An international cluster-randomized quality improvement trial to increase the adherence to evidence-based therapies for acute ischemic stroke and transient ischemic attack patients: Rationale and design of the BRIDGE STROKE Trial

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Background Translating evidence into clinical practice in the management of acute ischemic stroke (AIS) and transient ischemic attack (TIA) is challenging especially in low- and middle-income countries.

Objectives The aim of this study is to assess the effect of a multifaceted quality improvement intervention on adherence to evidence-based therapies for AIS and TIA patients care.

Design We designed a pragmatic, 2-arm cluster-randomized trial involving 36 clusters and 1624 patients from Brazil, Argentina, and Peru. Hospitals are randomized to receive a multifaceted quality improvement intervention (intervention group) or to routine care (control group). The BRIDGE Stroke multifaceted quality improvement intervention includes case management, reminders, health care providers' educational materials (including treatment algorithms), interactive workshops, and audit and feedback reports. Primary outcome is a composite adherence score to AIS and TIA performance measures. Secondary outcomes include an "all or none" composite end point to performance measures, the individual components of the composite end points, and clinical outcomes at 90 days following admission (stroke recurrence, death, and disability measured by the modified Rankin scale).

Summary The BRIDGE Stroke Trial is an international pragmatic evaluation of a multifaceted quality improvement intervention. If effective, this intervention could be potentially extended widely to improve the quality of care and outcomes of patients with AIS or TIA. (Am Heart J 2019;207:49-57.)

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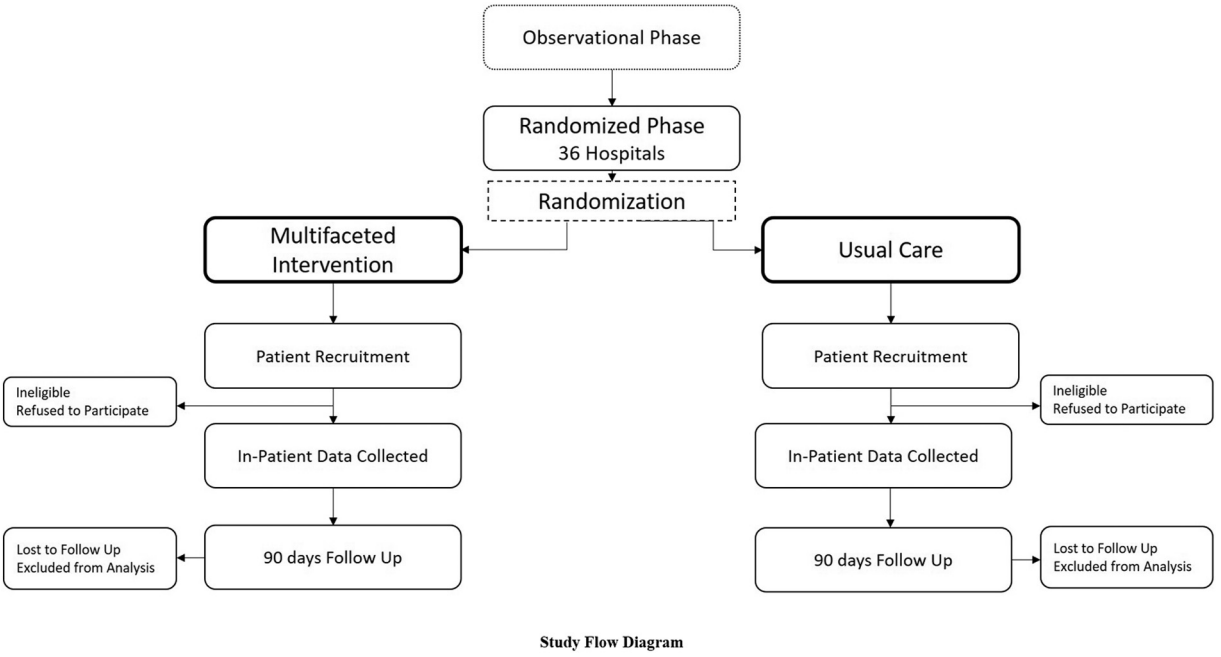
Cerebrovascular diseases represent the second leading cause of disease-adjusted life-year in middle and high-middle sociodemographic index countries[1] and the second cause of years per life lost in Latin American countries in 2015.[2,3] Large-scale randomized evidence has established the efficacy and safety of interventions for acute ischemic stroke (AIS) and transient ischemic attack (TIA), including intravenous recombinant tissue plasminogen activator (IV rt-PA),[4,5] mechanical thrombectomy,[6-8] antiplatelet therapy,[9-11] anticoagulation for patients with atrial fibrillation,[12] deep vein thrombosis prophylaxis,[13,14] dysphagia screening,[15,16] statin treatment,[17] and

Figure 1



Study flowchart.

