	1.06 (0.71, 1.58)	0.53
	ICH	881	2.28 (0.83, 6.29)	
Pre-function	Independent	8363	1.22 (0.76, 1.96)	0.37
	Slight disability	1097	1.85 (0.72, 4.77)	
	Moderate to severe disability	1119	0.87 (0.46, 1.64)	

N donates number of patients in each subgroup

NIHSS donates National Institute of Health Stroke Scale, AIS acute ischaemic stroke, ICH intracerebral haemorrhage, Pre-function refers to grade of pre-morbid physical function on the modified Rankin scale where 0-1 = independent, 2= mild disability but independent, and 3-5 = increasing grades of disability and dependence on others for care

Hierarchical mixed models were used in analyses

Figure S6. Effects of use of dysphagia screen on poor outcome (death and disability) at 90-day in 9310 patients by pre-defined subgroups

Variable	Subgroup	N	B. Poor Outcome OR (95% CI)	P-value
Sex	Male	5604	0.92 (0.76, 1.12)	0.55
	Female	3706	0.99 (0.79, 1.25)	
Age group	<60 yrs	2453	0.97 (0.73, 1.28)	0.20
	60-69 yrs	2417	0.80 (0.62, 1.04)	
	70-79 yrs	2341	0.96 (0.74, 1.26)	
	80+yrs	2099	1.13 (0.84, 1.52)	
Region	Australia and UK	3656	0.87 (0.62, 1.23)	0.77
	China include Taiwan	4147	0.92 (0.73, 1.16)	
	India and Sri Lanka	689	1.05 (0.57, 1.93)	
	South America	818	1.13 (0.75, 1.70)	
NIHSS at baseline	0-4	4945	0.98 (0.80, 1.22)	0.59
	5-42	4365	0.92 (0.74, 1.13)	
Stroke type	AIS	8012	0.93 (0.78, 1.11)	0.77
	ICH	773	1.03 (0.67, 1.58)	
Pre-function	Independent	7391	0.90 (0.75, 1.07)	0.21
	Slight disability	962	1.09 (0.74, 1.59)	
	Moderate to severe disability	957	1.31 (0.84, 2.03)	
Past history	Yes	4807	1.07 (0.88, 1.31)	0.55
	No	4503	0.82 (0.66, 1.01)	

Not screened ← 0 — 1 — 1.5 — 3 → Screened

Poor outcome is death or disability at 90-day according to scores 3-6 on the modified Rankin scale

N donates number of patients in each subgroup

NIHSS donates National Institute of Health Stroke Scale, AIS acute ischaemic stroke, ICH intracerebral haemorrhage

Pre-function refers to grade of pre-morbid physical function on the modified Rankin scale where 0-1 = independent, 2= slight disability but independent, and 3-5 = moderate to severe disability

Hierarchical mixed models were used in analyses

Figure S7. Effects of use of dysphagia screen on the clinical outcomes, according to head position
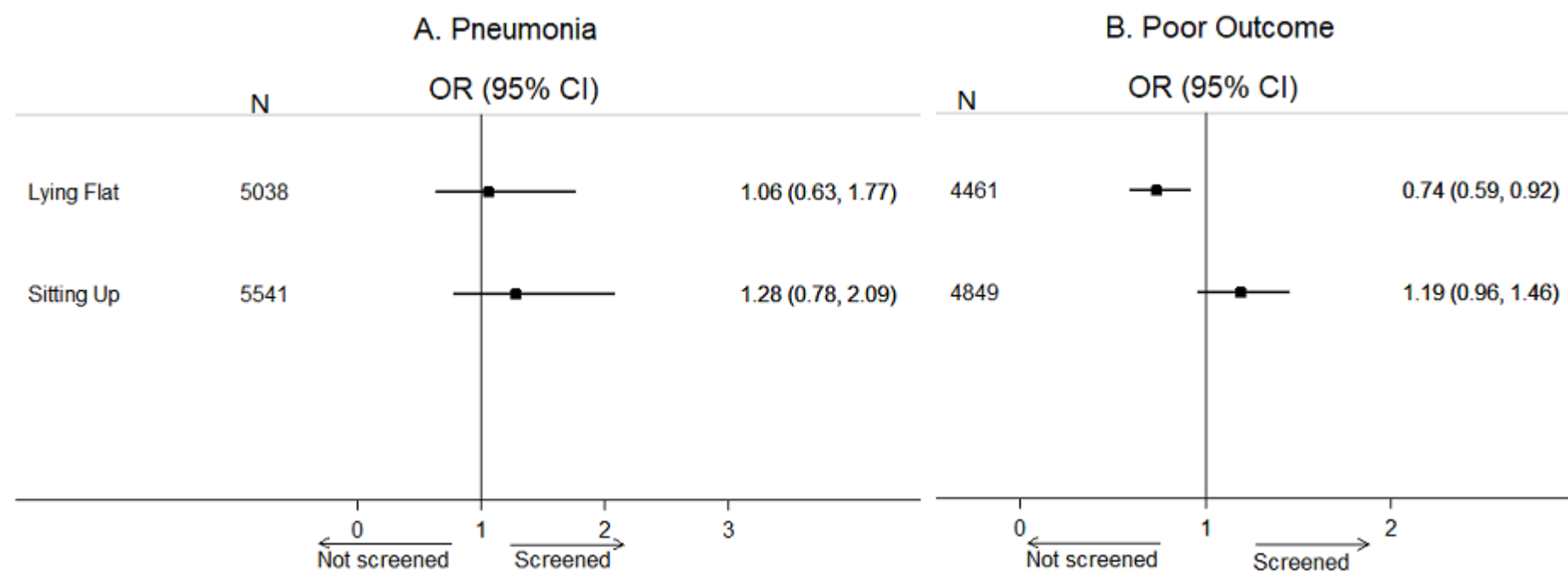
A. Pneumonia

	N	OR (95% CI)
Lying Flat	5038	1.06 (0.63, 1.77)
Sitting Up	5541	1.28 (0.78, 2.09)

B. Poor Outcome

	N	OR (95% CI)
Lying Flat	4461	0.74 (0.59, 0.92)
Sitting Up	4849	1.19 (0.96, 1.46)

N donates the number of patients in each head position subgroup

Poor outcome is death or disability at 90-day according to scores 3-6 on the modified Rankin scale

Hierarchical mixed models used in analyses

Figure S8. Effects of dysphagia screen on pneumonia in 8390 patients in pre-defined subgroups
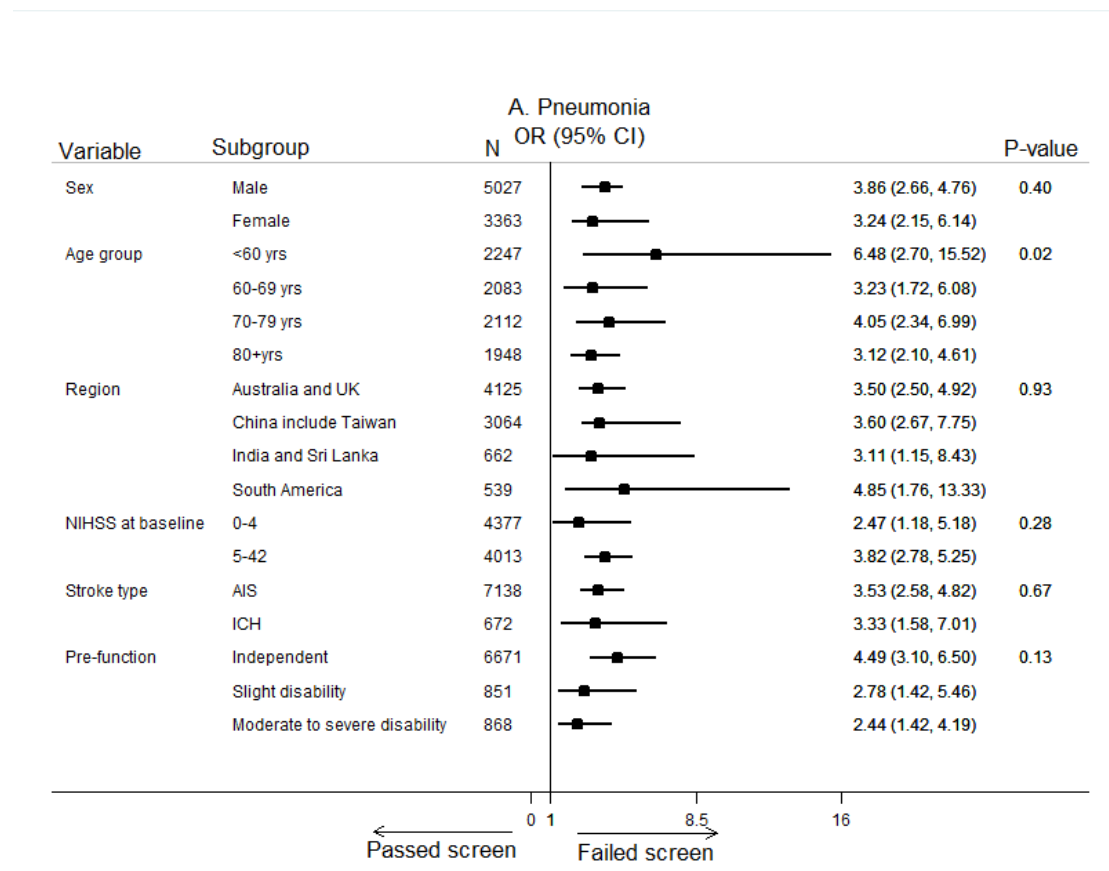
Variable	Subgroup	N	A. Pneumonia OR (95% CI)	P-value
Sex	Male	5027	3.86 (2.66, 4.76)	0.40
	Female	3363	3.24 (2.15, 6.14)	
Age group	<60 yrs	2247	6.48 (2.70, 15.52)	0.02
	60-69 yrs	2083	3.23 (1.72, 6.08)	
	70-79 yrs	2112	4.05 (2.34, 6.99)	
	80+yrs	1948	3.12 (2.10, 4.61)	
Region	Australia and UK	4125	3.50 (2.50, 4.92)	0.93
	China include Taiwan	3064	3.60 (2.67, 7.75)	
	India and Sri Lanka	662	3.11 (1.15, 8.43)	
	South America	539	4.85 (1.76, 13.33)	
NIHSS at baseline	0-4	4377	2.47 (1.18, 5.18)	0.28
	5-42	4013	3.82 (2.78, 5.25)	
Stroke type	AIS	7138	3.53 (2.58, 4.82)	0.67
	ICH	672	3.33 (1.58, 7.01)	
Pre-function	Independent	6671	4.49 (3.10, 6.50)	0.13
	Slight disability	851	2.78 (1.42, 5.46)	
	Moderate to severe disability	868	2.44 (1.42, 4.19)	

N donates the number of patients in each subgroup

NIHSS donates National Institute of Health Stroke Scale, AIS acute ischaemic stroke, ICH intracerebral haemorrhage

Pre-function refers to grade of pre-morbid physical function on the modified Rankin scale where 0-1 = independent, 2= slight disability but independent, and 3-5 = moderate to severe disability

Hierarchical mixed models were used in analyses

Figure S9. Effects of dysphagia screen on poor outcome at 90-day in 7341 patients according to pre-defined subgroups

Variable	Subgroup	N	OR (95% CI)	P-value
Sex	Male	4417	1.68 (1.37, 2.06)	0.84
	Female	2924	1.63 (1.30, 2.06)	
Age group	<60 yrs	1900	1.30 (0.95, 1.80)	0.01
	60-69 yrs	1853	1.46 (1.08, 1.97)	
	70-79 yrs	1872	2.03 (1.53, 2.69)	
	80+yrs	1716	1.75 (1.32, 2.32)	
Region	Australia and UK	3345	1.67 (1.35, 2.06)	0.68
	China include Taiwan	2895	1.88 (1.37, 2.59)	
	India and Sri Lanka	596	1.42 (0.91, 2.23)	
	South America	505	1.39 (0.81, 2.37)	
NIHSS at baseline	0-4	3836	1.69 (1.28, 2.24)	0.01
	5-42	3505	1.65 (1.36, 1.90)	
Stroke type	AIS	6296	1.63 (1.37, 1.93)	0.69
	ICH	577	1.73 (1.05, 2.84)	
Pre-function	Independent	5868	1.54 (1.29, 1.84)	0.04
	Slight disability	740	3.11 (1.87, 5.17)	
	Moderate to severe disability	733	1.73 (1.04, 2.88)	
Past history	Yes	3788	1.68 (1.37, 2.06)	0.87
	No	3553	1.63 (1.31, 2.05)	

B. Poor Outcome

Passed screen ← 0 1   4   7 → Failed screen

N donates the number of patients in each subgroup

Poor outcome is death or disability at 90-day according to scores 3-6 on the modified Rankin scale

NIHSS donates National Institute of Health Stroke Scale, AIS acute ischaemic stroke, ICH intracerebral haemorrhage.

Pre-function refers to grade of pre-morbid physical function on the modified Rankin scale where 0-1 = independent, 2= slight disability but independent, and 3-5 = moderate to severe disability

Hierarchical mixed models were used in analyses

Figure S10. Effects of dysphagia screen results on clinical outcomes, according to head position
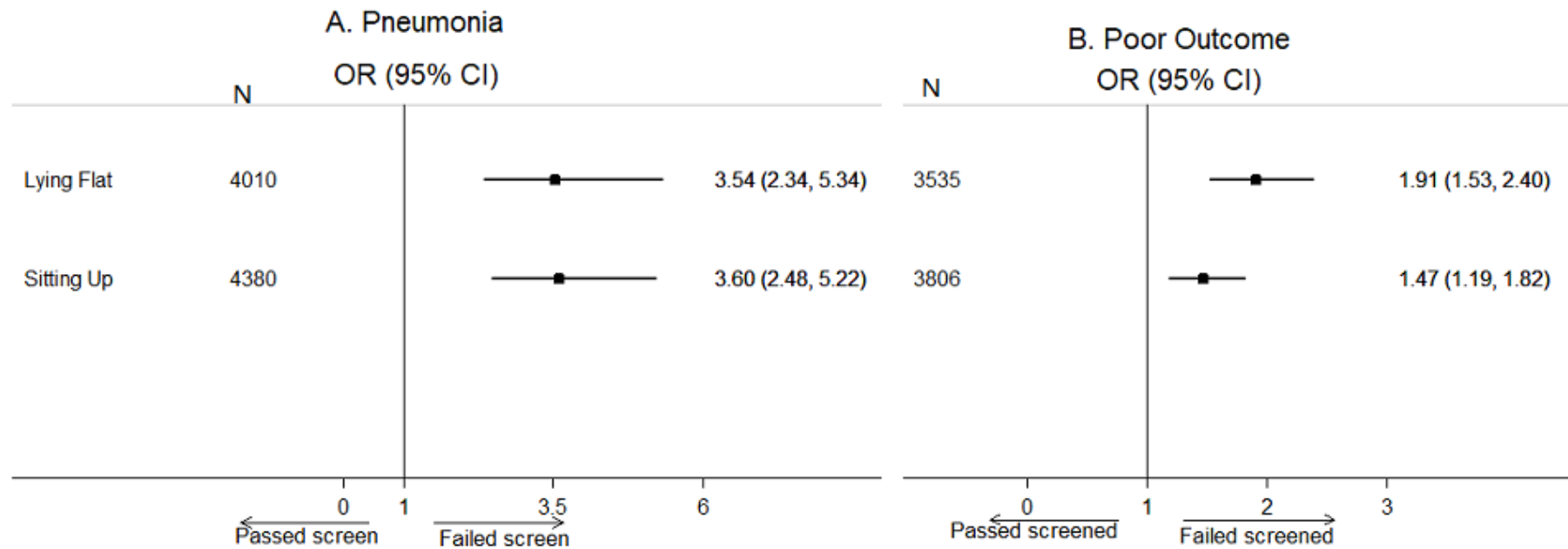
N donates the number of patients in each head position subgroup

Poor outcome is death or disability according to scores 3-6 on the modified Rankin scale

Hierarchical mixed models were used in analyses

Figure S11. Effects of use feeding restrictions on clinical outcomes in patients either failed dysphagia screen or assessment
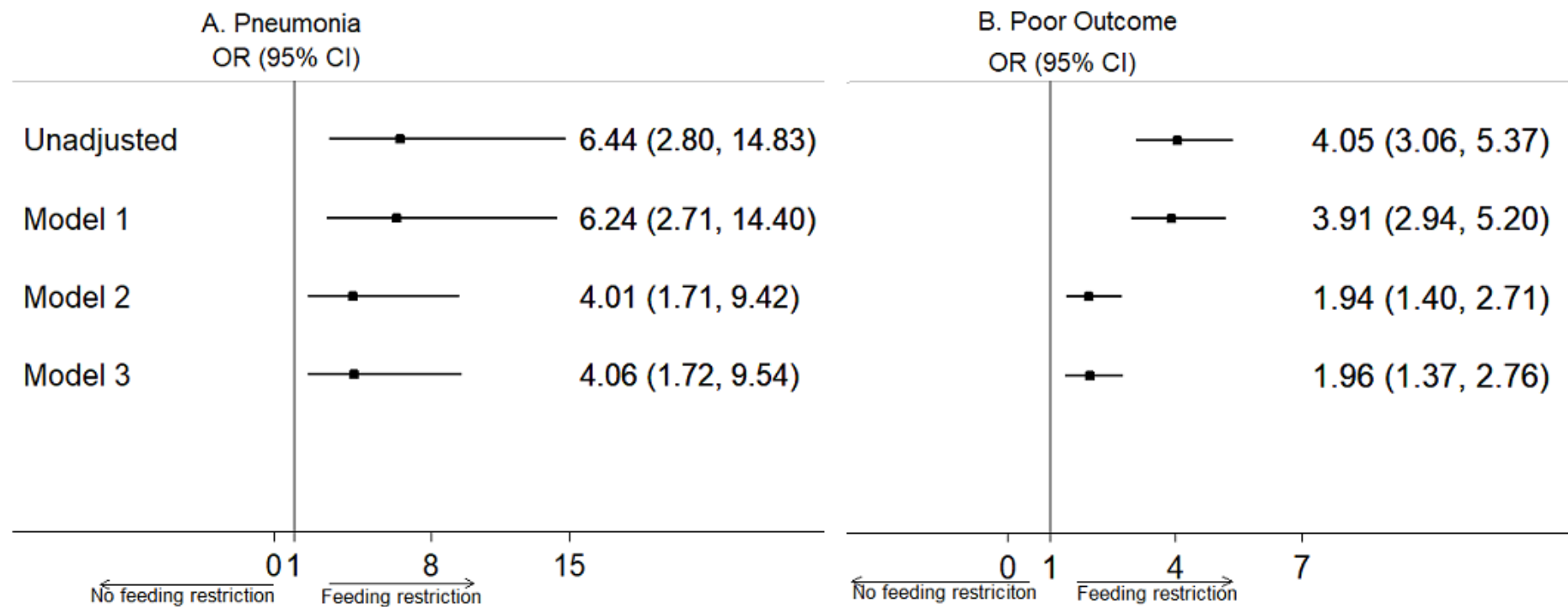
Poor outcome is death or disability according to scores 3-6 on the modified Rankin scale

Hierarchical mixed models were used in analyses

Figure S12. Multiple imputation analysis for effect of use of dysphagia screen on clinical outcomes
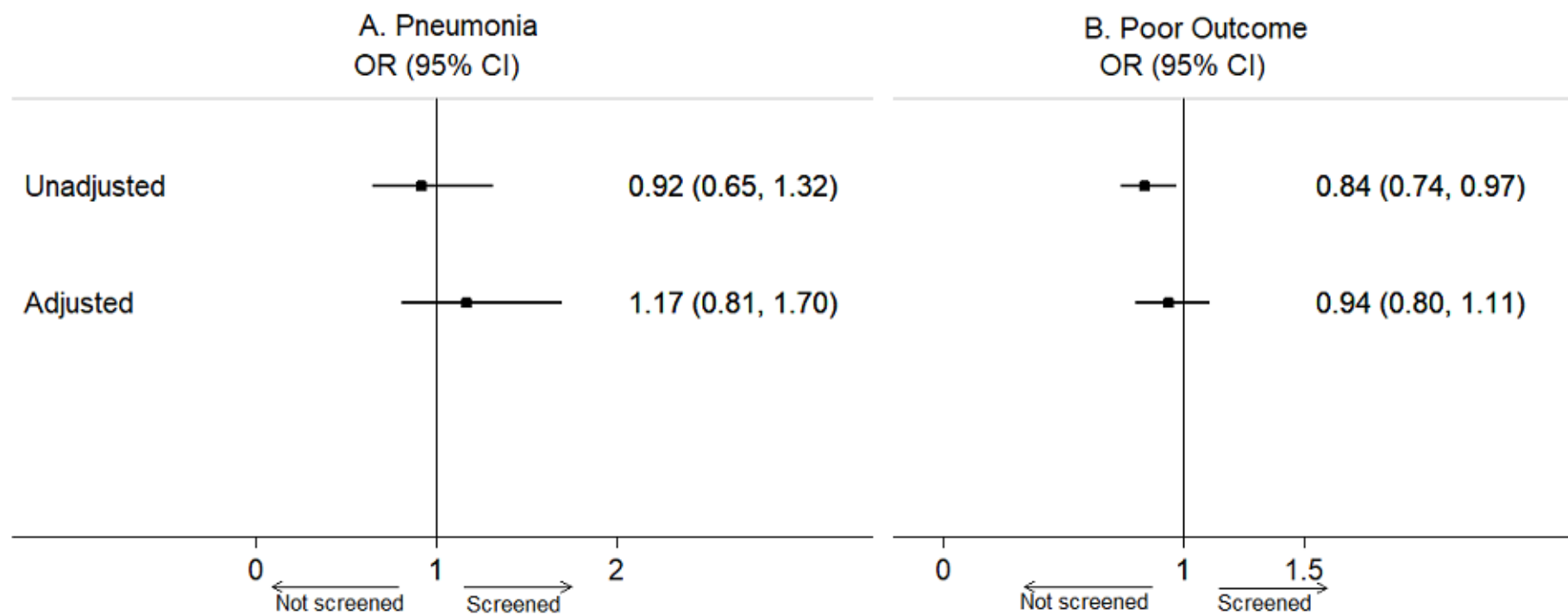
Poor outcome is death or disability according to scores 3-6 on the modified Rankin scale

Hierarchical mixed models were used in analyses

Figure S13. Multiple imputation analysis for effect of dysphagia screen results on clinical outcomes
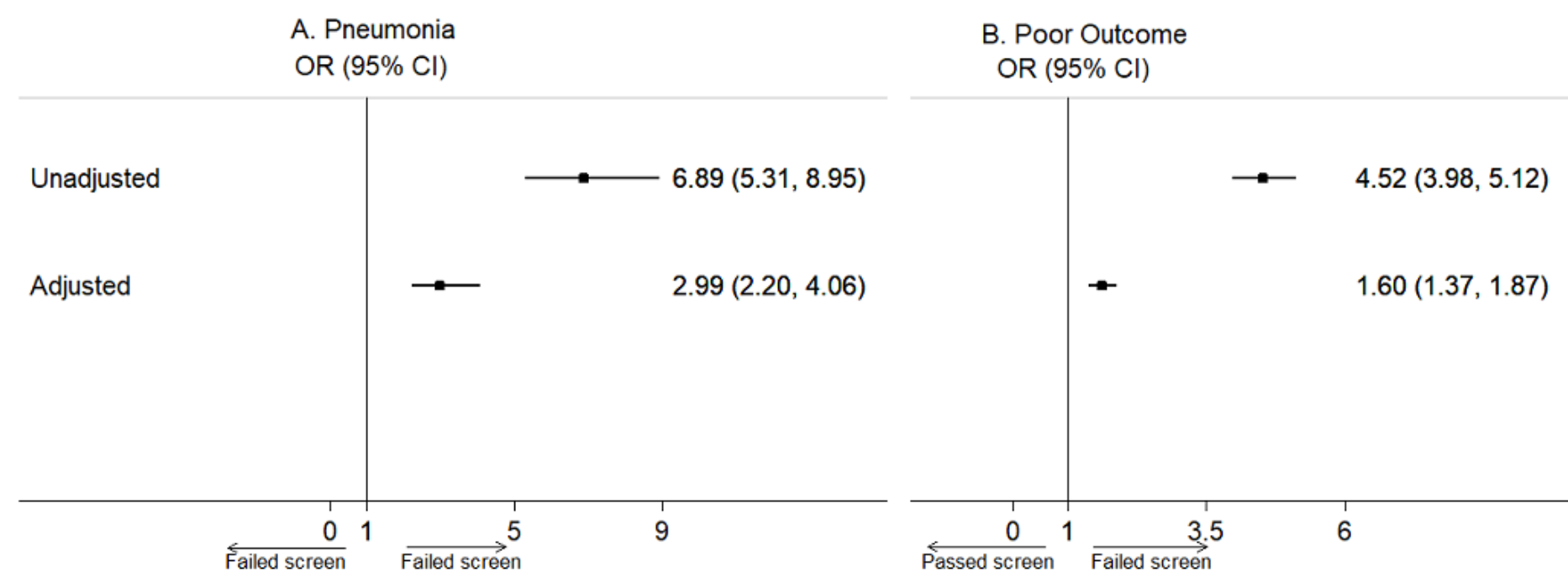
Poor outcome is death or disability according to scores 3-6 on the modified Rankin scale

Hierarchical mixed models were used in analyses

Supplementary Appendix of Chapter 2.2

Prognostic significance of urinary catheterisation after acute stroke: secondary analyses of the HeadPoST trial

Ouyang M, Billot L, Song L, Xia W, Roffe C et al.