rehabilitation. Nevertheless, the implementation of these evidence-based interventions in clinical practice remains suboptimal within different regions from Latin America.[18-24] Overall thrombolysis rates may vary from 1.05% in the ReNAcer Registry[21] and 1.60% in Brazilian public hospitals[22] to 8.9% in a private Joint Commission International–certified primary stroke center.[24]

Prior systematic reviews have demonstrated that certain quality improvement tools are associated with better quality of care. These include reminder systems and decision support tools, clinical pathway or standardized order sets, training and distribution of educational materials to health care providers, and case management and audit feedback.[25] Combined strategies targeting different barriers are more likely to be effective than single interventions.[26] Previous studies have assessed quality improvement interventions for acute stroke care in North America, Europe, and the Asia-Pacific region.[27-29] Nevertheless, unlike the appraisal of quality improvement interventions to acute coronary syndromes care,[30] quality improvement interventions aimed to improve stroke care have not been rigorously evaluated in Latin America. Thus, we designed an international cluster-randomized trial (BRIDGE Stroke) to assess the effect of a multifaceted quality improvement intervention on the composite adherence score and clinical outcomes in patients with AIS or TIA.

Methods

Study objectives

The main objectives of this trial are to evaluate whether a multifaceted quality improvement intervention can improve the adherence to evidence-based therapies for patients with AIS or TIA within the first 48 hours and at discharge, and reduce death, stroke recurrence, and disability at 90 days following the patients' admissions.

Design

BRIDGE Stroke is a pragmatic international, multicenter, 2-arm, cluster-randomized controlled trial (Figure 1) with blinded clinical outcome adjudication and intention-to-treat analysis. Thirty-six hospitals from Brazil, Argentina, and Peru and 1,624 patients participate in the trial. The trial is registered at ClinicalTrials.gov (NCT02223273).

Participants

Cluster eligibility criteria. *Clusters* are defined as hospital institutions—comprising the entire institution—that are eligible for the BRIDGE Stroke Trial if they are public or private hospitals offering 24/7 emergency care, with at least 1 routine physician in the unit for 24 hours and at least 1 on-call neurologist; if they had availability of a central nervous system imaging and alteplase (Table I);

Table I. Eligibility criteria

Cluster eligibility criteria
Inclusion criteria
Public and private hospitals offering 24/7 emergency care
At least 1 routine physician in the unit for 24 h and 1 on-call neurologist
Availability of central nervous system imaging
Availability of alteplase
Patient eligibility criteria
Inclusion criteria
All consecutive patients diagnosed with AIS or TIA with symptoms within 24 h at admission
Exclusion criteria
Hemorrhagic stroke
Expansive lesions
Central nervous system infections

Table II. Predefined performance measures for AIS and/or TIA included in the composite adherence score and "all or none" measures

Acute performance measures
Early antithrombotic therapy
IV rt-PA <3.5 h (rt-PA prescribed for eligible patients who arrived within 3.5 h from symptoms onset and received it up to 4.5 h)
Door to needle time ≤ 60 min
Deep venous thrombosis prophylaxis
Dysphagia screening
Discharge performance measures
Antithrombotic therapy
Anticoagulation for patients with atrial fibrillation or flutter
Lower lipids medications for patients with LDL ≥100 mg/dL or not documented
Assessment for rehabilitation
Smoke cessation education

and if, after the observational phase, they are able to follow the operational procedures required in this study, including patient enrollment and data collection. (See Table II.)

Patient eligibility criteria. At each participant site, all consecutive eligible patients diagnosed with AIS or TIA with symptoms lasting up to 24 hours up to admission (Table I) are included using the following standardized definitions:

- *AIS* is defined as a sudden onset of acute focal neurological deficit of ischemic vascular origin (*a*) that is not reversible in 24 hours or resulting in death (in <24 hours) and is not due to an identifiable cause of death (eg, tumor or trauma) or (*b*) that resolves in <24 hours and is accompanied by clear evidence of stroke on the brain imaging study.
- *TIA* is defined as (*a*) focal neurological deficit lasting <24 hours and not due to identifiable nonvascular cause (eg, brain tumor, trauma) and (*b*) no new infarction on brain imaging study (if available).

Hospitals are instructed to enroll patients as soon as they presented to the emergency department. The trial excludes patients with hemorrhagic stroke at admission, expansive lesions, and central nervous system infections, and patients for whom presumptive admission diagnosis was AIS or TIA but subsequently shown to have some other neurological or nonneurological cause for their presentation.

Randomization and allocation concealment

Eligible clusters are randomly allocated (1:1) to a multifaceted quality improvement intervention (intervention group) or to routine practice (control group). The intervention group should add the materials and techniques from the BRIDGE Stroke quality improvement intervention to their own practices, whereas the control group should maintain their usual practices. Thus, the sole difference between groups is the use of the BRIDGE Stroke quality improvement intervention materials and techniques. Randomization is stratified in terciles according to the performance considering the composite adherence score verified during the observational phase study. The parameter used was the composite adherence score observed in the observational phase (see the "Outcomes" section). To guarantee concealment of allocation, the randomization list was generated at once by a blinded statistician using a central Web-based randomization system developed by the Research Institute HCor (São Paulo, Brazil).