Supplemental tables: 7

Supplemental figures: 4

Multiple imputation method

Multiple imputation was used to impute missing outcome data, using PROC MI and PROC MIANALYZE in SAS version 9.2 (or later) software. Multiple imputation is generally considered the least biased method since it incorporates uncertainty to the imputed value, and a non-monotone missing pattern is assumed modified Rankin Scale (mRS) score at 90 days for urinary tract infection (UTI). A distribution for the outcome was derived from a regression model that accounts for covariates (listed in the hierarchical mixed model) and a random sample from this distribution was used to impute values for missing outcomes. Ten multiple sample data sets with complete outcome data were generated through PROC MI, and the results (regression parameter and covariance matrix estimates) for each sample combined and analysed with PROC MIANALYZE to derive a valid statistical inference about the association with outcomes.

Table S1. Characteristics of patients by modified Rankin scale (mRS) score at 90 days

Characteristic	Poor outcome (mRS 3-6) N=3826	Favourable outcome (mRS 0-2) N=5922	P value‡
Age (years)	72.8±13.2	65.1±13.0	<0.0001
Male	2023 (52.9)	3866 (65.3)	<0.0001
Region			<0.0001
Australia and UK	1687 (44.1)	2165 (36.6)	
China and Taiwan	1284 (33.6)	3063 (51.7)	
India and Sri Lanka	411 (10.7)	283 (4.8)	
South America	444 (11.6)	411 (6.9)	
Hypertension	2119 (55.4)	2876 (48.6)	0.0008
Previous stroke	619 (16.2)	728 (12.3)	<0.0001
Coronary artery disease	595 (15.6)	416 (7.0)	<0.0001
Atrial fibrillation	234 (6.1)	120 (2.0)	<0.0001
Heart failure	1123 (29.4)	1185 (20.0)	<0.0001
Diabetes mellitus	870 (22.7)	1110 (18.7)	0.842
Stroke category			<0.0001
AIS	3266 (85.6)	5103 (86.4)	
ICH	404 (10.6)	414 (7.0)	
Uncertain	146 (3.8)	387 (6.6)	
NIHSS at admission	8.0 (4.0, 14.0)	3.0 (2.0, 5.0)	<0.0001
GCS score at admission	15.0 (12.0, 15.0)	15.0 (15.0, 15.0)	<0.0001
Pre-morbid mRS 0-1*	2578 (67.3)	5131 (86.6)	<0.0001
NIHSS at 7 days/before discharge	6.0 (2.0, 12.0)	1.0 (0.0, 3.0)	<0.0001
mRS at 7 days/before discharge	4.0 (2.0, 4.0)	1.0 (1.0, 2.0)	<0.0001
ICU admission	2467 (64.6)	3136 (53.0)	<0.0001
ASU admission	2467 (64.6)	3136 (53.0)	<0.0001
Antibiotic treatment	1041 (27.4)	447 (7.6)	<0.0001
Underwent surgery†	26 (0.7)	9 (0.2)	<0.0001

Data are n (%), mean±SD and median (IQR)

AIS donates acute ischemic stroke, ASU acute stroke unit, GCS Glasgow coma scale, ICH intracerebral haemorrhage, ICU intensive care unit, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale, UK United Kingdom

*Estimated functional grade score 0-1 on the mRS

†Includes decompressive hemicranectomy, open craniotomy, minimally invasive surgery and intraventricular drainage of ICH

‡P value from Chi-squared test, T-test or Wilcoxon test as appropriate

Table S2. Characteristics of patients according to urinary tract infection (UTI) within 90 days

| Characteristics | UTI | | P value§ |
	Yes N=76	No N=11017	
Age (years)	77.6±11.6	67.9±13.8	<0.0001
Male	32 (42.1)	6632 (60.2)	0.001
Region			
Australia and UK	56 (73.7)	4705 (42.7)	<0.0001
China and Taiwan	5 (6.6)	4647 (42.2)	
India and Sri Lanka	5 (6.6)	765 (6.9)	
South America	10 (13.2)	900 (8.2)	
Hypertension	50 (65.8)	5567 (50.5)	0.061
Previous stroke	15 (20.0)	2591 (23.6)	0.464
Coronary artery disease	9 (11.8)	1530 (14.0)	0.591
Atrial fibrillation	17 (22.4)	1159 (10.5)	0.001
Heart failure	5 (6.6)	407 (3.7)	0.206
Diabetes mellitus	18 (23.7)	2203 (20.0)	0.757
Stroke category			
AIS	63 (82.9)	9404 (85.6)	0.772
ICH	8 (10.5)	922 (8.4)	
Uncertain	5 (6.6)	658 (6.0)	
NIHSS at admission	6.0 (4.0, 12.0)	4.0 (2.0, 8.0)	<0.0001
GCS score at admission	15.0 (13.0, 15.0)	15.0 (14.0, 15.0)	0.003
Pre-morbid mRS 0-1*	48 (63.2)	8681 (78.8)	<0.0001
NIHSS at 7 days or before discharge	5.0 (2.0, 15.0)	2.0 (1.0, 6.0)	<0.0001
mRS at 7 days/before discharge	4.0 (3.0, 5.0)	2.0 (1.0, 3.0)	<0.0001
ICU admission	2 (2.7)	515 (4.7)	0.585
ASU admission	67 (88.2)	6553 (59.5)	<0.0001

	UTI		
Characteristics	Yes N=76	No N=11017	P value§
Antibiotic treatment	49 (65.3)	1633 (14.9)	<0.0001
Underwent surgery†	0 (0.0)	36 (0.3)	0.781
Poor outcome‡	46 (71.9)	3780 (39.0)	<0.0001

Data are n (%), mean±SD and median (IQR)

AIS donates acute ischemic stroke, ASU acute stroke unit, GCS Glasgow coma scale, ICH intracerebral haemorrhage, ICU intensive care unit, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale, UK United Kingdom

*Estimated functional grade score 0-1 on the mRS

†Includes decompressive hemicranectomy, open craniotomy, minimally invasive surgery and intraventricular drainage of ICH

‡Poor outcome defined as modified Rankin scale scores 3-6
§P value from Chi-squared test, T-test or Wilcoxon test as appropriate

Table S3: Urine catheter use by region

Urinary catheter use	Australia + UK	China + Taiwan	India + Sri Lanka	South America	Overall	P value*
Yes	535 (11.4)	266 (5.7)	259 (33.8)	107 (11.8)	1167 (11.6)	<0.0001
No	4154 (88.6)	4371 (94.3)	507 (66.2)	797 (88.2)	9829 (88.6)	
Length of insertion, days						<0.0001
Median†	6.0 (3.0, 7.0)	6.0 (3.0, 7.0)	4.0 (3.0, 5.0)	5.0 (3.0, 7.0)	5.0 (3.0, 7.0)	

Data are n (%) and median (IQR)

*P value from chi-squared test or Wilcoxon rank sum test as appropriate

†Australia+UK (N=214), China+Taiwan (N=205), India + Sri Lanka (N=50), South America (N=46)

Table S4. Length of indwelling urinary catheter (IUC) use by outcomes

Outcomes	Length of IUC insertion, days Median (IQR)		P value*
Urinary tract infections			0.167
Yes	4.0 (3.0-6.0)	N=41	
No	5.0 (3.0-7.0)	N=469	
modified Rankin scale score at 90 days			0.013
0-2 (favourable)	5.0 (3.0-7.0)	N=262	
3-6 (poor)	6.0 (3.0-7.0)	N=147	

Data are median (IQR)

*Wilcoxon rank sum test for P value

Table S5. Clinical outcomes by use of urine catheter

Outcomes	Urinary catheter use		P value*
	Yes	No	
Urinary tract infection	18/1167 (1.5)	58/9829 (0.6)	0.0002
Poor outcome†	793/1167 (76.6)	2991/9829 (34.7)	<0.0001
Any SAE	431/1167 (36.9)	1087/9829 (11.1)	<0.0001
Any infection‡	43/1167 (3.7)	113/9829 (1.2)	<0.0001
Death	292/1167 (25.6)	490/9829 (5.1)	<0.0001
Death by any SAE	268/292 (91.8)	420/490 (85.7)	0.0116
Death by any infection‡	16/268 (6.0)	24/420 (5.7)	0.889
Death by UTI	3/268 (1.1)	9/420 (2.1)	0.317

Data are n/N (%).

UTI denotes urinary tract infection, SAE serious adverse event

*Chi-squared test for P value

†Defined as modified Rankin scale score 3 to 6

‡Any infection includes urinary tract infection, septicaemia or other type of infection in body or septic shock (except pneumonia).

Table S6. Duration of urinary catheterization and outcome in patients with catheterization.

Outcomes	OR* (95% CI)	P value	aOR† (95% CI)	P value
Poor outcome	1.14 (1.05-1.23)	0.002	1.03 (0.93-1.14)	0.534
UTI	0.86 (0.66-1.12)	0.252	Did not converge	

aOR denotes adjusted odds ratio, CI confidence interval, UTI urinary tract infection

*Unadjusted binomial logistic regression with adjustment for the fixed effects of head position (lying-flat versus sitting-up) and crossover period, and random effects of cluster, and random interaction effects between cluster and crossover period.

† Adjusted region as groups (Australia/UK, China and Taiwan, India/Sri Lanka, South America), baseline age as continuous, sex, premorbid grade according to modified Rankin scale (mRS) at admission, National Institutes of Health Stroke Scale (NIHSS) at baseline as continuous, past medical history of heart disease, diabetes or previous stroke and stroke type, intensive care unit admission, acute stroke unit admission, antibiotic treatment, NIHSS at Day 7/before discharge as continuous.

Table S7. Predictors of death or dependency (mRS 3-6) at 90 days (n=9155)

Covariate	aOR (95% CI)	P value
Indwelling urine catheter	1.41 (1.13-1.75)	0.002
Region (vs. South America)		<0.0001
China + Taiwan	0.52 (0.35-0.75)	
Australia + United Kingdom	0.76 (0.51-1.12)	
India + Sri Lanka	1.52 (0.91-2.53)	
Age, per 5 years	1.22 (1.19-1.25)	<0.0001
Female	1.29 (1.15-1.44)	<0.0001
NIHSS at admission, per unit	1.03 (1.02-1.05)	<0.0001
AIS (vs. ICH)	0.84 (0.68-1.04)	0.262
Pre-morbid mRS (vs. no symptoms)*		<0.0001
No significant disability	1.41 (1.20-1.65)	
History of heart disease, stroke or diabetes	1.42 (1.27-1.59)	<0.0001
ICU admission	1.25 (0.90-1.74)	0.192
ASU admission	0.98 (0.77-1.24)	0.861
Antibiotic treatment	1.44 (1.21-1.70)	<0.0001
NIHSS at day 7, per unit	1.27 (1.25-1.30)	<0.0001
Urinary Tract Infection	1.46 (0.70-3.04)	0.319

AIS denotes acute ischaemic stroke, aOR adjusted odds ratio, ASU acute stroke unit, CI confidence interval, GCS Glasgow coma scale, ICH intracerebral haemorrhage, ICU intensive care unit, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale

*Premorbid functional grade according to the full range of scores on the mRS assessed at admission: slight disability vs. no symptoms (aOR 2.09, 95% CI 1.73-2.51); moderate disability vs. no symptoms (aOR 3.81, 95% CI 3.01-4.82); moderate/severe disability vs. no symptoms (aOR 4.44, 95% CI 3.06-6.44); and severe disability vs. no symptoms (aOR 5.88, 95% CI 2.33-14.87)

Table S8. Stratified analysis of indwelling urinary catheterisation and death or dependency in patients without reported urinary tract infection (UTI)

Stratification	No UTI (N=11017)	
	aOR (95% CI)	P value
Unadjusted*	5.44 (4.63-6.39)	<0.0001
Model 1†	5.27 (4.49-6.18)	<0.0001
Model 2‡	2.34 (1.93-2.83)	<0.0001
Model 3§	1.43 (1.15-1.78)	0.001

aOR denotes adjusted odds ratio, CI confidence interval, UTI urinary tract infection

*Unadjusted binomial logistic regression with adjustment for the fixed effects of head position (lying-flat versus sitting-up) and crossover period, and random effects of cluster, and random interaction effects between cluster and crossover period.

†Model I: adjusted region as groups (Australia/UK, China and Taiwan, India/Sri Lanka, South America)

‡Model II: further adjusted baseline covariates, include age as continuous, sex, premorbid grade according to modified Rankin scale (mRS) at admission, National Institutes of Health Stroke Scale (NIHSS) at baseline as continuous, past medical history of heart disease, diabetes or previous stroke and stroke type.

§Model III: further adjusted individual characteristics at discharge, include intensive care unit admission, acute stroke unit admission, antibiotic treatment, NIHSS at Day 7/before discharge as continuous.

Figure S1. Plot of interaction between urinary catheter use and NIHSS at admission on death or dependency at 90 days

Predicted Probabilities for mrs_90_binary
With 95% Confidence Limits

P=0.0019

Urinary catheter inserted (Y/N) —— YES —— NO
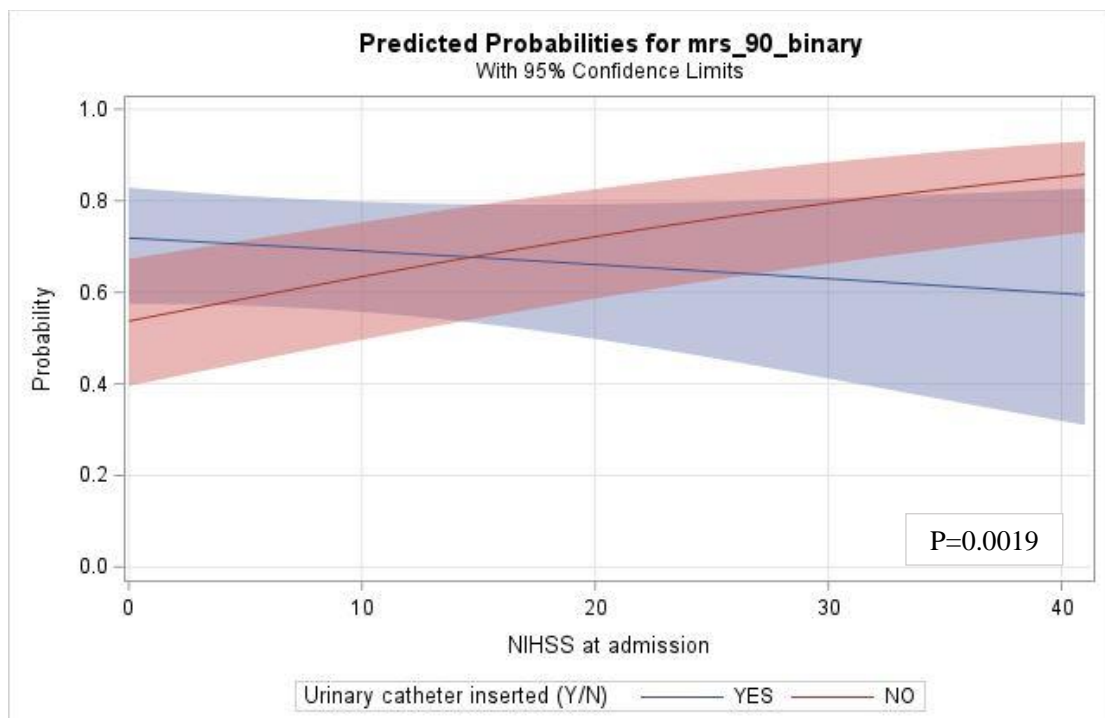
mrs_90_binary donates death or dependency at 90 days according to scores 3-6 on the modified Rankin scale

NIHSS denotes National Institutes of Health Stroke Scale

Hierarchical mixed models used in analyses

Figure S2. Distribution of time to urinary tract infection (UTI) events from stroke onset

N=74

Median (IQR): 17 (5-36)
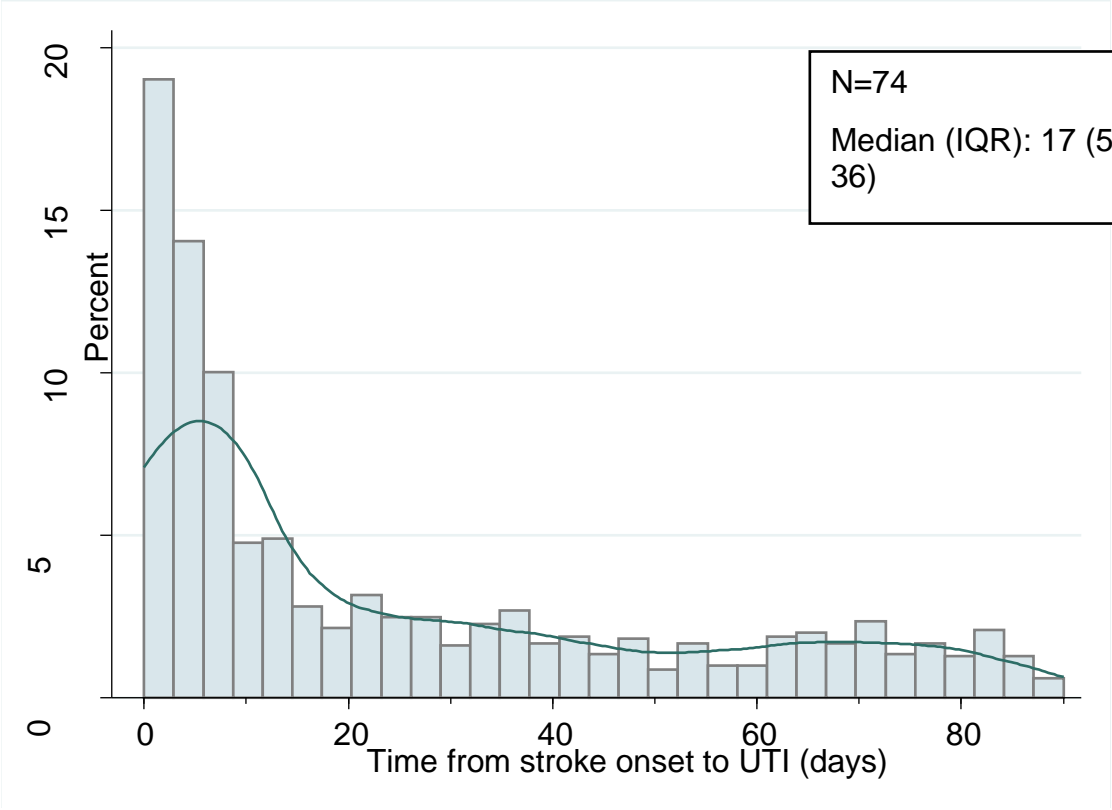
Figure S3. Subgroup analysis for death or dependency outcome (mRS 3-6) in 9192 patients

Variable	Subgroup	N	Poor OR (95% CI)		P value
Head Position	Lying flat	4401		1.18 (0.88, 1.60)	0.122
	Sitting up	4791		1.63 (1.22, 2.19)	
Age in years	<60	2480		1.19 (0.78, 1.82)	0.006
	60-69	2418		1.30 (0.85, 1.99)	
	70-79	2312		1.37 (0.93, 2.01)	
	80+	1982		1.72 (1.14, 2.59)	
Sex	Male	5585		1.12 (0.85, 1.47)	0.010
	Female	3607		1.92 (1.38, 2.66)	
Region group	Australia and UK	3425		1.64 (1.18, 2.29)	0.136
	China (include Taiwan)	4274		1.57 (1.07, 2.30)	
	India and Sri Lanka	659		1.08 (0.67, 1.74)	
	South America	834		0.76 (0.39, 1.50)	
NIHSS at admission	0-4	4951		2.42 (1.64, 3.58)	<0.0001
	5-42	4241		1.14 (0.89, 1.47)	
Stroke type	AIS	7939		1.43 (1.13, 1.81)	0.470
	ICH	746		1.44 (0.84, 2.45)	
mRS at admission	0-2	8270		1.48 (1.18, 1.86)	0.085
	3-5	922		0.83 (0.44, 1.57)	
Past Medical History	Yes	4721		1.40 (1.05, 1.87)	0.997
	No	4471		1.40 (1.04, 1.89)	

Scale: 0   1   2   4

IUC better ← → IUC worse

AIS donates acute ischemic stroke, ICH intracerebral haemorrhage, mRS modified Rankin scale, N number of patients in each subgroup, NIHSS National Institutes of Health Stroke Scale

Poor outcome is death or dependency at 90 day according to mRS scores 3-6

Hierarchical mixed models used in analyses

Figure S4. Subgroup analysis for urinary tract infection (UTI) within 90 days in 10419 patients
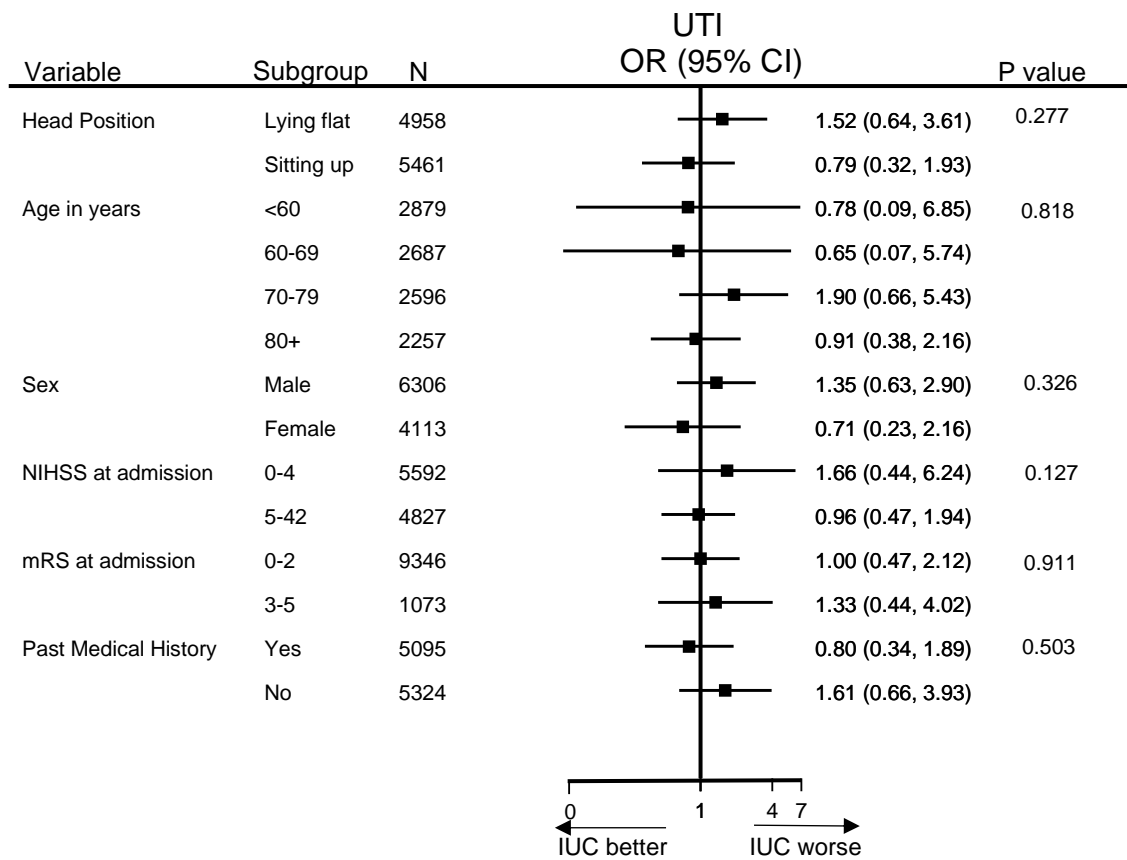
Variable	Subgroup	N	UTI OR (95% CI)	P value
Head Position	Lying flat	4958	1.52 (0.64, 3.61)	0.277
	Sitting up	5461	0.79 (0.32, 1.93)	
Age in years	<60	2879	0.78 (0.09, 6.85)	0.818
	60-69	2687	0.65 (0.07, 5.74)	
	70-79	2596	1.90 (0.66, 5.43)	
	80+	2257	0.91 (0.38, 2.16)	
Sex	Male	6306	1.35 (0.63, 2.90)	0.326
	Female	4113	0.71 (0.23, 2.16)	
NIHSS at admission	0-4	5592	1.66 (0.44, 6.24)	0.127
	5-42	4827	0.96 (0.47, 1.94)	
mRS at admission	0-2	9346	1.00 (0.47, 2.12)	0.911
	3-5	1073	1.33 (0.44, 4.02)	
Past Medical History	Yes	5095	0.80 (0.34, 1.89)	0.503
	No	5324	1.61 (0.66, 3.93)	

0   1   4 7
IUC better   IUC worse

AIS donates acute ischemic stroke, ICH intracerebral haemorrhage, mRS modified Rankin scale, N number of patients in each subgroup, NIHSS National Institutes of Health Stroke Scale

Hierarchical mixed models used in analyses

Supplementary Appendix of Chapter 3.1

Low presenting blood pressure was associated with adverse outcomes in acute stroke: HeadPoST study explanations

Ouyang M, Venturelli PM, Billot L, Wang X, Song et al.

Supplemental tables: 3

Supplemental figures: 6

Multiple imputation methods

Multiple imputation was used to impute missing outcome data, using PROC MI and PROC MIANALYZE in SAS version 9.2 (or later) software. Multiple imputation is generally considered the least biased method since it incorporates uncertainty to the imputed value, and a non-monotone missing pattern is assumed modified Rankin scale (mRS) score at 90 days. A distribution for the outcome was derived from a regression model that accounts for covariates (listed in the generalized linear mixed model) and a random sample from this distribution was used to impute values for missing outcomes. Ten multiple sample data sets with complete outcome data were generated through PROC MI, and the results (regression parameter and covariance matrix estimates) for each sample combined and analyzed with PROC MIANALYZE to derive a valid statistical inference about the association with outcomes.

Table e-1. Baseline characteristics by diastolic blood pressure

Variable	Diastolic blood pressure, mmHg			P value
	<70	70-89	≥90	
Number of patients	1301 (11.7)	5118 (46.2)	4664 (42.1)	
Age, yr	73 (±13.5)	69 (±13.5)	66 (±13.6)	<0.0001
Female	646 (49.7)	2048 (40.0)	1729 (37.1)	<0.0001
Region				<0.0001
Australia and UK	807 (62.0)	2209 (43.1)	1738 (37.3)	
China and Taiwan	330 (25.4)	2195 (42.9)	2127 (45.6)	
India and Sri Lanka	49 (3.8)	322 (6.3)	399 (8.6)	
South America	115 (8.8)	392 (7.7)	400 (8.6)	
Stroke type				<0.0001
AIS	1131 (87.2)	4436 (86.9)	3895 (83.7)	
ICH	71 (5.5)	320 (6.3)	539 (11.6)	
Uncertain	95 (7.3)	349 (6.8)	218 (4.7)	
NIHSS	5.0 (2.0-10.0)	4.0 (2.0-8.0)	4.0 (2.0-8.0)	<0.0001
NIHSS ≥15	201 (15.8)	524 (10.4)	482 (10.5)	<0.0001
Medical history				
Hypertension	814 (62.8)	3116 (61.0)	3218 (69.1)	<0.0001
Current treatment	690 (53.0)	2495 (48.7)	2431 (52.1)	<0.0001
Number of antihypertensive drugs	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	<0.0001
Diabetes mellitus	316 (24.4)	1282 (25.1)	1052 (22.6)	0.013
Atrial fibrillation	207 (16.0)	547 (10.8)	435 (9.4)	<0.0001
Coronary artery disease	268 (20.8)	733 (14.4)	539 (11.6)	<0.0001
Heart failure	88 (6.9)	204 (4.0%)	121 (2.6)	<0.0001
Previous stroke	307 (23.7)	1191 (23.3%)	1107 (23.8)	0.8596
Smoking	211 (16.4)	950 (18.8%)	963 (20.8)	0.0010
Pre-morbid mRS 0-1	928 (71.4)	4050 (79.3%)	3755 (80.6)	<0.0001
Hypercholesterolemia	435 (33.6)	1317 (25.9)	979 (21.1)	<0.0001
COPD/emphysema	74 (5.4)	180 (3.6)	152 (3.3)	0.0001

	Diastolic blood pressure, mmHg			
Variable	**<70**	**70-89**	**≥90**	**P value**
Number of patients	1301 (11.7)	5118 (46.2)	4664 (42.1)	
SBP, mmHg	132 (116-149)	144 (130-160)	167 (150-186)	<0.0001
DBP, mmHg	63 (60-66)	80 (75-84)	100 (92-106)	<0.0001
Time from stroke onset to hospital arrival, hr	5.6 (1.9-21.4)	8.1 (2.4-30.0)	7.4 (2.3-25.3)	<0.0001

Data are mean (±SD), median (IQR) and n (%). Analyses are ANOVA test for normally distributed variables, Kruskal-Wallis test for skewed continuous variables, and Chi-squared test for categorical variables.

AIS denotes acute ischaemic stroke, COPD chronic obstructive pulmonary disease, DBP denotes diastolic blood pressure, ICH intracerebral haemorrhage, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale, SBP systolic blood pressure, UK United Kingdom

Table e-2. Associations with low baseline systolic blood pressure

Predictors	aOR (95% CI)	P value
Age (every 10 years)	0.85 (0.80-0.90)	<0.0001
Stroke subtype		<0.0001
ICH vs. AIS	0.61 (0.42-0.89)	
Uncertain vs. AIS	1.75 (1.29-2.37)	
NIHSS	1.02 (1.00-1.03)	0.0320
History of hypertension	0.44 (0.37-0.52)	<0.0001
History of atrial fibrillation	1.47 (1.13-1.91)	0.0037
History of coronary artery disease	1.54 (1.22-1.94)	0.0003
History of heart failure	1.83 (1.28-2.62)	0.0010
Pre-morbid conditions (mRS 0-1 vs. 2-5)	0.78 (0.63-0.96)	0.0176

AIS denotes acute ischaemic stroke, aOR adjusted odds ratio, CI confidence interval, ICH intracerebral haemorrhage, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale

Generalized linear mixed model adjusted for the study design (fixed effects of head position lying-flat versus sitting-up and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and listed covariates in the baseline table. Backward elimination was used until all variables in the model with P <0.05 to obtain predictors for low BP.

Table e-3. Outcomes by categorical diastolic blood pressure

Outcome	Diastolic blood pressure, mmHg			P value*
	<70	**70-89**	**≥90**	
Death or dependency (mRS 3-6)	575/1128† (51.0)	1740/4473† (38.9)	1505/4138† (36.4)	<0.0001
Disability (mRS 3-5)	438/1128 (38.8)	1384/4473 (30.9)	1202/4138 (29.0)	<0.0001
Death	137/1128 (12.1)	356/4473 (8.0)	303/4138 (7.3)	<0.0001
SAE	233/1301‡ (17.9)	716/5118‡ (14.0)	590/4664‡ (12.7)	<0.0001
Recurrent stroke	81/1301 (6.2)	249/5118 (4.9)	197/4664 (4.2)	0.0098
Cardiac or other vascular events	30/1301 (2.3)	116/5118 (2.3)	89/4664 (1.9)	0.4161
Pneumonia	41/1301 (3.2)	136/5118 (2.7)	115/4664 (2.5)	0.3899
Other infection	22/1301 (1.7)	56/5118 (1.1)	43/4664 (0.9)	0.0617
Other SAE	54/1301 (4.2)	124/5118 (2.4)	107/4664 (2.3)	0.0006

Data are n/N (%)

DBP donates diastolic blood pressure, mRS modified Rankin Scale, SAE serious adverse event.

*Chi-squared p value

†N is according to total number of patients at 90-day follow up

‡N is according to total number of patients randomised

Table e-4. National Institute of Health Stroke Scale at Day 7/before discharge by categorical blood pressure (BP)

Categorical BP	NIHSS at day 7/before discharge	P value*
SBP, mmHg		0.0013
<120	2.0 (1.0-6.0)	
120-139	2.0 (1.0-5.0)	
≥140	2.0 (1.0-6.0)	
DBP, mmHg		0.0353
<70	2.0 (1.0-6.0)	
71-90	2.0 (1.0-6.0)	
≥90	2.0 (1.0-6.0)	

*Kruskal-Wallis Test for P value;

BP donates blood pressure, DBP diastolic blood pressure, NIHSS National Institute Health Stroke Scale, SBP systolic blood pressure

Figure e-1. Association of baseline blood pressure and any serious adverse events within 90 days

A. SAEs with in 90 days

SBP, mmHg	aOR (95% CI)
Trial population	
<120	1.22 (0.95, 1.57)
≥140	1.00 (0.86, 1.17)
Confirmed stroke	
<120	1.22 (0.94, 1.58)
≥140	0.97 (0.82, 1.14)
AIS	
<120	1.19 (0.91, 1.56)
≥140	0.92 (0.78, 1.08)
ICH	
<120	2.16 (0.66, 7.11)
≥140	2.23 (1.13, 4.39)

B. SAEs with in 90 days

DBP, mmHg	aOR (95% CI)
Trial population	
<70	0.89 (0.74, 1.08)
≥90	0.94 (0.82, 1.08)
Confirmed stroke	
<70	0.86 (0.71, 1.05)
≥90	0.91 (0.79, 1.05)
AIS	
<70	0.88 (0.72, 1.08)
≥90	0.91 (0.78, 1.05)
ICH	
<70	0.60 (0.28, 1.28)
≥90	0.99 (0.64, 1.53)
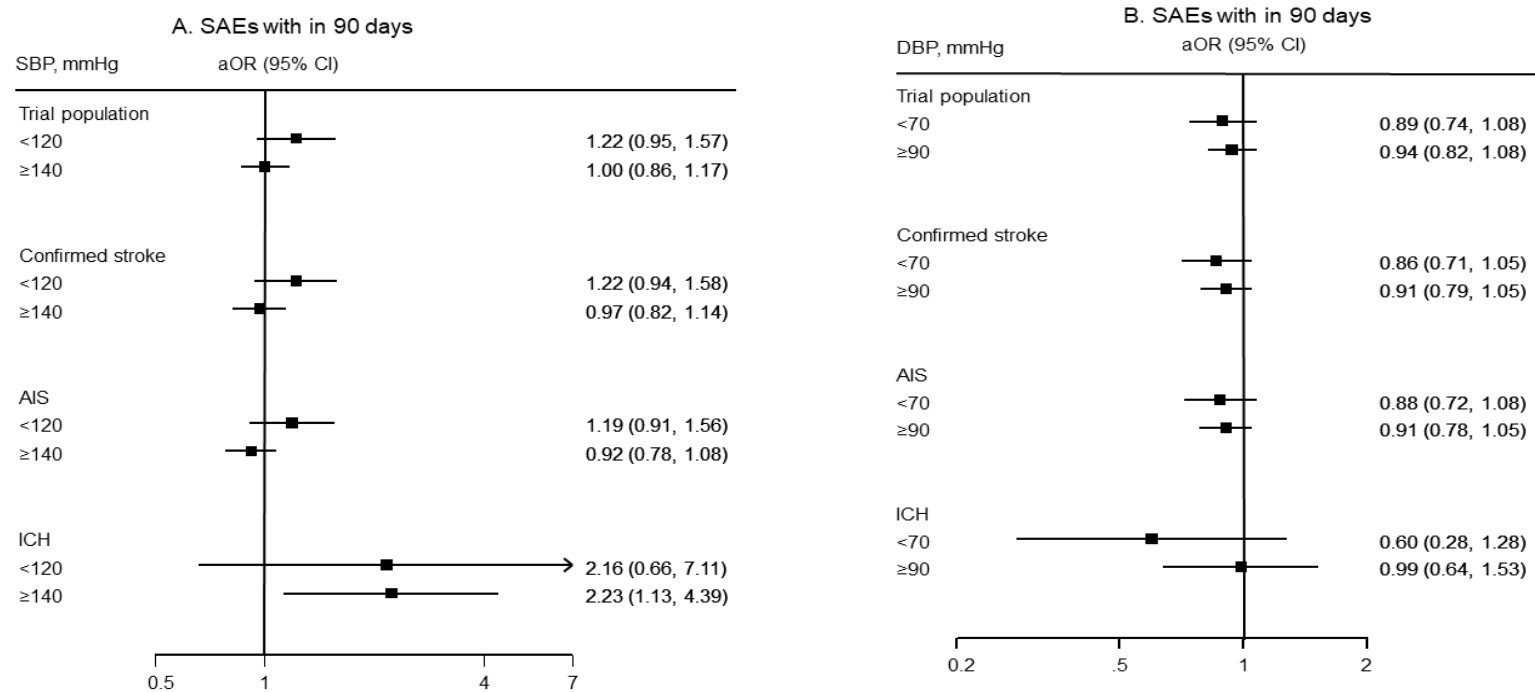
Footnote: AIS donates acute ischemic stroke, aOR donates adjusted odds ratio, CI confidence interval, DBP diastolic blood pressure, ICH intracerebral haemorrhage, SAE serious adverse events, SBP systolic blood pressure

Generalized linear mixed model adjusted for the fixed effects of head position (lying-flat versus sitting-up) and cross-over period, random effects of cluster, and random interaction effects between cluster and cross-over period, and prognostic variables including region, age, sex, National Institutes of Health Stroke Scale score, pre-morbid function according to the modified Rankin scale (0-1, independent; 2-5 disabled), stroke type, and history of coronary artery disease, heart failure, hypertension, atrial fibrillation, and diabetes mellitus, and smoking status. A. SBP reference 120-139 mmHg; B. DBP reference 70-89 mmHg. Square boxes indicate odds ratios; line indicates 95% confidence intervals.

Figure e-2. Restricted cubic spline regression of baseline diastolic blood pressure and clinical outcomes at 90 days

A. DBP and death or dependency at 90 days

B. DBP and SAEs within 90 days
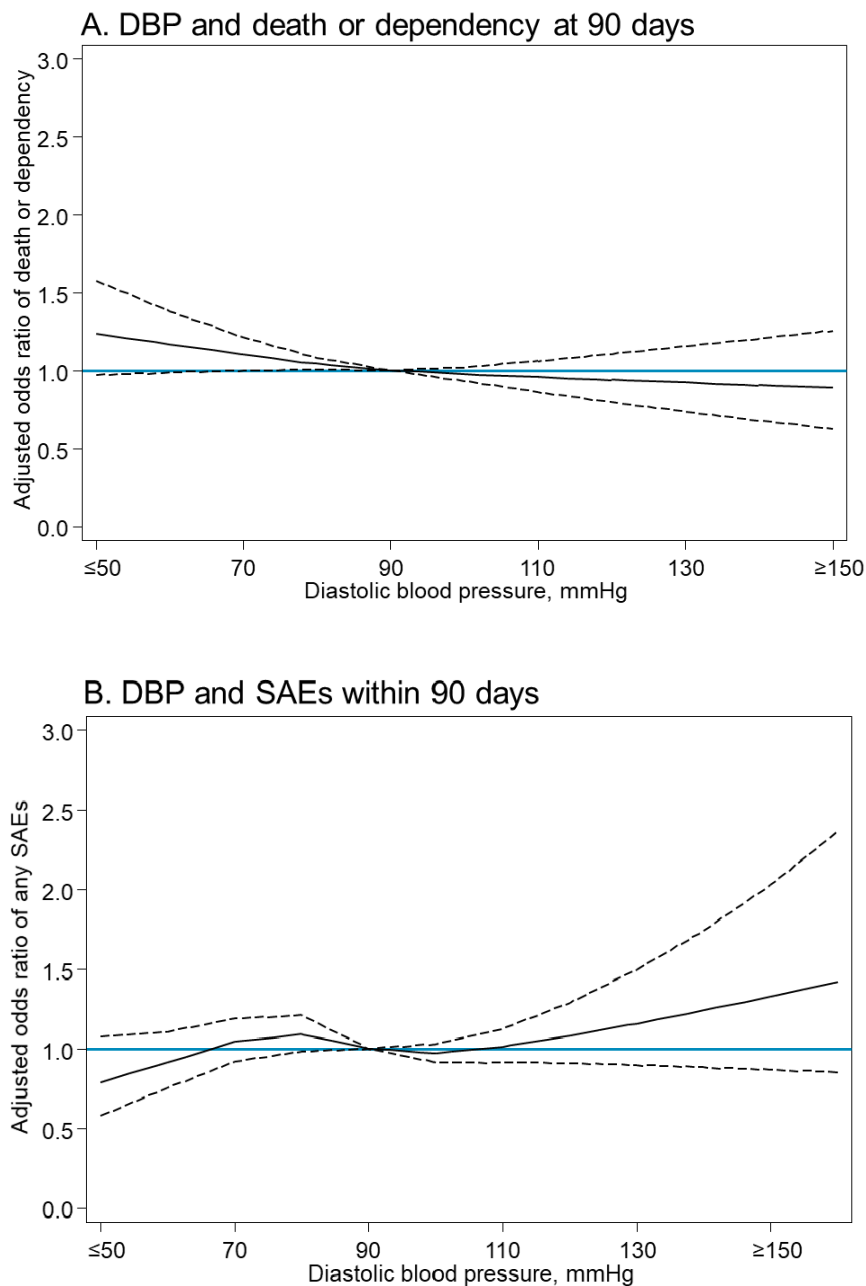
Footnote: DBP donates diastolic blood pressure, SAE serious adverse events, SBP systolic blood pressure. Generalized linear mixed models with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and potential confounders of age, sex, region, past history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, coronary heart disease, National Institutes of Health Stroke Scale, stroke type, pre-morbid score 0-1 on the modified Rankin Scale, and current smoking. A. Splines fitted with 3 knots (percentiles 10th, 50th, 95th) for DBP; B. Splines fitted with 4 knots (percentiles 5th, 35th, 65th, 95th) for DBP; Reference diastolic blood pressure 90 mmHg. Solid line indicates odds ratios; dotted line indicates 95% confidence intervals.

Figure e-3. Restricted cubic spline regression of baseline diastolic blood pressure and 90-day death or dependency (modified Rankin Scale 3-6), by stroke subtype

A. AIS patients

B. ICH patients

Footnote: AIS donates acute ischemic stroke, DBP diastolic blood pressure, ICH donates intracerebral haemorrhage. Generalized linear mixed model adjusted for the fixed effects of head position (lying-flat versus sitting-up) and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period and potential confounders: age, sex, region groups, past history of diabetes, past history of hypertension, heart failure, atrial fibrillation, coronary artery disease, National Institutes of Health Stroke Scale, stroke type and pre-morbid function 0-1 according to modified Rankin scale, and current smoking. Splines fitted with 3 knots (percentiles 10th, 50th, 95th) for DBP; Reference diastolic blood pressure 90 mmHg. Solid line indicates odds ratios; dotted line indicates 95% confidence interval

271

Figure e-4. Association of categorical baseline diastolic blood pressure and death or dependency (modified Rankin Scale 3-6) at 90 days, by type of dataset
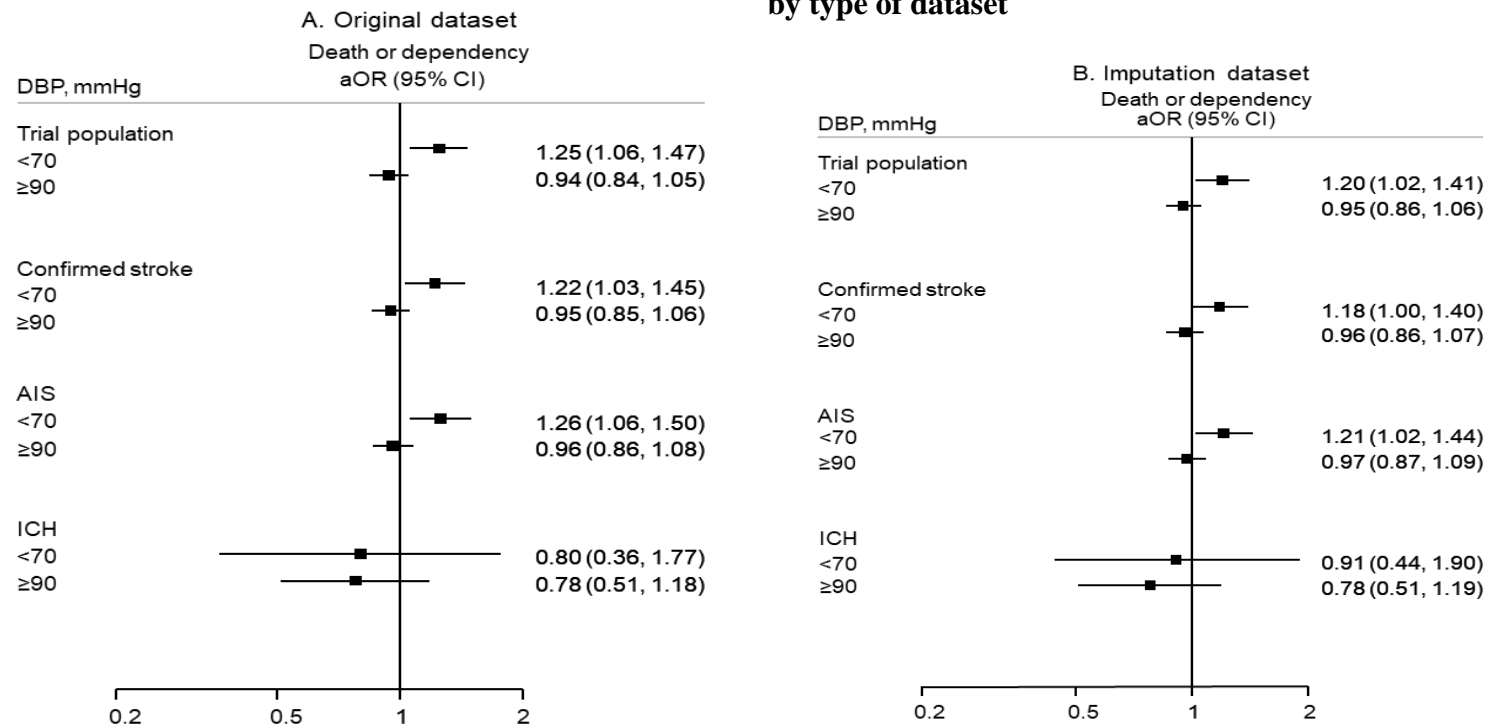
Footnote: AIS denotes acute ischaemic stroke, aOR adjusted odds ratio, CI confidence interval, DBP diastolic blood pressure, ICH intracerebral haemorrhage, mRS modified Rankin Scale

Generalized linear mixed model adjusted for study design (fixed effects of head position [lying-flat versus sitting-up] and cross-over period, random effects of cluster, and random interaction effects between cluster and cross-over period) and region, age, sex, National Institutes of Health Stroke Scale (NIHSS) score, pre-morbid function according to mRS, stroke type, and history of coronary artery disease, heart failure, hypertension, atrial fibrillation, diabetes mellitus and smoking status.

Reference diastolic blood pressure 70-89 mmHg; Square boxes indicate point estimate of odds ratios, solid line indicates 95% confidence intervals.

Figure e-5. Baseline systolic blood pressure and death or dependency (modified Rankin Scale 3-6) at 90 days, by pre-specified subgroups

Subgroup	SBP, mmHg	Death or dependency aOR (95% CI)	P interaction	n/N
Region				
Asian	<120	1.52 (1.09, 2.11)	0.0024	298/4947
	≥140	1.19 (0.99, 1.42)		3525/4947
non-Asian	<120	1.02 (0.75, 1.38)		346/4428
	≥140	0.78 (0.65, 0.94)		3181/4428
Intensive BP lowering				
Yes	<120	1.82 (0.47, 7.06)	0.5756	20/798
	≥140	1.58 (0.80, 3.10)		699/798
No	<120	1.27 (1.01, 1.59)		624/8576
	≥140	0.97 (0.85, 1.10)		6006/8576
Antihypertensive*				
Yes	<120	1.04 (0.74, 1.45)	0.2058	259/4781
	≥140	1.04 (0.87, 1.25)		3614/4781
No	<120	3.09 (1.36, 7.00)		43/1280
	≥140	1.04 (0.71, 1.55)		1027/1280
Head Positioning				
Lying flat	<120	1.32 (0.95, 1.83)	0.091	290/4506
	≥140	1.15 (0.96, 1.38)		3206/4506
Sitting up	<120	1.23 (0.91, 1.66)		354/4869
	≥140	0.88 (0.74, 1.05)		3500/4869

Footnote:

*Only includes patients with history of hypertension

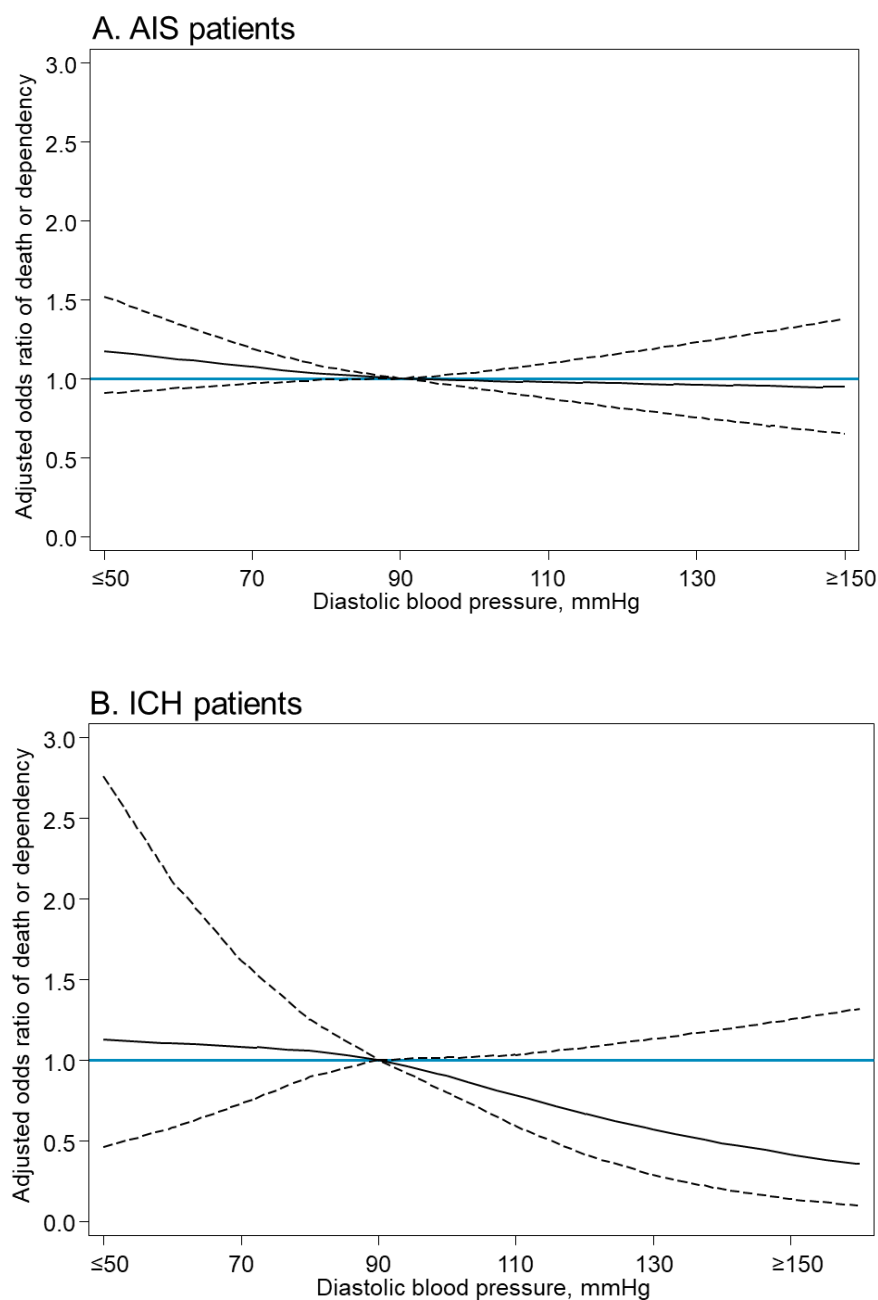aOR donates to adjusted odds ratio, BP blood pressure, mRS modified Rankin Scale, SBP systolic blood pressure

Generalized linear mixed models adjusted for the fixed effects of head position (lying-flat versus sitting-up) and cross-over period, random effects of cluster, and random interaction effects between cluster and cross-over period together with prognostic variables including age, sex, region, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, coronary artery disease, National Institutes of Health Stroke Scale, stroke type, pre-morbid function according to modified Rankin scale, and smoking status.

Reference systolic blood pressure120-139 mmHg. Square boxes indicate odds ratios; line indicates 95% confidence intervals.

Figure e-6. Baseline diastolic blood pressure and death or dependency (modified Rankin Scale 3-6) at 90 days, by pre-specified subgroups

Subgroup	DBP, mmHg	Death or dependency aOR (95% CI)	P interaction	n/N
Region				
Asian	<70	1.36 (1.03, 1.80)	0.0308	345/4947
	≥90	1.08 (0.93, 1.26)		2326/4947
non-Asian	<70	1.12 (0.91, 1.38)		728/4428
	≥90	0.80 (0.68, 0.94)		1669/4428
Intensive BP lowering				
Yes	<70	1.07 (0.47, 2.46)	0.6349	45/798
	≥90	0.87 (0.57, 1.33)		500/798
No	<70	1.28 (1.08, 1.51)		1028/8576
	≥90	0.94 (0.84, 1.06)		3495/8576
Antihypertensive*				
Yes	<70	1.17 (0.94, 1.47)	0.8062	578/4781
	≥90	1.00 (0.86, 1.17)		2089/4781
No	<70	1.57 (0.87, 2.84)		93/1280
	≥90	1.01 (0.74, 1.37)		674/1280
Head Positioning				
Lying flat	<70	1.19 (0.93, 1.52)	0.5631	489/4506
	≥90	1.00 (0.85, 1.17)		1912/4506
Sitting up	<70	1.30 (1.04, 1.62)		584/4869
	≥90	0.92 (0.79, 1.07)		2083/4869

Footnote:

*Only includes patients with history of hypertension

aOR donates to adjusted odds ratio, BP blood pressure, DBP diastolic blood pressure, mRS modified Rankin Scale

Generalized linear mixed models adjusted for the fixed effects of head position (lying-flat versus sitting-up) and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period together with prognostic variables including age, sex, region, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, coronary artery disease, National Institutes of Health Stroke Scale, stroke type, pre-morbid function according to modified Rankin scale, and smoking status.

Reference diastolic blood pressure 70-89 mmHg. Square boxes indicate odds ratios; line indicates 95% confidence interval.

Supplementary Appendix of Chapter 3.2

Oxygen desaturation and adverse outcome in acute stroke: secondary analyses of the HeadPoST study

Ouyang M, Roffe C, Billot L, Song L, Wang X, Venturelli PM et al.

Appendix: 2

Supplemental tables: 5

Supplemental figures: 6

Appendix 1. Summary of definitions of serious adverse events (SAEs)

Item	Definition
Acute stroke	Cerebral ischaemia, cerebral haemorrhage, cerebral oedema, brain herniation, raised intracranial pressure
Cardiac/ other vascular disease	Myocardial infarction, heart failure, arrhythmia, sudden death (cardiac, cardiogenic shock), pulmonary embolism, death of unknown cardiac origin, acute pulmonary oedema, epilepsy or seizures, carotid endarterectomy (CEA), hypertension, collapse, carotid angioplasty stenting (CAS) or other cardiac origin SAEs
Pneumonia	Pneumonia
Other infection	Urinary tract, septicaemia, other type of infection in body, septic shock
Other SAE	Fall, renal failure, death (non-cardiovascular), ulcers, tumour or cancer, depression, anxiety, uncertain death, deep vein thrombosis (DVT), confusion, limb ischemia, meningitis and other undefined

Appendix 2. Propensity score matching approach

The propensity score was generated from all the baseline characteristics listed in Table 1. The propensity matching cohort for the two groups of oxygen desaturation (SaO_2 <93%) and normal group (SaO_2 93-100%) was generated by balanced, parallel (1:1) nearest available neighbour matching with a maximum permitted difference of 0.1 (caliper: 0.1) approach. Absolute standardized difference (ASD) was calculated between the two groups and unbalanced covariates (ASD more than 0.10) were identified. All unbalanced covariates were then adjusted into the multivariable analysis using the generalised linear mixed (GLM) models to obtain the associations of oxygen desaturation and clinical outcomes of (i) death or dependency and (ii) any serious adverse events (SAEs).

Table S1. Baseline characteristics of stroke patients by missing data on arterial oxygen saturation (SaO$_2$)

Variable	Available (n=8067, 73%)	Missing (n=3026, 27%)	P value*
Age	69.0 (13.96)	65.1 (12.81)	0.496
Male	4726 (58.6)	1983 (64.4)	0.357
Region			
Australia/UK	4376 (54.3)	385 (12.7)	<0.001
China/Taiwan	2370 (29.4)	2282 (75.4)	
India/Sri Lanka	501 (6.2)	269 (8.9)	
South America	820 (10.2)	90 (3.0)	
Premorbid mRS scores 2-5	1597 (19.8)	739 (24.5)	<0.001
NIHSS score at baseline	4.0 (2.0-9.0)	4.0 (2.0-7.0)	0.134
≥15	1011 (12.8)	196 (6.5)	0.596
Systolic BP	152 (135-173)	150 (138-170)	0.438
Blood glucose level	6.1 (5.3-7.7)	6.0 (5.1-7.7)	0.677
Heart rate	76 (68-86)	76 (68-81)	0.009
Time from symptom onset to hospital arrival	6.0 (2.1-22.6)	17.6 (4.5-51.4)	0.444
Heart failure	328 (4.1)	85 (2.8)	0.054
COPD/emphysema	334 (4.2)	72 (2.4)	0.047
Hypertension	5162 (64.2)	1989 (65.9)	0.649
Atrial fibrillation	992 (12.4)	197 (6.6)	0.309
Coronary heart disease	1141 (14.2)	399 (13.3)	0.291
Diabetes mellitus	1907 (23.7)	745 (24.7)	0.870
Hyperlipidaemia	2296 (28.6)	436 (14.5)	0.308
Previous stroke	1776 (23.7)	831 (27.5)	0.113
Other major health conditions	1502 (18.9)	267 (9.0)	0.166
Current smoker	1402 (17.6)	723 (24.1)	0.809
Antiplatelet use in AIS	3410 (50.2)	1773 (66.3)	0.631
Anticoagulant use in AIS	611 (9.0)	112 (4.2)	0.328
Dysphagia	1634 (20.4)	411 (13.7)	0.375
Final diagnosis			

Acute ischemic stroke	6807 (84.5)	2678 (88.6)	0.006
Large vessel occlusion	2064 (30.3)	884 (33.0)	0.145
Cardioembolic	1068 (15.7)	167 (6.2)	
Lacunar	1756 (25.8)	1107 (41.3)	
Other	1919 (28.1)	520 (19.4)	
Intracerebral haemorrhage	703 (8.7)	228 (7.5)	
Presence of intraventricular blood	204 (29.3)	66 (29.0)	0.339
Haematoma volume	10 (3-15)	9 (4-15)	0.275
Not AIS/ICH	550 (6.8)	116 (3.8)	
Hospitalisation management			
Reperfusion therapy† for AIS	1181 (17.4)	160 (6.0)	<0.001
Surgical procedures‡ for ICH	7 (1.0)	5 (2.2)	0.623
Withdraw active care	92 (1.2)	21 (0.7)	0.657
Endotracheal intubation	81 (1.0)	20 (0.7)	0.198

Data are mean (SD), median (IQR), and n (%)

AIS denotes acute ischaemic stroke, COPD chronic obstructive pulmonary disease, ICH intracerebral haemorrhage, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale, UK United Kingdom

*P value from univariate analyses using generalized linear mixed models with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period)

†Reperfusion therapy includes recombinant tissue-type plasminogen activator (rt-PA) treatment (intravenous or intra-arterial) or endovascular clot retrieval

‡ICH surgical procedures include decompressive hemicranectormy, open craniotomy surgical evacuation, minimally invasive surgery or intraventricular drainage

Table S2. Desaturation (<92%) and clinical outcomes at 90 days

Outcome	SaO$_2$		Model 1		Model 2		Model 3	
	<92%	92-100%	aOR (95% CI)	P value	aOR (95% CI)	P value	aOR (95% CI)	P value
Death or dependency	214/365* (58.6)	2669/6584* (40.5)	1.31 (0.98-1.76)	0.069	1.28 (0.95-1.73)	0.105	1.21 (0.94-1.56)	0.136
Any SAEs	122/414† (29.5)	1160/7653† (15.2)	1.76 (1.33-2.32)	<0.001	1.62 (1.21-2.17)	0.001	1.46 (1.14-1.88)	0.004
Acute stroke	42/414 (10.1)	392/7653 (5.1)	1.73 (1.16-2.57)	0.007	1.42 (0.92-2.19)	0.110		
Cardiac/other vascular disease	16/414 (3.9)	179/7653 (2.3)	1.14 (0.63-2.08)	0.660	1.17 (0.64-2.14)	0.602		
Pneumonia	34/414 (8.2)	227/7653 (3.0)	1.58 (0.98-2.54)	0.059	1.51 (0.93-2.46)	0.093		
Other infection	7/414 (1.7)	91/7653 (1.2)	1.13 (0.49-2.26)	0.773	1.11 (0.47-2.59)	0.815		
Other SAE	22/414 (5.3)	268/7653 (3.5)	1.40 (0.86-2.29)	0.178	1.42 (0.87-2.32)	0.164		

Data are n/N (%).

CI denotes confidence interval, SAEs serious adverse events, aOR adjusted odds ratio

*Denominators represent the total number of patients with follow-up to 90-days

†Denominators represent the total number of randomized patients

Model 1: aOR obtained from generalized linear mixed models with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and baseline variables of age, sex, region, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, National Institutes of Health Stroke Scale score, pre-morbid score 0-1 on the modified Rankin scale, dysphagia, hyperlipidemia, other major health conditions, chronic obstructive pulmonary disease, stroke type, antithrombotic treatment, and time from symptom onset to hospital arrival

Model 2: further adjusted management variables include withdraw active care, endotracheal intubation and reperfusion therapy for ischemic stroke during hospitalisation and surgical procedures for intracerebral haemorrhage during hospitalisation

Model 3: imputation dataset analysis based on the variables adjusted in Model 2 with additional adjustment of imputed blood glucose level.

Table S3. Propensity score matching of baseline characteristics by lowest level of arterial oxygen saturation (SaO$_2$)

Variables	Original dataset Lowest SaO$_2$ <93% (n=784)	93-100% (n=7283)	ASD	Matching dataset Lowest SaO$_2$ <93% (n=784)	93-100% (n=784)	ASD
Age	72.7 (13.00)	68.6 (14.00)	0.30	72.7 (13.00)	71.0 (13.39)	0.13
Female	354 (45.2)	2987 (41.0)	0.08	354 (45.2)	345 (44.0)	0.02
Region			0.29			0.44
Australia/UK	418 (53.3)	3958 (54.5)		418 (53.3)	455 (58.0)	
China/Taiwan	176 (22.5)	2194 (30.1)		176 (22.5)	247 (31.5)	
India/Sri Lanka	44 (5.6)	457 (6.3)		44 (5.6)	30 (3.8)	
South America	146 (18.6)	674 (9.3)		146 (18.6)	52 (6.6)	
Premorbid mRS scores 2-5	196 (25.1)	1401 (19.3)	0.14	196 (25.1)	177 (22.6)	0.06
NIHSS score	6 (3-13)	4 (2-9)	0.32	6 (3-13)	5 (2-10)	0.20
Systolic blood pressure, mmHg	152 (135-176)	152 (135-172)	<0.01	152 (135-176)	151 (137-170)	<0.01
Blood glucose level, mmol/L	6.5 (5.6-8.5)	6.1 (5.3-7.7)	0.16	6.5 (5.6-8.5)	6.3 (5.4-8.3)	0.07
Time from symptom onset to hospital arrival, hrs	4.1 (1.8-14.1)	6.2 (2.1-23.5)	0.20	4.1 (1.8-14.1)	5.1 (2.0-19.6)	0.14
Medical history and medications						
Heart failure	49 (6.3)	279 (3.9)	0.11	49 (6.3)	41 (5.3)	0.05

COPD/emphysema	72 (9.3)	262 (3.6)	0.23	72 (9.3)	54 (6.9)	0.09
Hypertension	541 (69.2)	4621 (63.6)	0.12	541 (69.2)	502 (64.3)	0.10
Atrial fibrillation	117 (15.0)	875 (12.1)	0.09	117 (15.0)	108 (13.9)	0.04
Coronary heart disease	114 (14.7)	1027 (14.2)	0.01	114 (14.7)	119 (15.2)	0.02
Diabetes mellitus	202 (25.8)	1705 (23.5)	0.05	202 (25.8)	181 (23.2)	0.06
Hyperlipidaemia	245 (31.5)	2051 (28.3)	0.07	245 (31.5)	248 (31.7)	<0.01
Previous stroke	178 (22.8)	1598 (22.0)	0.02	178 (22.8)	186 (23.8)	0.02
Other major health conditions	184 (23.8)	1318 (18.3)	0.13	184 (23.8)	159 (20.4)	0.08
Current smoker	127 (16.4)	1275 (17.7)	0.04	127 (16.4)	139 (17.9)	0.04
Antiplatelet use in AIS	318 (48.1)	3092 (50.4)	0.04	318 (48.1)	368 (47.1)	0.04
Anticoagulant use in AIS	82 (12.4)	529 (8.7)	0.01	82 (12.4)	80 (10.2)	<0.01
Dysphagia	264 (34.2)	1370 (19.0)	0.35	264 (34.2)	206 (26.4)	0.17
Final diagnosis			0.04			0.08
AIS	664 (84.7)	6143 (84.4)		664 (84.7)	671 (85.8)	
ICH	74 (9.4)	629 (8.6)		74 (9.4)	58 (7.4)	
Not AIS/ICH*	46 (5.9)	504 (6.9)		46 (5.9)	53 (6.8)	

Data are mean (SD), median (IQR), and n (%)

Analyses were T-test for normally distributed variables, Wilcoxon rank sum test for skewed continuous variables, and Chi-squared test for categorical variables.

AIS denotes acute ischaemic stroke, ASD absolute standardized difference, COPD chronic obstructive pulmonary disease, ICH intracerebral haemorrhage, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale, UK United Kingdom

*includes transient ischemic attack, migraine, seizure, functional weakness, syncope, transient global amnesia, metabolic disorder, tumor or other sources

Table S4. Association of arterial oxygen saturation (SaO$_2$) and clinical outcomes at 90 days after acute stroke using propensity matching dataset

Outcome	SaO$_2$		Model 1		Model 2	
	<93%	93-100%	aOR (95% CI)	P value	aOR (95% CI)	P value
Death or dependency	380/683* (55.6)	298/692* (43.1)	1.27 (0.97-1.68)	0.088	Didn't converge	-
Any SAEs	197/784† (25.1)	1355/784† (17.2)	1.38 (1.03-1.85)	0.030	1.40 (1.02-1.90)	0.035

Data are n/N (%)

aOR adjusted odds ratio, CI denotes confidence interval, SAEs serious adverse event

*Denominators represent total number of patients with follow-up to 90-days

†Denominators represent total number of randomized patients

Model 1: aOR obtained from generalized linear mixed models with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and baseline variables of age, region, hypertension, National Institutes of Health Stroke Scale score, dysphagia, and time from symptom onset to hospital arrival

Model 2: further adjusted management variables include withdraw active care, endotracheal intubation and reperfusion therapy for ischemic stroke and surgical procedural intervention for intracerebral haemorrhage during hospitalisation

Table S5 Post-hoc power calculations

Outcome	Lowest Oxygen Saturation		Power
	<93%	93-100%	
Death or dependency	380/683* (55.6)	2503/6266* (40.0)	>99.9%
Any SAEs	197/784† (25.1)	1085/7283† (14.9)	>99.9%
Acute stroke	70/784 (8.9)	364/7283 (5.0)	99.2%
Cardiac/other vascular disease	27/784 (3.4)	168/7283 (2.3)	50.6%
Pneumonia	49/784 (5.1)	212/7283 (2.9)	90.0%
Other infection	12/784 (1.5)	86/7283 (1.2)	13.3%
Other SAEs	38/784 (4.5)	252/7283 (3.4)	40.9%

Figure S1. Flow chart

*SaO$_2$ denotes arterial oxygen saturation

Figure S2. Distribution of the arterial oxygen saturation
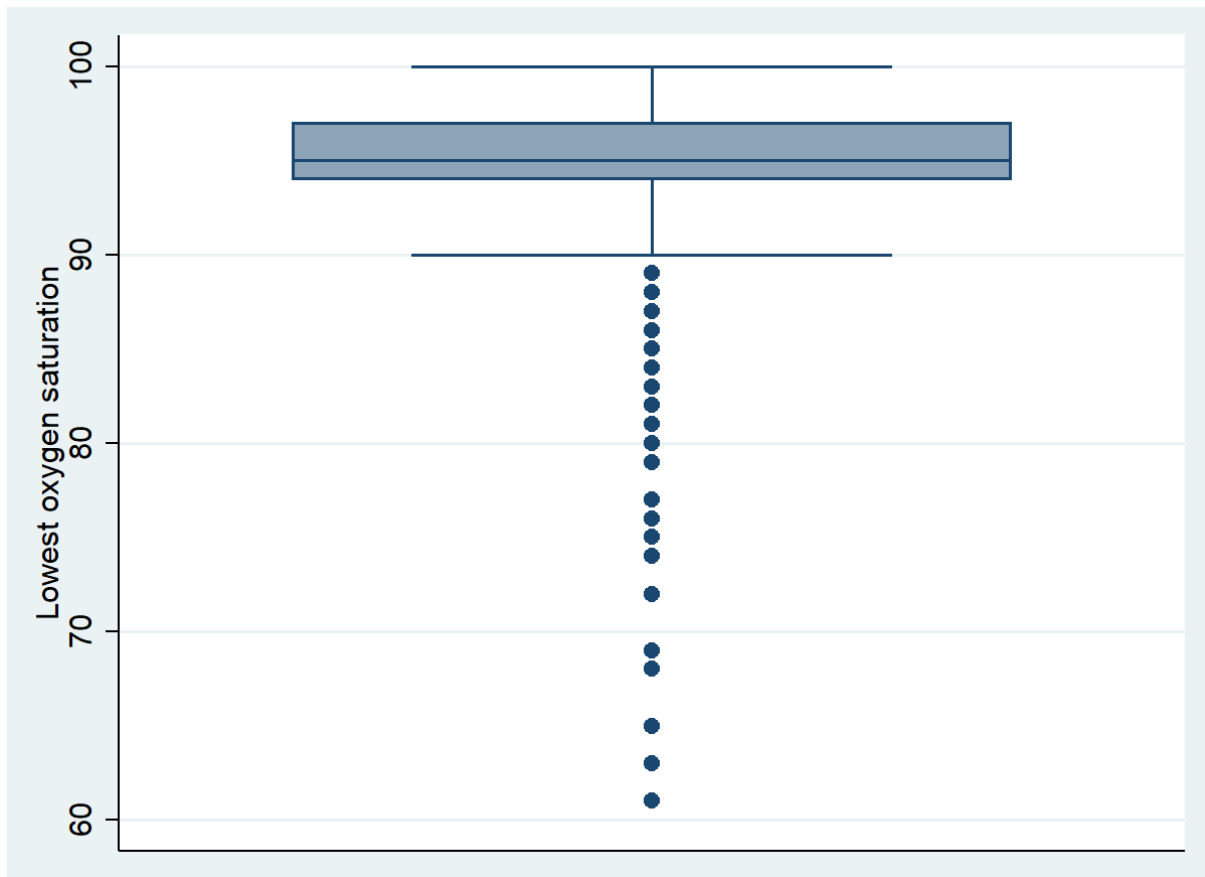
Boxes indicate first quartile (Q1) to third quartile (Q3); inner line indicates median; dots indicate outliers (N=8067).

Figure S3. Subgroup analysis of association of arterial oxygen saturation and death or dependency at 90 days

Subgroup	n/N	Death or dependency aOR (95% CI)		P for interaction
Region				
Australia/UK	311/3136		1.05 (0.77, 1.43)	0.417
China	157/2084		1.43 (0.91, 2.24)	
India/Sri Lanka	31/440		2.42 (0.77, 7.61)	
South America	127/710		1.12 (0.67, 1.87)	
Age group, years				
<60	99/1555		1.19 (0.72, 1.99)	0.776
60-69	138/1559		0.97 (0.61, 1.55)	
70-79	174/1652		1.31 (0.88, 1.95)	
>=80	215/1604		1.28 (0.86, 1.89)	
Sex				
Male	346/3773		1.33 (1.00, 1.78)	0.216
Female	280/2597		1.02 (0.74, 1.41)	
Stroke subtype				
AIS	527/5425		1.16 (0.91, 1.48)	0.587
ICH	61/540		1.68 (0.81, 3.48)	
Uncertain	38/405		1.01 (0.43, 2.35)	
Baseline NIHSS				
<5	250/3234		1.31 (0.94, 1.82)	0.840
5-9	167/1639		1.16 (0.80, 1.69)	
10-14	80/709		1.15 (0.65, 2.04)	
≥15	129/788		0.95 (0.49, 1.81)	
Pre-morbid level				
mRS 0-1	471/5197		1.12 (0.88, 1.45)	0.352
mRS 2-5	155/1173		1.45 (0.90, 2.35)	
Cardiac-respiratory comorbidity				
Yes	87/461		1.68 (0.85, 3.32)	0.151
No	539/5909		1.14 (0.90, 1.44)	
Head Positioning				
Lying flat	279/3040		1.21 (0.87, 1.89)	0.852
Sitting up	347/3330		1.16 (0.86, 1.57)	
Dysphagia				
Yes	214/1284		0.96 (0.63, 1.47)	0.258
No	412/5086		1.27 (0.99, 1.64)	
Time from onset to hospital arrival				
≤6 hours	361/3175		1.24 (0.89, 1.72)	0.756
>6 hours	265/3195		1.15 (0.86, 1.54)	

Footnote: AIS denotes acute ischaemic stroke, aOR adjusted odds ratio, CI confidence interval, ICH intracerebral haemorrhage, NIHSS National Institutes of Health Stroke Scale
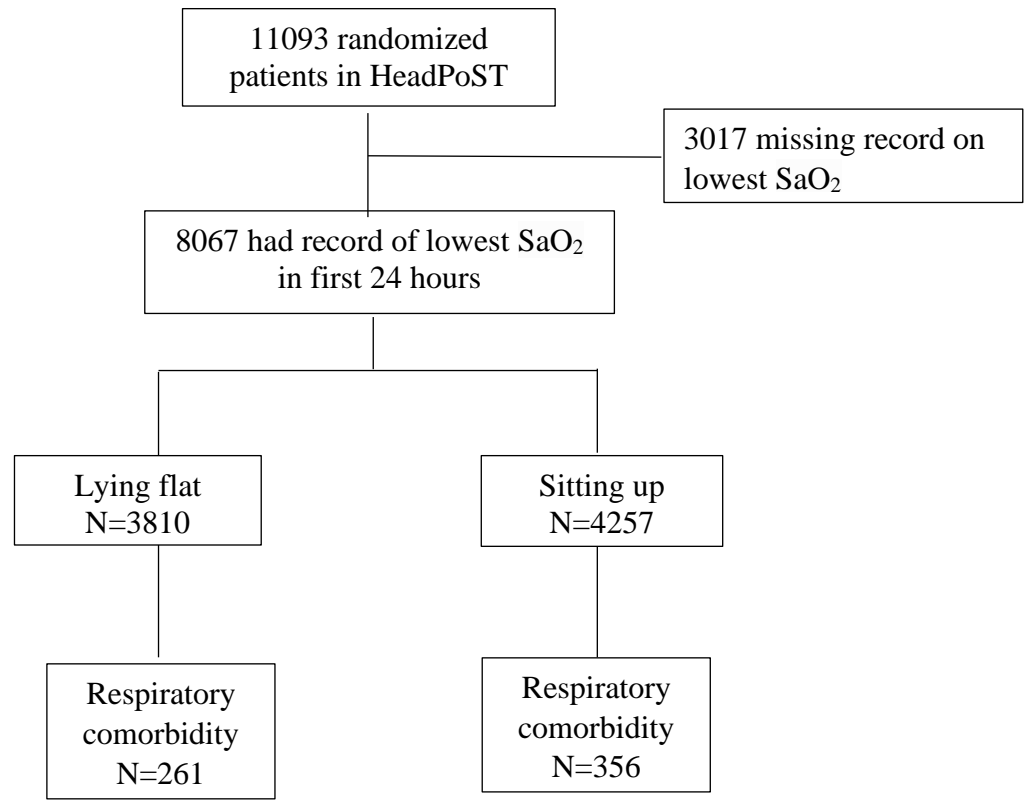
aOR obtained from generalized linear mixed models with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and baseline variables of age, sex, region, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, National Institutes of Health Stroke Scale score, pre-morbid score 0-1 on the modified Rankin scale,

dysphagia, hyperlipidaemia, other major health conditions, chronic obstructive pulmonary disease, stroke type, antithrombotic treatment, and time from symptom onset to hospital arrival, withdraw active care, endotracheal intubation and reperfusion therapy for ischemic stroke and surgical procedures for intracerebral haemorrhage during hospitalisation
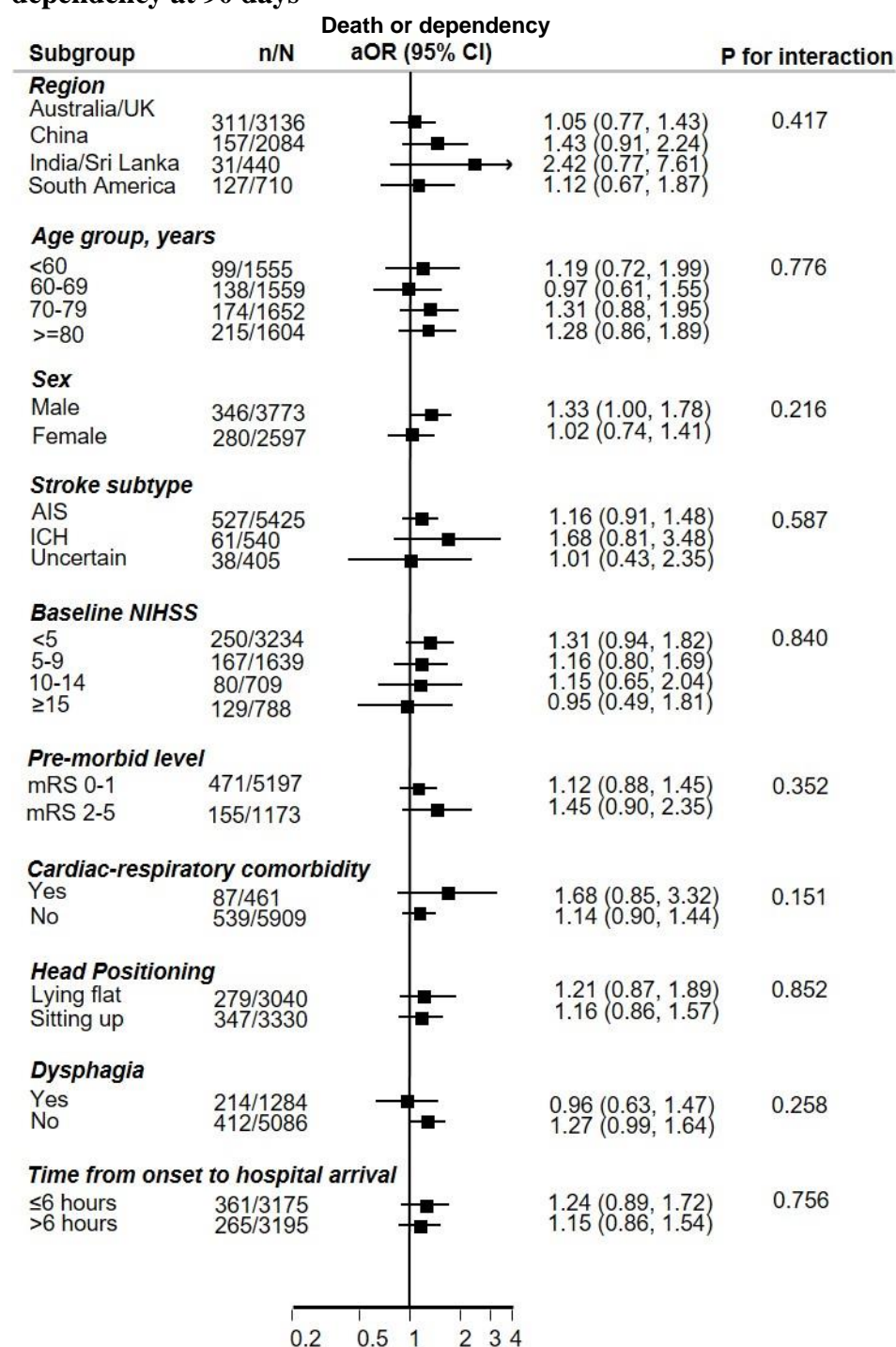
Figure S4. Subgroup analysis of the association between arterial oxygen saturation and serious adverse events at 90 days

SAE

| Subgroup	n/N	aOR (95% CI)	P for interaction
Region			
Australia/UK	369/3880	1.26 (0.94, 1.67)	0.331
China	172/2248	1.35 (0.71, 2.58)	
India/Sri Lanka	41/492	0.77 (0.29, 2.05)	
South America	133/747	1.95 (0.96, 3.26)	
Age group, years			
<60	121/1875	1.75 (0.96, 3.20)	0.778
60-69	156/1768	1.62 (1.00, 2.64)	
70-79	202/1879	1.34 (0.89, 2.02)	
>=80	236/1845	1.13 (0.79, 1.60)	
Sex			
Male	400/4346	1.41 (1.04, 1.91)	0.614
Female	315/3021	1.26 (0.91, 1.75)	
Stroke subtype			
AIS	604/6230	1.29 (1.01, 1.65)	0.418
ICH	67/628	2.00 (1.04, 3.85)	
Uncertain	44/509	1.12 (0.47, 2.69)	
Baseline NIHSS			
<5	292/3761	1.59 (1.08, 2.33)	0.158
5-9	186/1881	1.54 (1.03, 2.30)	
10-14	94/822	0.72 (0.38, 1.37)	
≥15	143/903	1.27 (0.83, 1.94)	
Pre-morbid level			
mRS 0-1	547/5978	1.37 (1.05, 1.79)	0.774
mRS 2-5	168/1389	1.28 (0.85, 1.91)	
Cardiac-respiratory comorbidity			
Yes	100/542	1.85 (1.06, 3.24)	0.165
No	615/6825	1.26 (0.99, 1.62)	
Head Positioning			
Lying flat	321/3492	1.60 (1.21, 2.23)	0.128
Sitting up	394/3874	1.14 (0.83, 1.56)	
Dysphagia			
Yes	239/1475	1.29 (0.92, 1.82)	0.781
No	476/5892	1.38 (1.02, 1.85)	
Time from onset to hospital arrival			
≤6 hours	415/3701	1.34 (1.01, 1.78)	0.596
>6 hours	300/3666	1.33 (0.94, 1.91)	

0.2   0.5   1   2 3 4

Footnote: AIS denotes acute ischemic stroke, aOR adjusted odds ratio, CI confidence interval, ICH intracerebral haemorrhage, NIHSS National Institutes of Health Stroke Scale

aOR obtained from generalized linear mixed models with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and baseline variables of age, sex, region, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, National
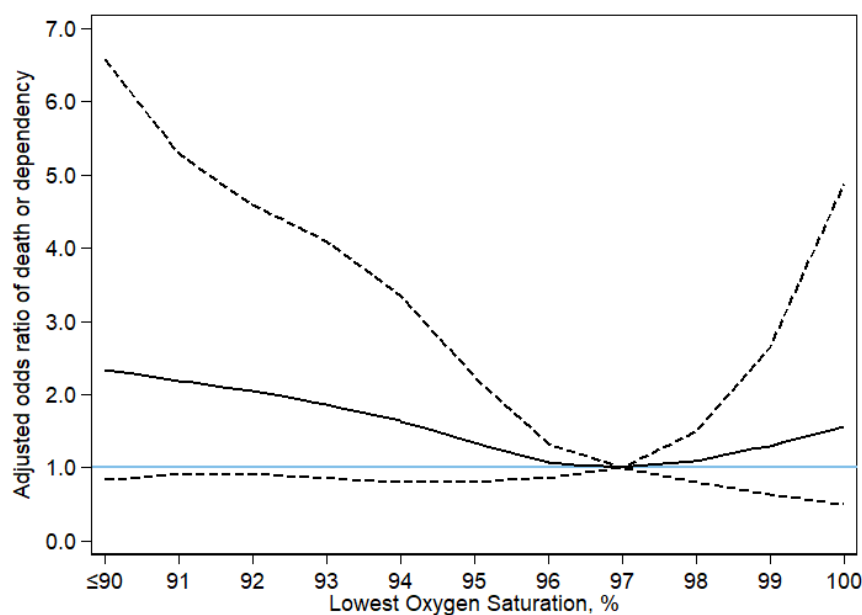
Institutes of Health Stroke Scale score, pre-morbid score 0-1 on the modified Rankin scale, dysphagia, hyperlipidaemia, other major health conditions, chronic obstructive pulmonary disease, stroke type, antithrombotic treatment, and time from symptom onset to hospital arrival, withdraw active care, endotracheal intubation and reperfusion therapy for ischemic stroke and surgical procedures for intracerebral haemorrhage during hospitalisation

Figure S5. Spline of lowest oxygen saturation and death or dependency at 90 days by stroke subtype

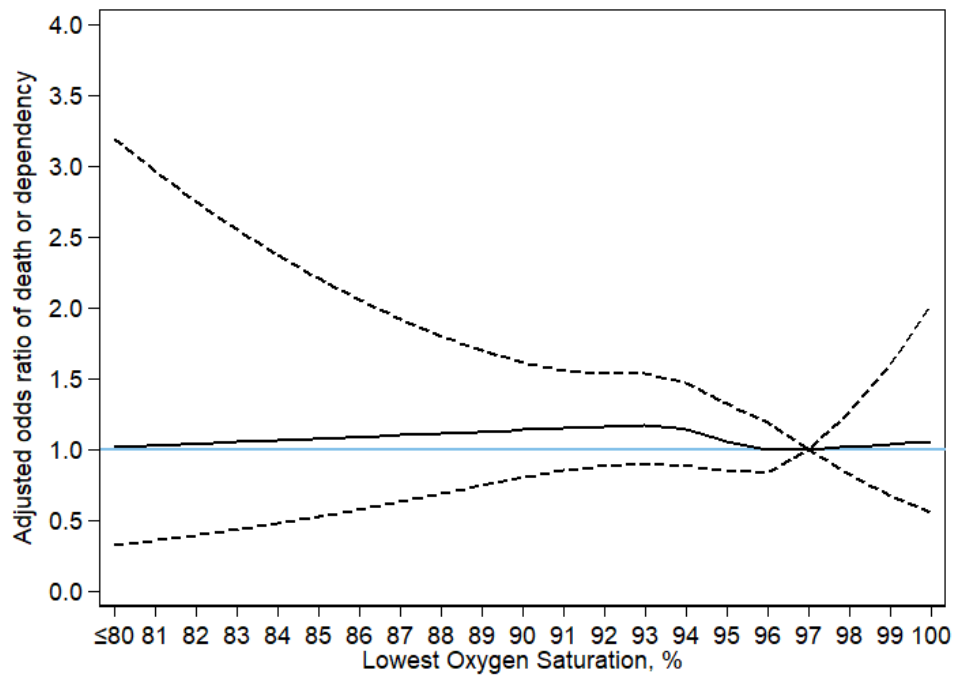### A. Ischaemic stroke
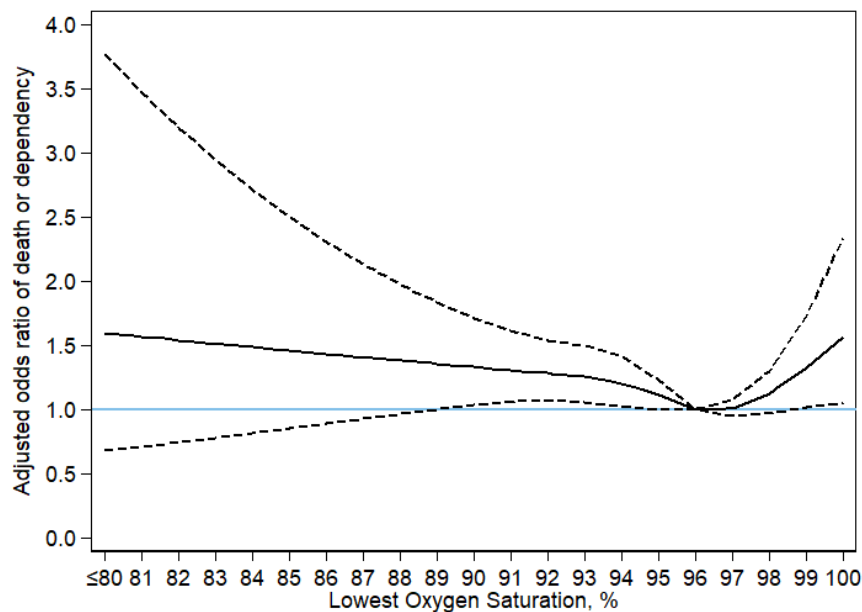
B. Haemorrhagic stroke

Footnote: Generalised linear mixed models with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and baseline variables of age, sex, region groups, history of coronary heart disease, diabetes mellitus, hypertension, heart failure, atrial fibrillation, National Institutes of Health Stroke Scale score, pre-morbid score 0-1 on the modified Rankin scale, dysphagia, hyperlipidaemia, other major health conditions, chronic

obstructive pulmonary disease, antithrombotic treatment, and time from symptom onset to hospital arrival, withdraw active care, endotracheal intubation with A. further adjusted reperfusion therapy and stroke subtype for ischemic stroke and B. further adjusted surgical procedures for haemorrhagic stroke
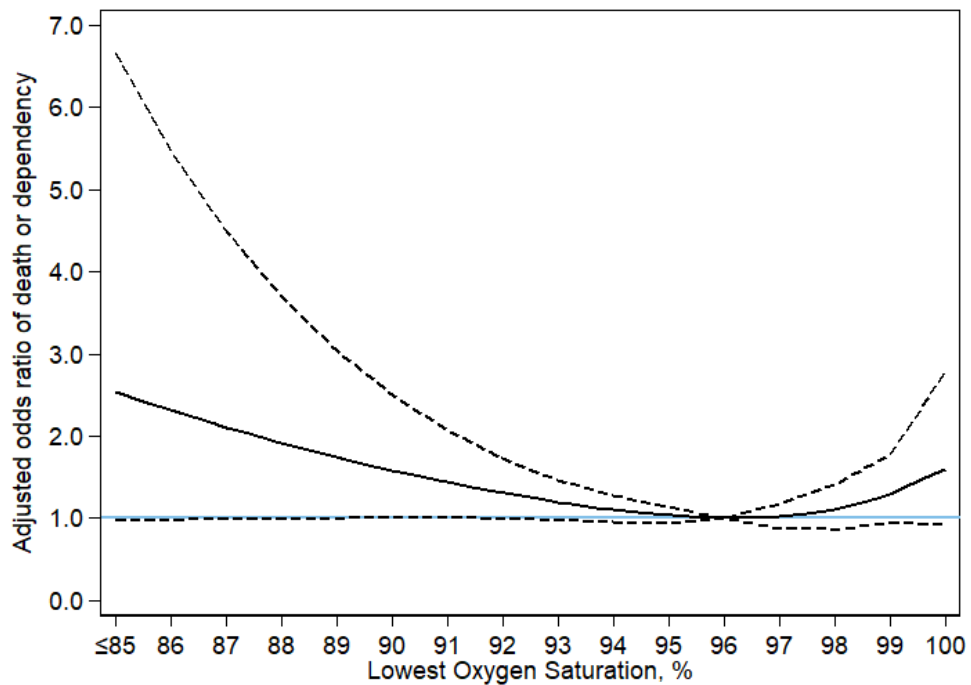
Spline fitted with 4 knots (percentiles 5th, 35th, 65th, 95th) for oxygen saturation, with lowest point as reference; solid line indicates adjusted odds ratio; dotted lines indicates 95% confidence intervals.

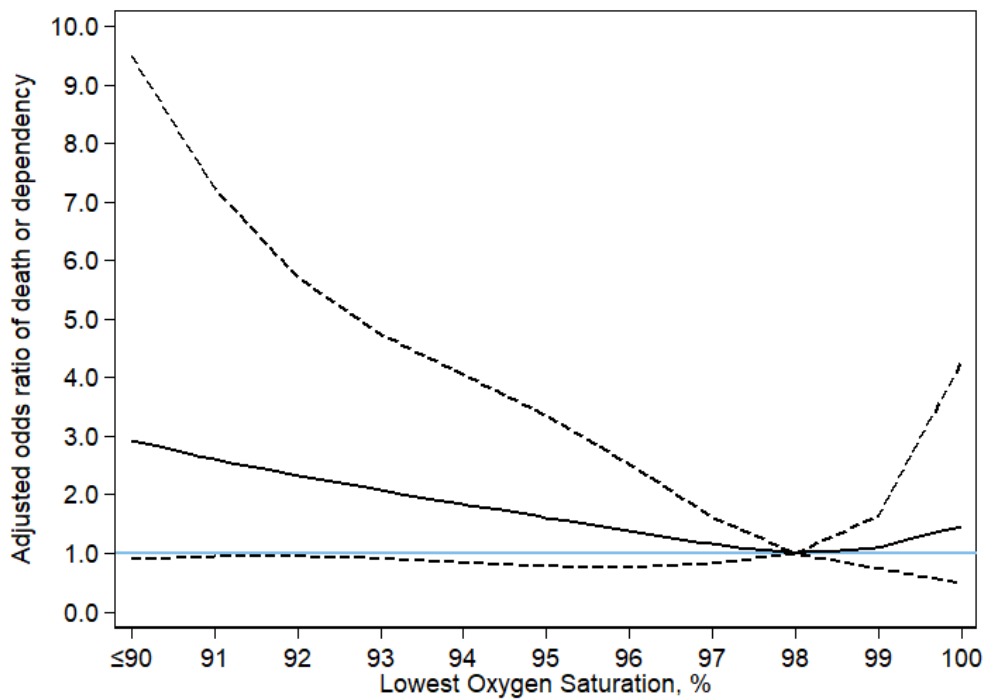**Figure S6. Spline of lowest oxygen saturation and death or dependency at 90 days by region**
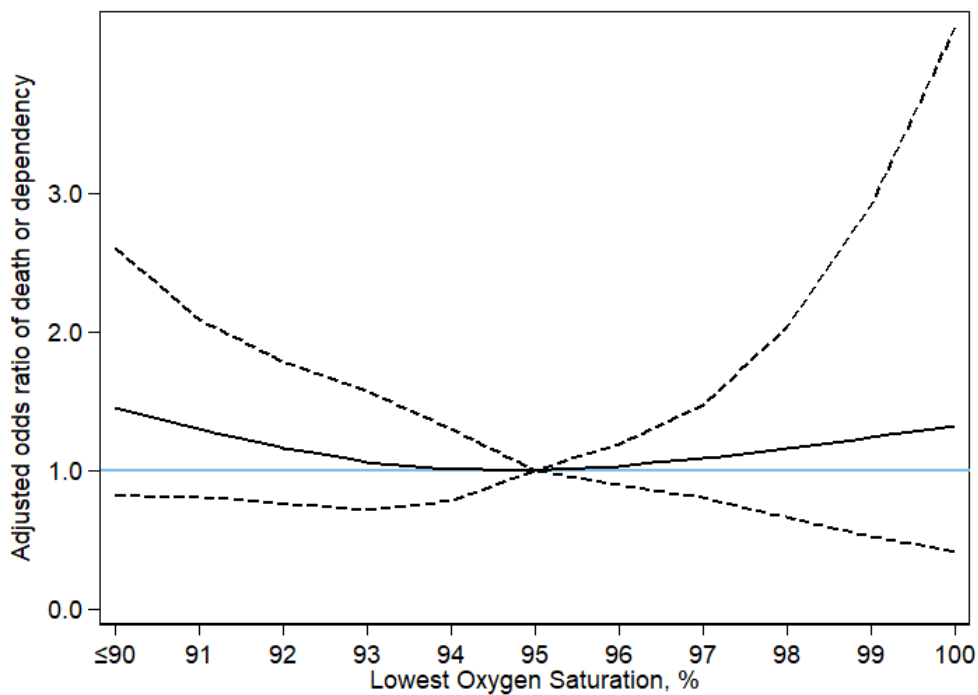
A. Australia and UK

B. China

C. India and Sri Lanka

D. South America

Footnote: Generalised linear mixed models with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and baseline variables of age, sex, history of coronary heart disease, diabetes mellitus, hypertension, heart failure, atrial fibrillation, National Institutes of Health Stroke Scale score, pre-morbid score 0-1 on the modified Rankin scale,

dysphagia, hyperlipidaemia, other major health conditions, chronic obstructive pulmonary disease, stroke subtype, antithrombotic treatment, and time from symptom onset to hospital arrival, withdraw active care, endotracheal intubation, reperfusion therapy for ischemic stroke and surgical procedures for haemorrhagic stroke

Spline fitted with 4 knots (percentiles 5th, 35th, 65th, 95th) for oxygen saturation, with lowest point as reference; solid line indicates adjusted odds ratio; dotted lines indicates 95% confidence intervals.

Supplementary Appendix of Chapter 4

Regional variations in components of acute stroke unit care in the international HeadPoST study

Ouyang M, Zhang Y, Wang X, Song L, Billot L et al.

Supplementary Tables: 4

Supplementary Figure: 1

Table S1. Process of care definitions

Care indicators	Definition
Reperfusion therapy for AIS	Intravenous or intra-arterial rtPA/other thrombolytic therapy for acute ischaemic stroke patients within the first 7 days of hospitalisation/before discharge if earlier
Antiplatelets for AIS	Antiplatelet therapy for acute ischaemic stroke patients initiated within the first 7 days of hospitalisation/before discharge if earlier
Anticoagulation for AF	Anticoagulant therapy for acute stroke patients with AF initiated within the first 7 days of hospitalisation/before discharge if earlier
Antihypertensive for secondary prevention	Oral antihypertensive agents for secondary prevention initiated within the first 7 days of hospitalisation/before discharge if earlier
Intensive BP lowering	Multidrug antihypertensive therapy with a BP target <140/90mmHg initiated within the first 7 days of hospitalisation/before discharge if earlier
Dysphagia screen	Initial screening for swallowing function within 24 hours of hospital arrival
Formal dysphagia assessment	Formal assessment for swallowing function by speech pathologist/allied health professionals if screening failed
Assisted feeding for dysphagia	Assisted feeding included modified diet (liquid, puree, soft food), nasogastric tube or percutaneous gastrostomy provided to acute stroke patients with diagnosed dysphagia within the first 7 days of hospitalisation/before discharge if earlier
Physiotherapy	Formal assessment by physiotherapist within the first 7 days of hospitalisation/before discharge if earlier
Occupational therapy	Formal assessment by occupational therapist within the first 7 days of hospitalisation/before discharge if earlier
Psychological therapy	Formal assessment by psychologist within the first 7 days of hospitalisation/before discharge if earlier

AF denotes atrial fibrillation, AIS acute ischaemic stroke, BP blood pressure, rtPA recombinant tissue plasminogen activator

Table S2. Number of acute stroke unit (ASU) admission by region

Region	ASU admission		
	Yes	**No**	**Total**
Australia	590 (98.2)	11 (1.8)	601
Brazil	81 (30.7)	183 (69.3)	264
Chile	272 (45.0)	333 (55.0)	605
China	891 (20.0)	3588 (80.0)	4479
Colombia	20 (52.6)	18 (47.4)	38
India	400 (80.2)	99 (19.8)	499
Sri Lanka	247 (91.1)	24 (8.9)	271
Taiwan	40 (23.1)	133 (76.9)	4156
United Kingdom	4079 (98.2)	77 (1.9)	173
Total	*6620 (59.7)*	*4466 (40.3)*	*11086*

Data are N (%), % are row percent.

Table S3. Outcomes by acute stroke unit (ASU) admission across region

	ASU admission			
	Total	**Yes**	**No**	**P value***
Time from hospital arrival to discharge/transfer, days				
Australia/UK (N=3697)	4.0 (2.0-10.0)	4.0 (2.0-10.0)	4.0 (2.0-10.0)	0.4306
China (includes Taiwan) (N=4193)	11.0 (8.0-15.0)	10.0 (7.0-14.0)	12.0 (8.0-15.0)	<0.0001
India/Sri Lanka (N=592)	5.0 (3.0-8.0)	5.0 (3.0-8.0)	3.0 (2.0-6.0)	<0.0001
South America† (N=741)	6.0 (3.0-10.0)	6.0 (3.0-11.0)	5.0 (3.0-9.0)	0.1345
Death				
Australia/UK (N=4703)	454 (9.7)	442 (9.6)	12 (13.8)	0.1869
China (includes Taiwan) (N=4489)	157 (3.5)	44 (4.9)	113 (3.2)	0.0110
India/Sri Lanka (N=748)	90 (12.0)	61 (9.7)	29 (25.0)	<0.0001
South America† (N=907)	93 (10.3)	32 (8.6)	61 (11.4)	0.1647
Death and dependency‡				
Australia/UK (N=3848)	1684 (43.7)	1653 (43.7)	31 (45.6)	0.7595
China (includes Taiwan) (N=4347)	1284 (29.5)	303 (34.1)	981 (28.3)	0.0003
India/Sri Lanka (N=694)	411 (59.2)	331 (55.6)	80 (80.8)	<0.0001
South America† (N=852)	442 (51.9)	180 (51.4)	262 (52.2)	0.8265

Data are median (IQR) and N (%)

ASU denotes acute stroke unit, AU Australia, UK United Kingdom

*P values were obtained from Wilcoxon rank sum test for time to hospital discharge and Chi-squared test for death, death and dependency.

†South America including Brazil, Chile and Colombia.

‡defined by scores 3-6 on the modified Rankin Scale

Table S4. Process of care patterns according to acute stroke unit (ASU) admission by regions

| | AU/UK | | | China (includes Taiwan) | | | India/Sri Lanka | | | South America‡ | | |
| | ASU care | | | ASU care | | | ASU care | | | ASU care | | |
Process of care	Yes N=4669 (98.2)	No N=88 (1.9)	SD*	Yes N=931 (20.0)	No N=3721 (80.0)	SD*	Yes N=647 (84.0)	No N=123 (16.0)	SD*	Yes N=373 (41.3)	No N=534 (58.7)	SD*
Reperfusion therapy for AIS†	838 (22.4)	15 (23.1)	0.02	145 (17.0)	115 (3.5)	0.46	62 (11.1)	8 (8.2)	0.10	86 (25.7)	68 (14.7)	0.28
Antiplatelets for AIS	3412 (91.3)	57 (90.5)	0.03	808 (94.5)	3157 (95.0)	0.02	532 (95.0)	82 (83.7)	0.37	302 (91.0)	437 (94.8)	0.15
Anticoagulation for AF	368 (44.4)	9 (39.1)	0.11	20 (30.3)	69 (45.7)	0.32	18 (90.0)	1 (33.3)	1.43	29 (82.9)	35 (85.4)	0.07
Antihypertensive for secondary prevention	3196 (69.2)	60 (69.0)	<0.01	442 (47.5)	1662 (44.7)	0.06	397 (61.6)	87 (70.7)	0.19	252 (67.7)	352 (65.9)	0.04
Intensive BP lowering	257 (5.5)	9 (10.2)	0.18	139 (14.9)	398 (10.7)	0.13	63 (9.7)	2 (1.6)	0.36	32 (8.6)	20 (3.7)	0.20
Dysphagia screen	4254 (91.3)	83 (94.3)	0.12	681 (73.1)	2537 (68.2)	0.11	585 (90.4)	85 (69.1)	0.55	150 (40.3)	406 (76.2)	0.78
Formal dysphagia assessment	958 (80.8)	27 (93.1)	0.37	52 (72.3)	128 (51.4)	0.49	72 (32.7)	12 (32.4)	<0.01	25 (54.4)	127 (77.0)	0.49
Assisted feeding for dysphagia	726 (68.6)	26 (89.7)	0.54	67 (65.7)	184 (44.8)	0.43	121 (92.4)	31 (63.3)	0.75	80 (81.6)	135 (89.4)	0.22
Physiotherapy	4302 (92.8)	73 (83.9)	0.28	168 (18.1)	663 (17.8)	<0.01	429 (67.2)	45 (37.2)	0.63	332 (89.2)	348 (65.3)	0.60
Occupational therapy	4027 (86.8)	66 (75.9)	0.28	39 (4.2)	82 (2.2)	0.11	111 (17.2)	1 (0.8)	0.60	92 (24.7)	37 (6.9)	0.50
Psychological therapy	60 (1.3)	2 (2.3)	0.08	12 (1.3)	39 (1.1)	0.02	18 (2.8)	1 (0.8)	0.15	47 (12.7)	28 (5.3)	0.26

Data are n (%); AF denotes atrial fibrillation, AIS acute ischaemic stroke, ASU acute stroke unit, AU Australia, BP blood pressure, SD standardised difference, UK United Kingdom; *Standardised difference = absolute difference in means or proportions divided by standard error; imbalance defined as value greater than 0.20 ; †includes intravenous and intra-arterial thrombolysis; ‡South America including Brazil, Chile and Colombia.

Figure S1. Functional outcomes in patient by regions, stratified by acute stroke unit (ASU) admission
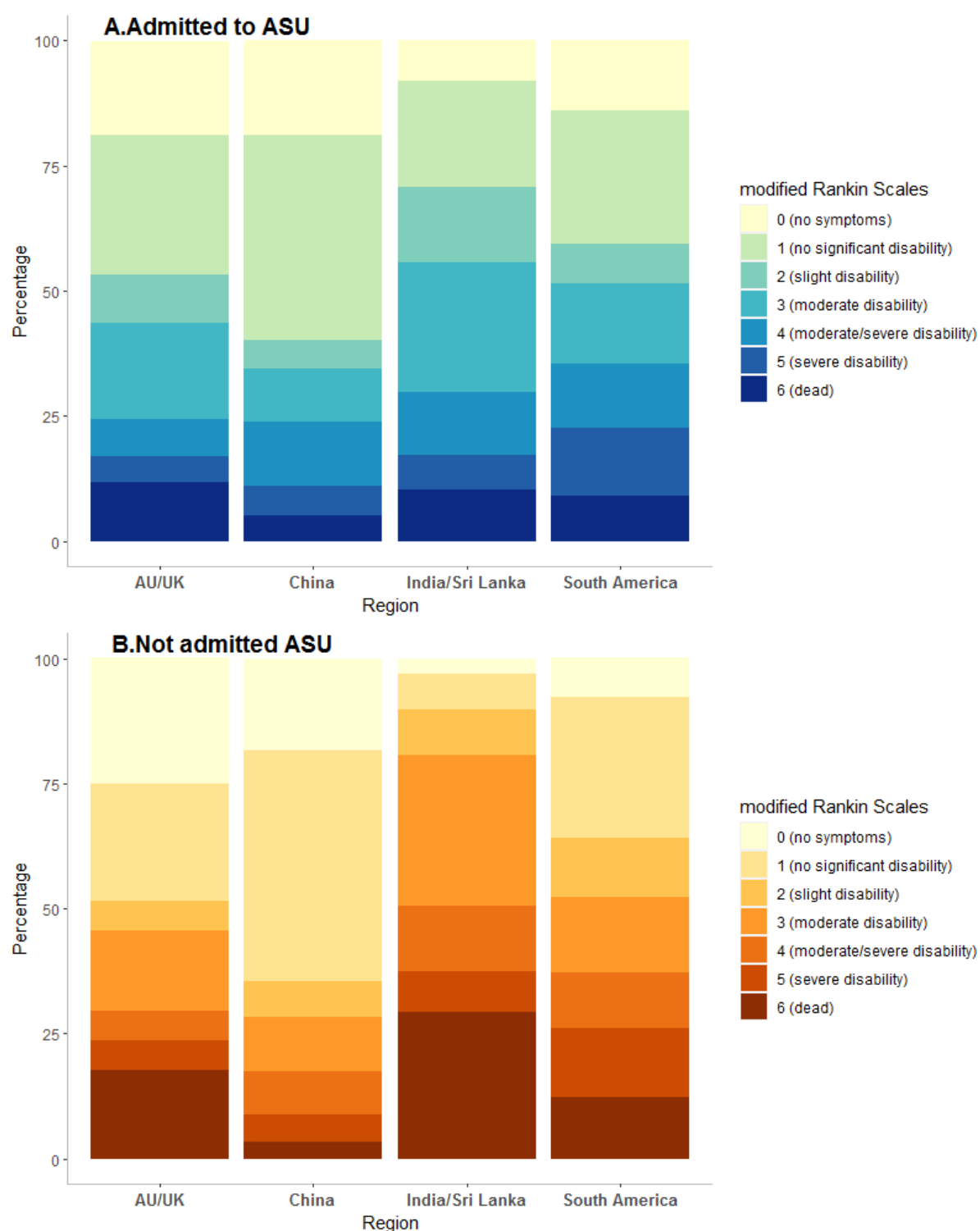
Footnote: ASU denotes acute stroke unit, AU Australia, UK United Kingdom

Supplementary Appendix of Chapter 5.1

Understanding implementation of the guideline-recommended care bundle in the INTERACT3 study: process evaluation protocol for an international cluster randomized control trial

Appendix 1. Semi-structured interview guide

Section One
Warm-up questions:
- Name   - What is your role at the hospital, and what are your main responsibilities?
Section Two
Perceptions about the intervention (NPT domain: coherence)
- How did you hear about INTERACT3? Did the PI tell you about it?   - What did you think was the aim of the INTERACT3 study? (probes: any concerns regarding clinical aspects of the intensive blood pressure reduction in stroke care? any clinical concerns regarding the care bundle in INTERACT3?)   - When you compare the care bundle in INTERACT3 and routine care in your hospital, which one was easier to deliver? Please explain why.   - What do you think about the training provided by CRAs for this INTERACT 3 study? (probe: did we need to more training once you were in the intervention phase?)
Section Three
Implementation/delivery and actions needed (NPT domain: cognitive participation and collective action)
<u>Reach</u>
- How have you found patient recruitment? Have you had any difficulties in recruiting patients for INTERACT3 at your hospital? Please explain why and can you give me an example?   - Did you recruit all eligible patients? Why or why not?
<u>Intervention Fidelity</u>

- How was the cross over to the INTERACT care bundle? Did you experience any difficulties? (probes: staff understanding or concerns, patients' and carers' understanding or concerns, or other?)

- Did the patients receive all the components of care bundle? (probe: If not, please explain why, separate components of BP lowering, glycaminc control, treatment of pyrexia, and reveral of anticoagulation).

- You have since recruited 5-10 patients, has there been any changes in how you implemented the care bundle? (probe: separate components)

- How well were the care bundle targets reached in the first hour when abnormal blood pressure, blood sugar level, body temperature and INR were detected? (Probe: reasons for not achieving the targets, provide an example)

Implementation

- What difficulties have you experienced in implementing INTERACT3 so far?
  (i.e. Such as paperwork, data entry, communication with other health professionals/departments, equipment, What were the patients' and their carers responses when you implemented the care bundle?)
- What could we do to support the implementation of INTERACT 3 at your hospital? (probe: BP lowering guidance, data entry)

Context/external factors
- Were there any external factors that affected the implementation of the care bundle to the patients? (e.g. availability of medication, any changes or events at your hospital during INTERACT3 that impacted on participation or recruitment?)
- If we want to implement the care bundle as a guideline widely in hospitals across your country, what would be the main barriers ? Please explain.

Section Four

Perceived effects (NPT domain: reflexive monitoring)
- How well do you think INTERACT3 worked overall in your hospital?

- What is the role of PI? What was done by PI regarding the project process? (probe: What additional support could have helped from PI or from the clinical trial team?)

- Do you have any suggestions on how to improve recruitment and implementation of the INTERACT 3 bundle? (probe: do they anticipate any further issues)

- Concluding question: Do you have any other thoughts about INTERACT3 besides what we talked about above?
  (Thank you so much for your participation in this research and for sharing your insights)

Appendix 2. Focus group discussion guide

Introduction: This focus group discussion is designed to assess your current thoughts and feelings about the intervention implementation in INTERACT3 project. The focus group discussion will take no more than 1.5 hour.

Anonymity: The discussion will be audio-recorded. I would like to assure you that the discussion will be anonymous. The record will be kept safely in a locked facility until they are transcribed word for word, then they will be destroyed. The transcribed notes of the focus group will contain no information that would allow individual subjects to be linked to specific statements. You should try to answer and comment as accurately and truthfully as possible. I and the other focus group participants would appreciate it if you would refrain from discussing the comments of other group members outside the focus group. If there are any questions or discussions that you do not wish to answer or participate in, you do not have to do so; however please try to answer and be as involved as possible.

Information consent: Before we start our discussion, I would like you to express your decision to participate. If you are fully understand above information and agree to participate in this interview, please repeat:

"I fully understand the background, aim, procedure, risk and benefit of participating the discussion for INTERACT3 process evaluation. I have enough time and chance to raise questions and satisfied with the answers. I agree to participate in this discussion. I acknowledge I can reject to participate at any time with no reason."

Introductory question

I am just going to give you a couple of minutes to think about your experience of participating the INTERACT3 project. Is anyone happy to share his or her experience?

Guiding questions for CRAs

- What are the attitudes of you and clinicians towards the intervention from your training and communication? (What did clinician think/say/do?)

- What drove the positive/negative reaction? If negative, how could it be rectified?

- What has been challenging
    (e.g. any difficulties did you have to deliver trainings for physicians? any difficulties did you meet when monitoring the sites (include daily monitor, remote monitor and on-site monitor)?

- How many hours did you spend for INTERACT3 training (include on-site training, remote training via phones, email or messages)? How well did you think of the training you provided to the implementers (those who recruit patients and implement care bundle)?

- What are the physician's aspects / feedbacks on how and why to implement the care bundle and for whom the care bundle works for? (any concerns regarding to the interventions implementation?)

- Does the physicians involve in the program over time? If they withdrawal, what was the reason?

- Were there any barriers or facilitators did you think affect the implementation of care bundle by physicians? *Make examples and explain. (have you noted any difference across sites?)*

- *How can we support you in your role better?*

Guiding questions for PIs

- What are your attitudes towards the interventions in INTERACT3? (What did clinician think/say/do?)

- What do you think about the aims of having the care bundle for ICH patients?

- Do you think the intervention will improve the outcome of patients? If not, why not? (specified in each components of the intervention)

- What are the main issues around implementation of the care bundle in your ward? (implementation process, cooperation with ED, interaction between clinicians and nurses) What are the barriers to implement? What are the enablers?

- How far will existing work practices and the division of labor have to be changed or adapted to implement the intervention?

- Is any challenges you met when conducting the project in your ward (explore patient involvement, clinician teamwork and communication, data collection)? Are there any factors we can assist with?

- Did you feel comfortable to implement this intervention as routine care? Do you think this intervention can be widely used at a national level? Is the intervention consistent with the workplace and overall organization?

Concluding question

- Of all the things we've discussed today, what would you say are the most important issues you would like to express about the implementation? Are there any other things you would like to raise about the INTERACT3 that we haven't covered?

Appendix 3. Non-participant observation documentary notes

Name of observer:

Date:

Length of time of observation:

Site No. / Location(s) of observation:

Trial implementation	Description	Comments
Enrolment procedure		
-if eligible patients being recruited		
-inform consent procedure (any difficulties in these procedures? e.g. patients concerns, family concerns etc.)		
Care bundle (intervention)		
-workload (number of patients, number of ward rounds, number of observations or inspections on patients)		
-interactions/ communication with patients/family surrogates		
-interactions between the clinicians and nurses -Is care bundle implementation in accordance with the order prescribed by clinicians?		
-what intervention were delivered? -Observe and record the procedure of blood pressure lowering/blood glucose control/temperature control/anticoagulant reversal -Is the intervention implemented in accordance with the protocol? -any barriers to implement each components of the complex interventions (etc. medication use, equipment, staffs)		
-what reactions of the patients regarding to the interventions implementation -patient cooperation		

Appendix 4. Hospital Organisation Questionnaire

Name：	Hospital：
Address：	
Telephone：	
E-mail：	Department：

1. General information		
1.1	□Y □N	Is the hospital a teaching hospital?
1.2	Location of the hospital: *(tick one answer)*	
	□Y	Metropolitan / urban
	□Y	Semi-metropolitan / semi-urban
	□Y	Rural / countryside
1.3	Level of hospital: *(tick one answer)*	
	□Y	Primary hospital
	□Y	Secondary hospital
	□Y	Tertiary hospital
1.4	□Y □N	Do you have research experience in clinical trials?
		If had, please specify:

1.5	☐Y ☐N	Is your department participating in research of ICH? Especially research involves one or more following interventions: blood pressure (BP) reduction, blood glucose (BG) level control, body temperature control, dysfunction of coagulation regulation.
1.6	☐Y ☐N	Do you have experience of research with online data collection?
1.7.1	☐Y ☐N	Are you familiar with National Institute of Health Stroke Scale (NIHSS) assessment?
1.7.2	☐Y ☐N	Are your staff familiar with National Institute of Health Stroke Scale (NIHSS) assessment?
1.8.1	☐Y ☐N	Are you familiar with modified Rankin Scale (mRS) assessment?
1.8.2	☐Y ☐N	Are your staff familiar with modified Rankin Scale (mRS) assessment?
1.9.1	☐Y ☐N	Did you received NIHSS assessment training before?
1.9.2	☐Y ☐N	Did your staff received NIHSS assessment training before?
1.10	☐Y ☐N	Do you have certificate of NIHSS assessment?
1.11	☐Y ☐N	Does your hospital have a dedicated acute stroke unit?
1.11.1	|__|__| beds	If yes, number of beds in the stroke unit?
2. Intracerebral Haemorrhage (ICH) related information		
2.1	|__|__|__|__|	How many spontaneous ICH patients admitted in your department last year (except intracerebral aneurysm and AVM)?
2.2	|__|__| %	Proportion of admitted ICH patients with time of ICH stroke onset to admission ≤ **6 hours**

2.3	|__|__|__|	How many ICH patients received surgery treatment?
2.4	□Y □N	Are the intracerebral haemorrhage (ICH) patients admitted into the hospital through Emergency Department (ED)?
2.4.1	|__|__|hours	If Yes, how long will the patients stay in the ED?
2.5	Which of stroke ward/unit that is in the hospital for ICH care:	
	□Y	Acute stroke unit *(ie accept patients acutely but aims for early discharge (usually within seven days))*
	□Y	Rehabilitation stroke unit *(ie accept patients after a delay, usually 7 or more days, with a focus on rehabilitation)*
	□Y	Comprehensive stroke units *(ie combined acute and rehabilitation, accept patients acutely but also provides early rehabilitation for up to several weeks if necessary)*
2.5.1	What is the kind of care provided (are respondents to choose 1 option or all that applies?):	
	□Y	'**Intensive**' with continuous monitoring, high staffing levels and life support facilities
	□Y	'**Semi-intensive**' with continuous monitoring, high staffing but no life support facilities
	□Y	'**Non-intensive**' with none of the above.

3. Investigations for diagnosis and monitoring devices

3.1	□Y □N	Is urgent CT scan available on arrival at the hospital?
3.1.1		If YES, what is the availability?
	□Y	24 hours, 7 days of the week

	☐Y	Working hours only (8am-5pm)
	☐Y	Working hours (8am-5pm) and on – call after hours
3.2	☒Y ☐N	MR Imaging
3.3	☐Y ☐N	Is INR testing available at your site?
3.4	☐Y ☐N	Is emergency laboratory testing available at all times?
3.5	Which device do you use to monitor blood pressure?	
	☐Y	Automatic monitoring device
	☐Y	Electronic sphygmomanometer
	☐Y	Mercury sphygmomanometer
3.6	☐Y ☐N	Do you have adequate devices for blood pressure monitoring at your site?
3.7	☐Y ☐N	Do you have insulin bump or intravenous infusion bump at your site?
3.8	☐Y ☐N	Do you use fingertip glucometers to monitor blood glucose level? *If not,* please answer question 3.8.1
3.8.1	☐Y ☐N	Do you have any method to monitor blood glucose level?
		If yes, please specify: _____
4. Management for ICH		
4.1	*Are there local protocols (including management/monitoring) for any of the following situations? (tick all that apply)*	
	☐Y	Intensive blood pressure (BP) lowering

		□Y	Reducing elevated blood glucose (BG) levels
		□Y	Fever (Body temperature) control
		□Y	Reversal of anticoagulation (if INR>1.5)
4.2	**Intensive blood pressure (BP) lowering**		
4.2.1	□Y □N		Is there a policy indicating early commencement of intensive blood pressure lowering in admitted ICH patients at your hospital?
4.2.1.1			**If yes**, which is the first ward/unit to commence intensive BP lowering for ICH patients arrived hospital?
		□Y	ED
		□Y	Neurology Department
		□Y	Neurosurgical Department
		□Y	NICU
		□Y	ICU
		□Y	Acute Stroke Unit
		□Y	Others, please specify_____
4.2.1.2	When will the intensive BP lowering commence after admission?		
		□Y	<1 hour
		□Y	1-6 hour
		□Y	>6 hours
4.2.2	SBP: _____mmHg DBP: _____mmHg		What is the recommended target of blood pressure lowering in your site? (SBP: systolic BP, DSP: diastolic BP)

4.2.3	_____hrs	How long does it take to reach the target SBP?
4.2.4	What is the duration for maintaining the target SBP control?	
	□Y	24 hour
	□Y	48 hours
	□Y	72 hours
	□Y	7 days or before discharge
	□Y	None of above, please specify_____
4.2.5	*What are the routine IV medications used in your department for BP lowering? (tick all that apply)*	
	□Y	Urapidil
	□Y	Metoprolol
	□Y	Atenolol
	□Y	Nicardipine
	□Y	Clevidipine
	□Y	Nimodipine
	□Y	Nifedipine
	□Y	Labetalol
	□Y	Nitroprusside Sodium
	□Y	Nitro-glycerine
	□Y	Isosorbide Dinitrate
	□Y	Frusemide
	□Y	Mannitol

	☐Y	Furazosin	
	☐Y	Hydralazine	
	☐Y	Clonidine	
	☐Y	Enalapril	
	☐Y	Others, Please specify _____	
4.2.6	*What are the routine oral medications used in your department for BP lowering?* *(tick all that apply)*		
	☐Y	Angiotensin II receptor antagonist	
	☐Y	Diuretic	
	☐Y	β blocker	
	☐Y	Calcium channel blocker (CCB)	
	☐Y	Angiotensin-converting-enzyme inhibitor (ACEI)	
	☐Y	Central antihypertensive medications	
	☐Y	Others, Please specify _____	
4.3	**Blood glucose (BG) level control**		
4.3.1	Which kind of patients do you routinely manage for glycaemia in acute ICH phase? *(tick all that apply)*		
	☐Y	Diabetes patients only	
	☐Y	Patients with increased blood glucose (BG) level, no matter diabetic or non-diabetic patients	
	☐Y	None of above	

4.3.2	D: _____mmol/L N: _____mmol/L	When will you commence BG lowering for diabetes and Non-diabetic patients respectively? Specify BG level. (D: diabetes, N:non-diabetic patients)
4.3.3	D: _____mmol/L N: _____mmol/L	When managing glycaemia level, what is the recommended target of BG level in your site for diabetes and non-diabetic patients respectively? Specify BG level.
4.3.4	What agents do you use for hyperglycaemic control in your site? *(tick all that apply)*	
	☐Y	Insulin
	☐Y	Oral hypoglycaemia agents
	☐Y	Never use
4.3.5	_____times per day	How often will BG level be monitored per day for patients with high level of BG?
4.4	**Fever (body temperature) control**	
4.4.1	_____℃	For ICH patients, when will you commence fever control? Please specify level of body temperature.
4.4.2	☐Y ☐N	Do you routinely use paracetamol (oral or rectal administration) as antifebrile medication?
4.4.3	☐Y ☐N	Do you use IV infusion of 4℃ Normal Saline (0.9% NaCl) to control body temperature?
4.5	**Reversal of anticoagulation**	
4.5.1	INR _____	For ICH patients previously used anticoagulants, what level of INR will you commence reversal of anticoagulation?
4.5.2	|__|__|min	How long does it take to complete evaluation of coagulation function?

4.5.3	|__|__|min	How long does it take to cross-match and take blood?
4.5.4	Which agents do you usually used for anticoagulation reversal in your site?	
	☐Y	Vitamin K
	☐Y	Prothrombin Complex Concentrates (PCC)
	☐Y	Fresh Frozen Plasma (FFP)

5. Epilepsy prevention after acute ICH

5.1	☐Y ☐N	Does your department conduct preventative treatment for patients with epilepsy after acute ICH?	
5.2	If YES, what is the scope of prevention?		
	☐Y	Routine prevention for all ICH patients	
	☐Y	Selective prevention	
5.2.1		*If selective prevention*, what factors considered:	
		☐Y	Haemorrhage in cerebral cortex
		☐Y	Age
		☐Y	Haematoma volume> 30ml
		☐Y	Surgery treatment
		☐Y	Others, please specify : _____
5.3	What medications will you use (please specify dosage, methods and period of treatment after the option, you can have multiple options)?		
	☐Y	Sodium Valproate	
	☐Y	Carbamazepine	
	☐Y	Levetiracetam	

	☐Y	Lamotrigine
	☐Y	Diazepam
	☐Y	Oxcarbazepine
	☐Y	Topiramate

6. Ethics		
6.1	☐Y ☐N	Does your hospital have any concerns of undertaking INTERACT3? If YES, please specify：_____
6.2	☐Y ☐N	Do you have any concerns of undertaking INTERACT3 in your department? If YES, please specify: _____
6.3	☐Y ☐N	Does ethics committee (EC) in your hospital accredited central ethic approval (enter into an agreement with an ethics committee from another institution to serve as its ethics committee of record)?
6.4	How long will take to get EC approval in your hospital?	
	☐Y	1 to 2 months
	☐Y	3 months
	☐Y	More than 3 months

Appendix 5. Quality control survey

1. Position (select one only).
Resident
Attending physician ☐
Deputy chief physician ☐
Chief physician ☐
Nurse ☐
2. Department
Neurosurgery ☐
Neurology ☐
Neurological Intensive Care Unit(NICU) ☐
Emergency Department ☐
Others ☐
Please specify_____
3. Working years
< 1year ☐
1-6 years ☐
6-10 years ☐
More than 10 years ☐
4. Do you have any experience in research (before INTERACT3)?
Yes ☐
No ☐
4.1 If yes, how many clinical trial involved?
|__|__|

5. Your role in INTERACT3 (*you can choose more than one option*)**.**	
PI	☐
Sub-PI	☐
Study coordinator	☐
Attending physician	☐
Research nurse	☐
Others	☐
Please specify_____	
5.1 Please specify your familiarity of the trial protocol:	
Very familiar	☐
Familiar	☐
Uncertain	☐
Unfamiliar	☐
Very unfamiliar	☐
6. How would you rate the conduct of INTERACT3 at your site?	
Very good	☐
Good	☐
Uncertain	☐
Not good	☐
Very bad	☐
6.1 Please explain why: _____	
7. Has your treatment and management of ICH changed after participating in INTERACT3?	

Yes ☐ No ☐

7.1 If yes, please specify which part has changed（you can choose more than one option）

Blood pressure control	☐
Glycemic control	☐
Body temperature control	☐
Anticoagulation reversal	☐
Others	☐
Please specify：	

8. Are all eligible patients enrolled in INTERACT3?

Yes ☐ No ☐

8.1 If no，which kind of patients were not enrolled？

Patient underwent surgery	☐
Severe patient	☐
Patient unable to do inform consent☐	
Others	☐
Please specify	

9.Is there any delay of providing the intervention？

Yes ☐ No ☐

9.1 If yes, what is the reason for delay (you can choose more than one option)?

Patient underwent surgery	☐
Long stay at Emergency	☐
Others	☐
Please specify	

The following questions help us understand your concepts on intervention.

10. Regarding the target of intensive blood pressure lowering (reduce to 140mmHg within 1 hour and maintain for 7 days/before discharge), do you think it is easy to achieve?

Very Easy	☐
Easy	☐
Unsure	☐
Hard	☐
Very hard	☐

11. What is the barrier to intensive blood pressure lowering （*you can choose more than one option*）

No ideal procedure	☐
Patients blood pressure hard to control	☐
Medication limitation	☐
Concerns of adverse effect	☐
Physicians unfamiliar with protocol	☐
Others	☐
Please specify	

12. What do you think of the procedure of intensive blood pressure lowering in your department?

Very satisfied	☐
Satisfied	☐
Unsure	☐
Not satisfied, can be improved	☐
Very unsatisfied and hard to improve	☐

Please specify what need to be improved in detail

13. Regarding the target of glycemic control (non-diabetic patient maintain blood glucose level [BGL] at 6.1 to 7.8mmol/L while diabetic patients at 7.8-10.0mmol/L), do you think it is easy to achieve?

Very Easy	☐
Easy	☐
Unsure	☐
Hard	☐
Very hard	☐

14. What is the barrier to achieve the target of glycemic control? (tick more than one)

Considering stress hyperglycemia therefore did not control	☐
Patients BGL hard to control	☐
Physicians unfamiliar with protocol	☐
Others	☐

Please specify

*14.1．For patients with increased glycaemia（**non-diabetic patients>=7.8mmol/L, diabetic patients>=10.0mmol/L**）,what is the reason for not commencing glycemic control immediately：*
Considering stress hyperglycemia ☐
Patient not cooperated ☐
Not control glycaemia routinely ☐
Others ☐
Please specify_____

15. What do you think the procedure of glycemic control in your department?

Very satisfied ☐
Satisfied ☐
Unsure ☐
Not satisfied, can be improved ☐
Very unsatisfied and hard to improve ☐
Please specify what need to be improved in detail

16. Regarding the target of body temperature control (<37.5 C), do you think it is easy to achieve

Very Easy ☐
Easy ☐
Unsure ☐
Hard ☐
Very hard ☐

17. Regarding the intervention of anticoagulation reversal, do you think it is easy to implement？

Very Easy ☐
Easy ☐
Unsure ☐
Hard ☐

Very hard ☐	

18. What are the factors that impede the implementation of the goal-directed care bundle?

19. Is there any unexpected serious adverse event when implementing the care bundle?

Yes ☐   No ☐

19.1If yes，did you report the event？

Yes ☐   No ☐

Please specify the event：

20. Did you have any difficulty when change over from control to intervention phase?

Yes ☐   No ☐

If yes, please specify

21. Did you experience difficulty in the following aspects when you conducting INTERACT3? (you can tick more than one)

Data collection	Yes ☐
Data entering	Yes ☐
Communicate with other staffs in the department	Yes ☐
Research equipment	Yes ☐
Concerns of the intervention	Yes ☐
Information consent	Yes ☐
Others	Yes ☐

Please specify:	
22. If you have experienced problems in the implementation of the trial, what could we do to support you better? (you can tick more than one)	
Additional site training	Yes ☐
Availability of research staff to call- when experiencing issues Yes ☐	
Online resources	Yes ☐
More frequent site visits	Yes ☐
Others	Yes ☐
Please specify:	

Appendix 6. Patient interview information sheet and consent form

Understanding the implementation of the care bundle for intracerebral haemorrhage management: process evaluation of INTERACT3 trial

Study Interview evaluation

INFORMATION FOR IMPLEMENTERS

Introduction

We are going to conduct process evaluation for the intervention implementers in INTERACT3 (Intensive care bundle with blood pressure reduction in acute cerebral haemorrhage trial). You are invited to participate in this interview for the study. The Principal Investigators of this project are Professor Chao You from West China Hospital and Professor Craig Anderson from The George Institute for Global Health.

The study aim is to understand the implementation of intervention in INTERACT3, include your perspectives of this project, adherence to the care bundle intervention and barriers to implement interventions. This interview is initiated and conducted by The George Institute for Global Health.

Who can participate in the interview?

Clinicians and nurses will be selected to participate in the interview evaluation.

What is required in the interview?

If you participate in this study you will be interviewed by a study team member who is skilled in this type of research. We would like to talk to you for around 20-30 minutes. The interview process is informal and flexible as our main aim is to encourage you to articulate your experiences and views. We appreciate your work commitments and will fit with your schedule and if necessary talk to you over more than one visit if that is more convenient. Please let us know what works best for you.

Privacy

If you wish to participate in this interview, your participation and personal information will be protected as privacy. Information of this interview will be coded as number instead of your name. Your identity will not be disclosed to others (except the study team), only if under your permission or legal request. The interview record as well as transcript documents will be restored with encryption and only can be accessed by study team. Your personal information will not be disclosed in the publications or disseminations of this study.

Autonomy

It is entirely voluntary for you to participate in this research. If you worried about some questions is related to your privacy or you would not like to response, you can request to skip this question in this interview. In the process of interview, you can request terminate the interview at any time if you want. We acknowledge your right to refuse and fully respect your decision.

What will happen once we have collected your information?

We would like to tape your interview(s) and will provide you with an audio copy after the interview. We would like you to listen the interview transcript and give us feedback on its contents by either;

- Agreeing that the transcript is a satisfactory representation of your views,
- Asking for minor changes to be made to the existing transcript,
- Asking us for a repeat interview to expand on or change things that you said, or

- Withdrawing your data and consent to participate in the interview evaluation.

All information will remain confidential. Study information will be stored in a securely locked file at the George Institute for Global Health and will be accessed only by study team members. Nothing written in reports will link you personally to the study.

Further Information

The research interviewer can discuss this information with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact the following interview evaluation investigator:

Investigator: ,

The George Institute for Global Health

Tel:

Address: Fax:

Ethics Approval

This study has been approved by the Ethical review pathways for *insert central EC*. Any person with concerns or complaints about the conduct of this study should contact the *insert central EC address*, telephone *insert central EC*.

<p align="center">This information sheet is for you to keep.</p>

Understanding the implementation of the care bundle for intracerebral haemorrhage management: process evaluation of INTERACT3 trial

Study Interview evaluation

IMPLEMENTER CONSENT FORM

Participant:

Name: ……………………………………………………………………………………

Address: …………………………………………………………………………………

☐   I have read the participant information sheet

☐   I feel free to accept or refuse to participate in the interview

☐   I have had a chance to ask questions and all of my questions have been answered to my satisfaction

☐   I have been given and I understand the information on the interview concerning its nature, purpose, and duration, including any known or expected inconvenience.

☐   I agree that some of my words (not my name) will be used in the study reports
☐   I agree that the interview will be taped
☐   I do not have any objections to the interview record being kept at the end of the study
☐   By signing this form, I give my free and informed consent to take part in this study as outlined in the information sheet and this consent form. I understand that I am free to withdraw from the study at any given time. I have been given a copy of this consent form. By signing this form I have not given up my legal rights.

Name of participant:…………………………………………………………………… ……

Signature of participant: ……………………………………..**Date:** ……………………

Name of interviewer: …….……………………………………………………………………

Signature of interviewer: …………………………………………….**Date:** ……………

INTERACT3 Study Interview evaluation

INFORMATION FOR PARTICIPANTS

Introduction

You are invited to take part in the interview evaluation of the INTERACT3 study, which is part of the process evaluation of the study. As a patient or carer involved in this study you would be aware that this is a research study which looks to compare a goal-directed care bundle for intracerebral haemorrhage management with usual care. You are invited to take part in the study to share your views about your health care experience and also about the study.

We know that patients' outcome is likely to be improved by things such as systems of care, costs of medications and additional support, relationships with your health providers. This might be very important in whether the goal-directed care bundle is effective. We are therefore seeking to explore your views on the advantages and disadvantages of the goal-directed care bundle during your hospitalization.

Your views on these issues will help us understand what intervention has in providing best practice care for intracerebral haemorrhage patients. The findings will help us understand the research and how it could work to improve outcomes.

Who can participate in the interview?

Participants or Participant Responsible (carer) from intervention arm in the INTERACT3 trial will be invited to participate in this interview evaluation from a sample of participating sites. This interview will be conducted in patients when their condition is stable in hospital.

What is required in the interview?

If you participate in this study you will be interviewed by a study team member. We would like to talk to you for around 30-60 minutes. The interview process is informal and flexible as our main aim is to hear your experiences and views. We will fit within your schedule and if necessary speak with you over more than one visit if that is more convenient. Please let us know what works well for you.

What will happen once we have collected your information?

We would like to record your interview(s).

All information will remain confidential. Study information will be stored in a securely locked file and password assessed electronic folder at the George Institute for Global Health and will be accessed only by study team members. Nothing written in reports will link you personally to the study.

Ethics Approval

This study has been approved by the Human Research Ethics Committee (West China Hospital, China) and your local Ethics Committee.

Contact Details
If you have any problems, concerns, questions or complaints about this study, you should preferably contact

<Investigator Name>

<Designation>

<Site Name>

<Site Address>

<Contact Number>

OR

Name of the ethics committee	: _____
Designation	: _____
Contact No	: _____

This information sheet is for you to keep.

<Contact Number>

INTERACT3 Study Interview evaluation

PARTICIPANT CONSENT FORM

Participant:

Name:

………………………………………………………………………………………….

Address:

…………………………………………………………………………………………..

ϒ   I have read the participant information sheet

ϒ   I feel free to accept or refuse to participate in the interview

ϒ   I have had a chance to ask questions and all of my questions have been answered to my satisfaction

ϒ   I have been given and I understand the information on the interview concerning its nature, purpose, and duration, including any known or expected inconvenience.

☐   I agree that some of my words (not my name) will be used in the study reports
☐   I agree that the interview will be taped
☐   I do not have any objections to the interview record being kept at the end of the study
☐   By signing this form, I give my free and informed consent to take part in this study as outlined in the information sheet and this consent form. I understand that I am free to withdraw from the study at any given time. I have been given a copy of this consent form. By signing this form I have not given up my legal rights.

Name of
participant/carer:………………………………………………………………………………

Signature of participant:
………………………………………………………...Date:…..…………………

Name of interviewer:
…….…………………………………………………………………….…………

Signature of interviewer: ……………………………… Date: ……………………

Supplementary Appendix of Chapter 5.2

Implementing a goal-directed care bundle after acute intracerebral haemorrhage: process evaluation for INTERACT3 study in China

Ouyang M, Anderson CS, Song L, Jan S, Sun L, et al.

Supplemental Table: 2

Supplemental Figure: 4

Appendix: 3

Supplementary Table S1. Characteristics of the purposive sampled interview participants

Hospital	Region	Location	Level of hospital	Department	Doctor (N)*	Nurse (N)	Rate of recruitment †	Data entry quality‡	Average time to reach BP target (SBP<140 mmHg), hours
1	West	Urban	Tertiary	Neurosurgery	3 (2 in-training, 1 attending specialist)	1	0.56	2	3
2	North	Urban	Tertiary	Neurosurgery	3 (1 in-training, 2 attending specialist)	1	0.31	2	3
3	East	Urban	Tertiary	Neurology	2 (1 principle doctor, 1 attending specialist)	1	0.74	1	2.5
4	Middle	Semi-urban	Tertiary	Neurology and Neurosurgery	3 (1 principle doctor, 2 attending specialist)	1	0.53	1	0.75
5	West	Urban	Tertiary	Neurosurgery	2 (1 associate principle doctor, 1 attending specialists)	1	0.53	3	4
6	East	Urban	Tertiary	Neurosurgery	2 (attending specialists)	1	0.45	3	-
7	West	Urban	Tertiary	Neurosurgery	1 (principle doctor)	0	0.43	2	4
8	East	Urban	Tertiary	Emergency	1 (attending specialist)	0	0.52	2	0.5
9	East	Semi-urban	Secondary	Neurosurgery	2 (1 attending specialist, 1 principle doctor)	1	0.19	3	0.83

BP denotes blood pressure, SBP systolic blood pressure

*Medical doctor professorial grades in China include (from junior to senior)[1]: in-training (intern or resident); attending specialist (equivalent to lecturer grade in universities); associate principle doctor (equivalent to associate professor grade in universities); principle doctor (equivalent to professor grade in universities).

†Rate of recruitment is calculated according to actual enrolment number divided by expected weekly enrolment. A low rate of recruitment is defined by less than 50% of expected enrolment.

‡Data entry quality evaluated according to routine monitoring data, field notes and monthly implementation performance reports extracted from case report forms with scale 1 indicates good, 2 indicates moderate, and 3 indicates poor.

Data sources: Hospital Organization Questionnaire, routine monitoring data, field notes and performance reports.

Supplemental Table S2. Core constructs of Normalisation Process Theory (NPT) against categories and codes identified through interviews

Core constructs and generative mechanisms of NPT[1]	Questions illustrative of NPT constructs	Codes lists
Coherence *Definition: how the work that defines and organizes a practice/intervention is understood, rendered meaningful and invested in, in respect of the knowledge, skills, behaviours, actors and actions required to implement it.*	1. What the implementers think about care bundle? 2. How do the implementer compare the care bundle to routine care?	Established protocol and knowledge challenging the integration: • Agree the care bundle is more standardised than routine management • Not meaningful due to established similar practice and knowledge
Cognitive participation *Definition: commitment to and engagement of participants with the intervention. Do participants view the intervention as something worthwhile and appropriate to commit their individual time and effort [signing up] to bring about the intended outcome?*	3. How did the implementer come to take part in implementing the care bundle? 4. What keeps the implementers motivated to continue recruitment and implementation?	Getting participation relies on: • Assigned responsibility • Capacity of individual in the work • Commission to implementers
Collective action *Definition: the work that will be required of participants to implement the intervention, including preparation and/or training. How far will existing work practices and the division of labour have to be changed or adapted to implement the intervention? Is the intervention consistent with the existing norms and goals of the groups, the workplace and overall organization [this is policy, practice and service user linked]*	5. How do implementers make the care bundle work? 6. What are the changes/difficulties met when transferred from routine care to care bundle? 7. What are the contextual factors that affected the implementation of the care bundle?	Optimising workflow and dedicated team • Changing the workflows and develop a standardized procedure to fit into routine care • Have a dedicated team with better cooperation between physicians and nurses • Difficulties to optimise the process if involved multiple departments
Reflexive monitoring *Definition: participants' individual and collective*	8. How do the implementers evaluate the implementation of care bundle?	Acknowledged benefits and reflections

ongoing formal and informal appraisal of the intervention and its benefits for participants, in relation to realizing individual and organizational goals.	9. How does the care bundle implementation change over time and what are the effects?	• Recognition of the intervention benefits (e.g. increased awareness of monitoring) • Case review, expertise consultation to improve quality of care • Identified the important factors for wider application: e.g. staff resources, equipment, medication supply, patient insurance and payment and implementer commission

Data sources: semi-structured interviews.

Reference:

1. Murray, Elizabeth, Shaun Treweek, Catherine Pope, Anne Macfarlane, Luciana Ballini, Christopher Dowrick, Tracy Finch, *et al.* "Normalisation Process Theory: A Framework for Developing, Evaluating and Implementing Complex Interventions." *BMC Medicine* 8, no. 1 (2010): 63.

Supplementary Figure S1. MRC Guidance Framework[1]
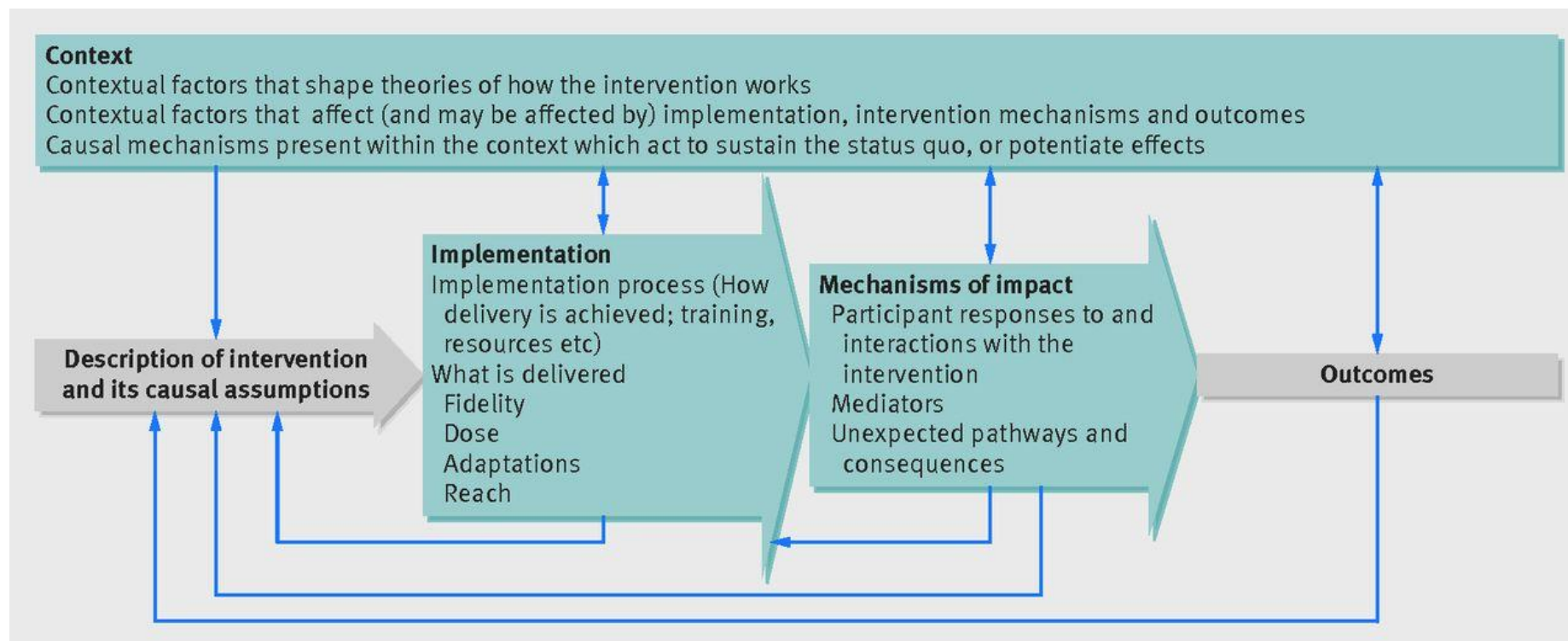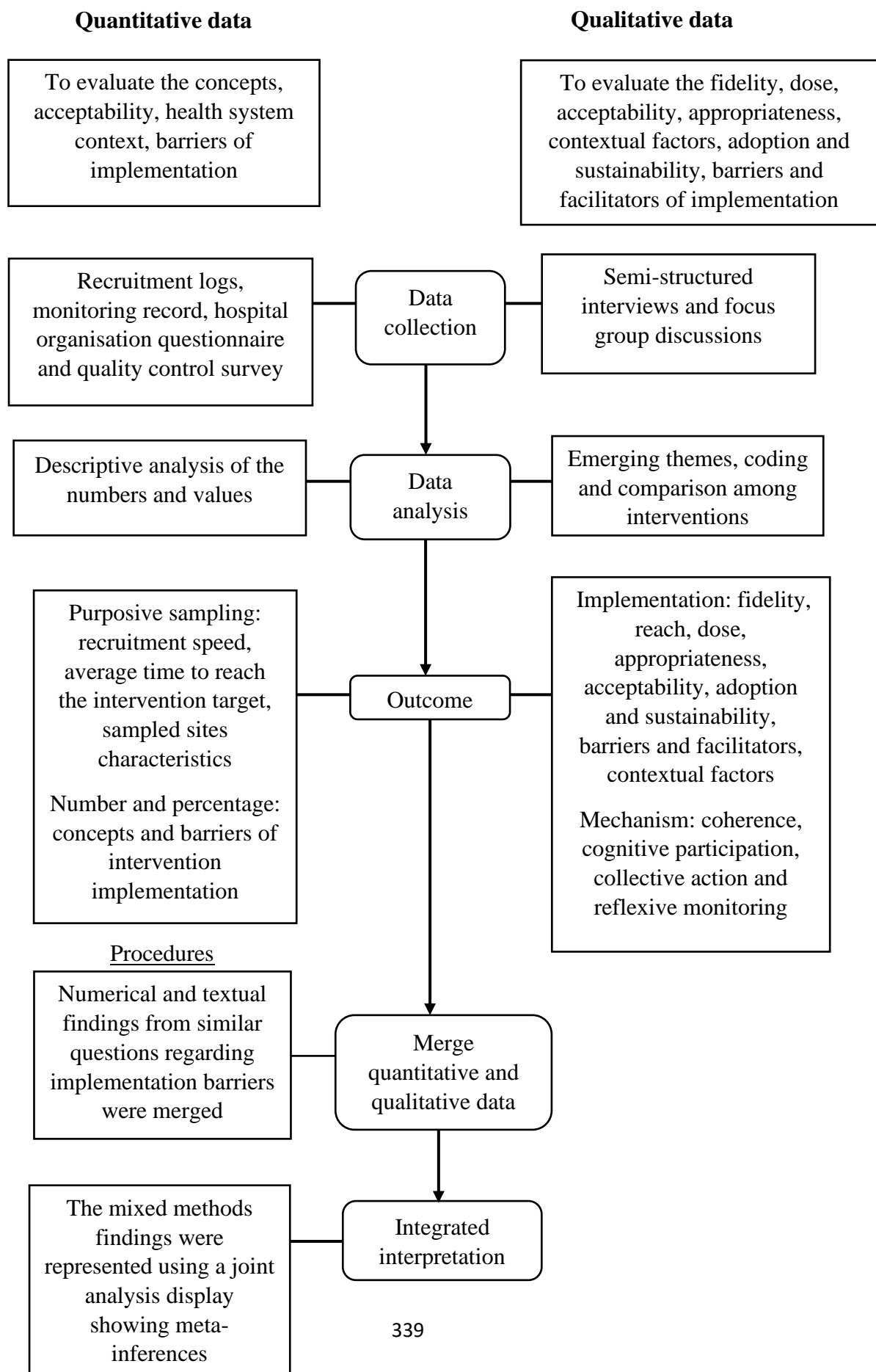

References

1. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: The new medical research council guidance. *BMJ*. 2008;337:29-983

Supplemental Figure S2. Data source and flow work of mixed-method approach

Quantitative data   **Qualitative data**

| To evaluate the concepts, acceptability, health system context, barriers of implementation | | To evaluate the fidelity, dose, acceptability, appropriateness, contextual factors, adoption and sustainability, barriers and facilitators of implementation |

| Recruitment logs, monitoring record, hospital organisation questionnaire and quality control survey | Data collection | Semi-structured interviews and focus group discussions |

| Descriptive analysis of the numbers and values | Data analysis | Emerging themes, coding and comparison among interventions |

| Purposive sampling: recruitment speed, average time to reach the intervention target, sampled sites characteristics

Number and percentage: concepts and barriers of intervention implementation | Outcome | Implementation: fidelity, reach, dose, appropriateness, acceptability, adoption and sustainability, barriers and facilitators, contextual factors

Mechanism: coherence, cognitive participation, collective action and reflexive monitoring |

Procedures

| Numerical and textual findings from similar questions regarding implementation barriers were merged | Merge quantitative and qualitative data |

| The mixed methods findings were represented using a joint analysis display showing meta-inferences | Integrated interpretation |

339

Supplemental Figure S3. Joint analysis of barriers to reach the intensive blood pressure control target
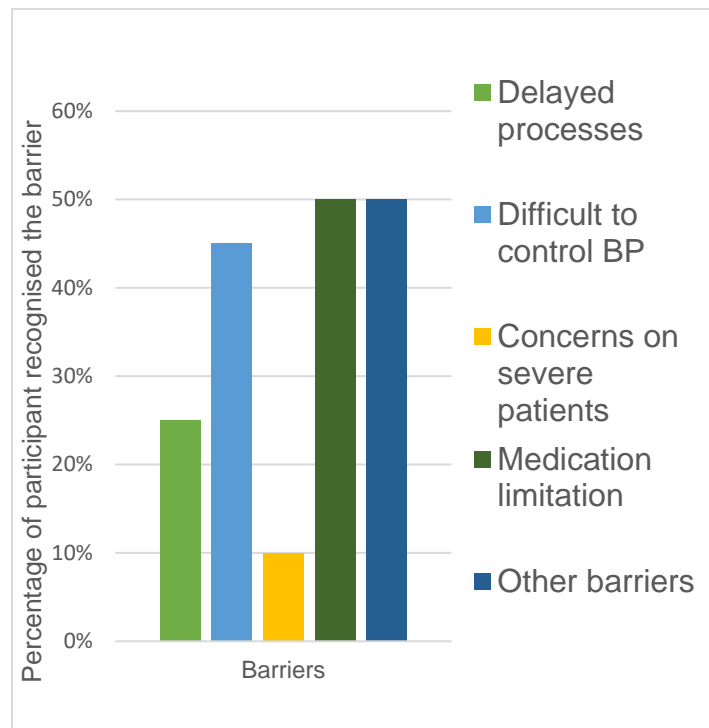
Delayed processes

"The process of intensive BP lowering was delayed due to surgical procedure or underwent other investigation, made it difficult to reach target BP level within one hour."

"For the ICH patient, you need to confirm diagnosis by CT scan and other investigations; and within counted time for waiting diagnosis as well as information consent, it is hard to reduce the BP within one hour."

Difficult to control BP

"Some patients had very high BP and became aggressive in the acute phase, make it difficult to reduce the blood pressure to target level within one hour."

"For patients with renal hypertension, it was difficult to reduce BP."

Concerns on severe patients

"Patients with comorbidity of heart disease felt uncomfortable and agitated after intensive lowering blood pressure, then we feared to reduce the BP."

"Patients with elder age and constant high BP with 180/190 mmHg regularly, the doctors will not reduce BP to 140mmHg because they though it is too low, instead 150 is more acceptable."

Medication limitation

"The medication supply was limited and most of the BP medications out of stock at the middle of the months, which influenced the intensive BP reduction."

"Unlike other hospitals, we did not have too much more choices on effective antihypertensive agent such as Urapidil due to hospital policy…The supply sometimes is not consistently."

Other barriers

"The cooperation issue between multiple departments made the intervention implementation delayed such as administration of the antihypertensive agent."

"Some very severe patients self-discharged because economic burden and refused administration of antihypertensive agent."

"Patient did not accept the intensive BP antihypertensive agents since they thought they have already had medications routinely."

Footnote: data sources are from quality control survey, semi-structured interviews and focus group discussions.

Supplemental Figure S4. Joint analysis of barriers to reach the blood glucose level control target
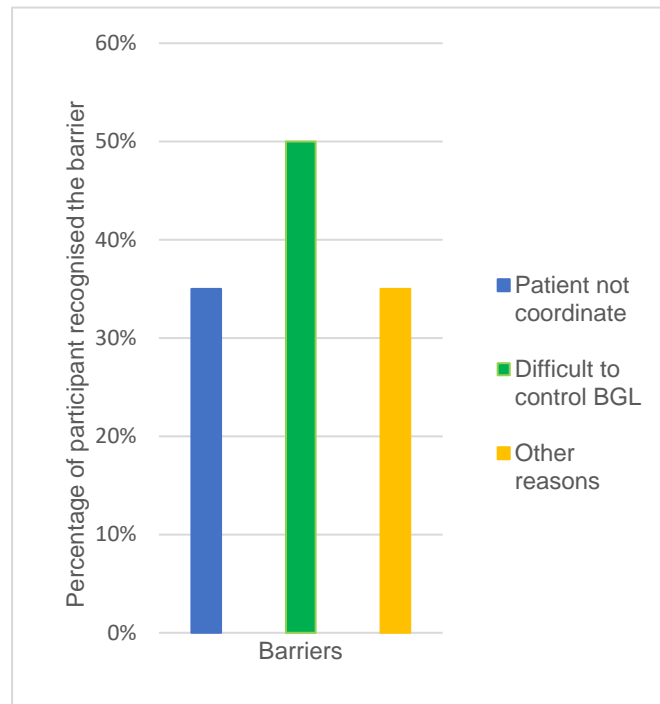
Poor patient cooperation

"They did not accept the high frequent testing of BGL, especially to those patients without diabetes history, mainly their carers did not understand."

"It's hard to make patients to accept continuing use insulin pump to maintain BGL."

Difficult to control BGL

"Patients admitted to hospital usually intravenous medication with glucose solution, which made it difficult to control the BGL."

"The target range is narrow and difficult to control BGL to reach…"

"Surgical doctors lack of experience of using internal medicine to control BGL make it difficult to reach the target, so better to have endocrine department to engage."

"Some patients had high BGL regularly, make it difficult to control in a certain time."

Other reasons

"The nurses are generally very busy and have a heavy workload so that it's difficult to give monitoring on time."

"We don't have sufficient pump to administrate insulin because we need also use this equipment to reduce BP."

"You can't always have enough pump to use in our ward because only specialized doctor prescribed then it can be used according to our hospital policy."
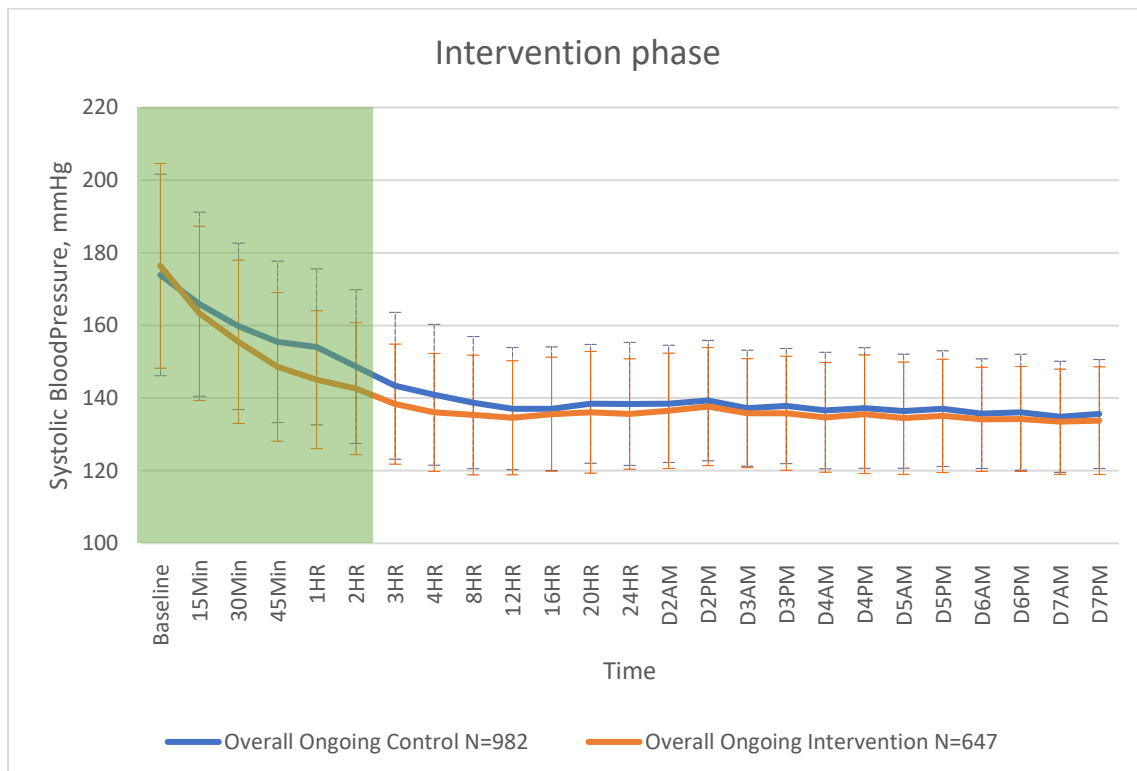
Footnote: data sources are from quality control survey, semi-structured interviews and focus group discussions.

Supplemental Figure S5. Comparison of the improvements on blood pressure lowering before and after the training

A. Blood pressure lowering report before the training (May 2020)
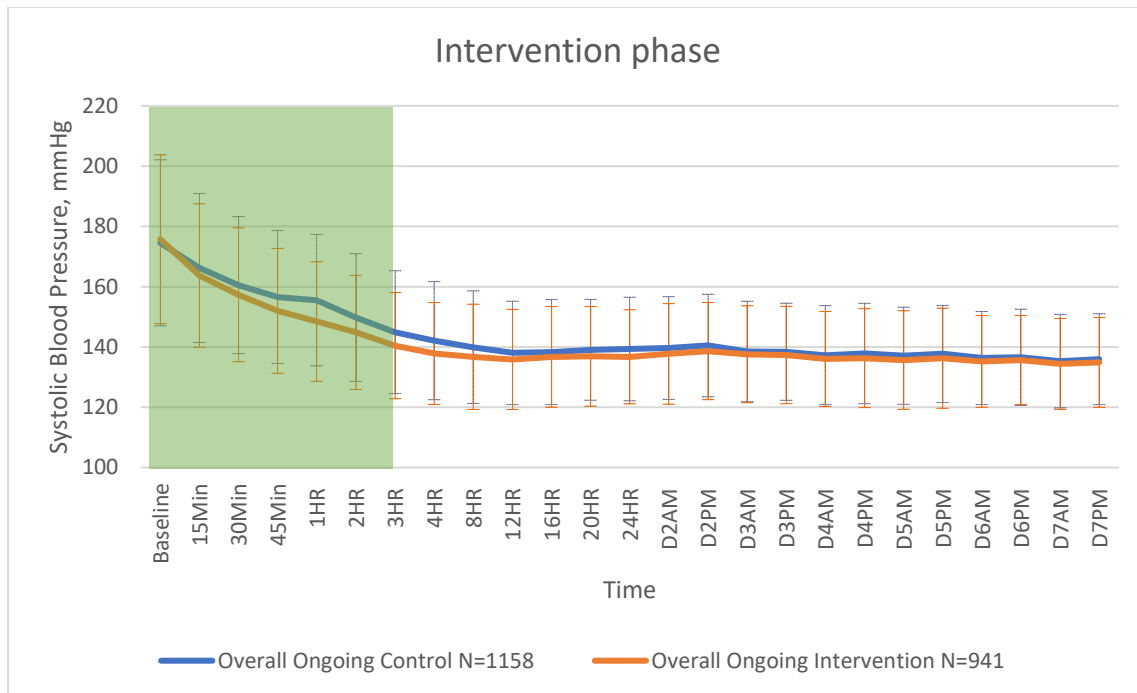
B. Blood pressure lowering report after the training (July 2020)

Footnote: data sources are from monthly performance report.

Appendix 1. COREQ checklist

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	161
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	163
Occupation	3	What was their occupation at the time of the study?	163
Gender	4	Was the researcher male or female?	163
Experience and training	5	What experience or training did the researcher have?	161, 163
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	161
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	161
Interviewer characteristics	8	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	N/A
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	159
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	162
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	163
Sample size	12	How many participants were in the study?	164
Non-participation	13	How many people refused to participate or dropped out? Reasons?	164
Setting			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	162
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	162
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	164
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	163
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	N/A
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	163
Field notes	20	Were field notes made during and/or after the inter view or focus group?	162

Duration	21	What was the duration of the inter views or focus group?	N/A
Data saturation	22	Was data saturation discussed?	163
Transcripts returned	23	Were transcripts returned to participants for comment and/or	N/A
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	153
Description of the coding tree	25	Did authors provide a description of the coding tree?	N/A
Derivation of themes	26	Were themes identified in advance or derived from the data?	164
Software	27	What software, if applicable, was used to manage the data?	164
Participant checking	28	Did participants provide feedback on the findings?	172
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	166-7, 174-5
Data and findings consistent	30	Was there consistency between the data presented and the findings?	177
Clarity of major themes	31	Were major themes clearly presented in the findings?	165-76
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	N/A