Blinding

In view of the nature of the multifaceted intervention, patients and investigators are blinded to the allocation of treatment. Independent outcome assessors and statisticians, on the other hand, are blinded to the nature of the intervention.

Quality improvement intervention

The multifaceted quality improvement intervention includes case management, a therapeutic plan roadmap and checklist, educational materials, interactive workshops, and periodic audit and feedback reports to each cluster (Figures 2 and 3).

Case management. Case management is conducted by a team of health professionals from each cluster, including a physician leader and trained nurses. The teams are responsible for the timely delivery of the materials and for checking the implementation of effective management, supporting the management when it is needed, and acting as quality improvement monitors.

Reminders and treatment algorithm. To facilitate the visualization of important interventions and their relation to the time of care, different reminders may be used, as follows: (*a*) patient wristband (patient bracelet) and (*b*) a therapeutic plan (treatment algorithm) to be attached to the admission form or medical record. The reminders and treatment algorithm were designed to be implemented in sequence during the management of AIS and TIA patients. First, a colored wristband is given to an AIS or TIA potential patient. Once a potential diagnosis is given to a patient, the nurse gives the attending physician a treatment

algorithm. This algorithm consists of a therapeutic plan "roadmap" for quick reference and checking, guiding the physician and nurses from appropriate AIS or TIA diagnosis confirmation to the complete sequence of adequate treatments required during hospitalization until hospital discharge. The treatment management plan requires that the attending physician check and confirm the use of all suggested evidence-based interventions. The colored wristband (bracelet) helps promptly identify AIS or TIA patients in the emergency department and in subsequent units (eg, intensive care units, infirmary) to avoid delays in initiating recommended therapies.

Educational posters. These posters are distributed in the emergency department and in all hospital units to draw the attention of the team about techniques that can support better practices.

Educational materials. To each hospital, printed, physical, or electronic materials are provided to support and motivate best practices. These materials included an rt-PA kit case, a bedside dysphagia screening test, the NIH Stroke Scale, a medication brochure, and a patient educational brochure.

Audit and feedback reports. Periodical audit and feedback reports on performance are provided to each hospital allocated to the intervention group. This strategy stimulates the teams to seek continuous improvement. Additionally, this report is discussed in periodic Web or phone conferences were conducted to review the performance measures and set with aspects needed to improve.

Interactive training workshops. Interactive training workshops are planned as follows: (*a*) during an investigators' meeting where the principal investigator and lead case manager from each site allocated to the intervention group will receive a simulation-based training developed in small groups and addressing the techniques to implement the intervention or (*b*) during outreach visits developed in each hospital when members of the quality improvement committee perform a diagnostic visit addressing the actual clinical pathway at each hospital and together with the local teams help tailor the intervention to the needs of each site. It will also be encouraged that each participating site disseminates the intervention to other professionals from the institution. The BRIDGE Stroke training techniques will also be available in a video that will be used during the training sessions. This video is also available for the hospitals so that they can use it as a continuous improvement tool.

Outcomes

Primary outcome.

- Composite Adherence Score: consists of an *opportunity scoring*[31] defined as the sum of usage of evidence-based therapies in the first 48 hours and at discharge among the patients' total eligible opportunities including early antithrombotic therapy, deep venous thrombosis prophylaxis, rt-PA among ischemic stroke arriving <3.5 hours and treated <4.5 hours, door to needle time ≤60 minutes, dysphagia screening, assessment for rehabilitation, antithrombotic at discharge, lipid-lowering medications for patients with low-density lipoprotein (LDL) ≥100 mg/dL or not documented, anticoagulants for atrial fibrillation or flutter, and smoke cessation education.

Secondary outcomes.

- Proportion of prescription of evidence-based strategies in the first 48 hours and at discharge ("all or none" measures),[31] including early antithrombotic therapy, deep venous thrombosis prophylaxis, IV rt-PA <3.5 hours, door to needle time <60 minutes, dysphagia screening, assessment for rehabilitation, antithrombotic at discharge, lipid-lowering medications for patients with LDL ≥100 or not documented, anticoagulants for atrial fibrillation or flutter, and smoke cessation education.
  - rt-PA rate in stroke patients admitted within 24 hours of symptoms.
  - Antihypertensive agents at discharge.
  - Door to needle time ≤45 minutes.
  - Clinical outcomes at 90 days: disability assessed by the modified Rankin scale, stroke recurrence, and deaths.

The detailed outcome definitions and variables descriptions are provided in the Supplementary Appendix 1.

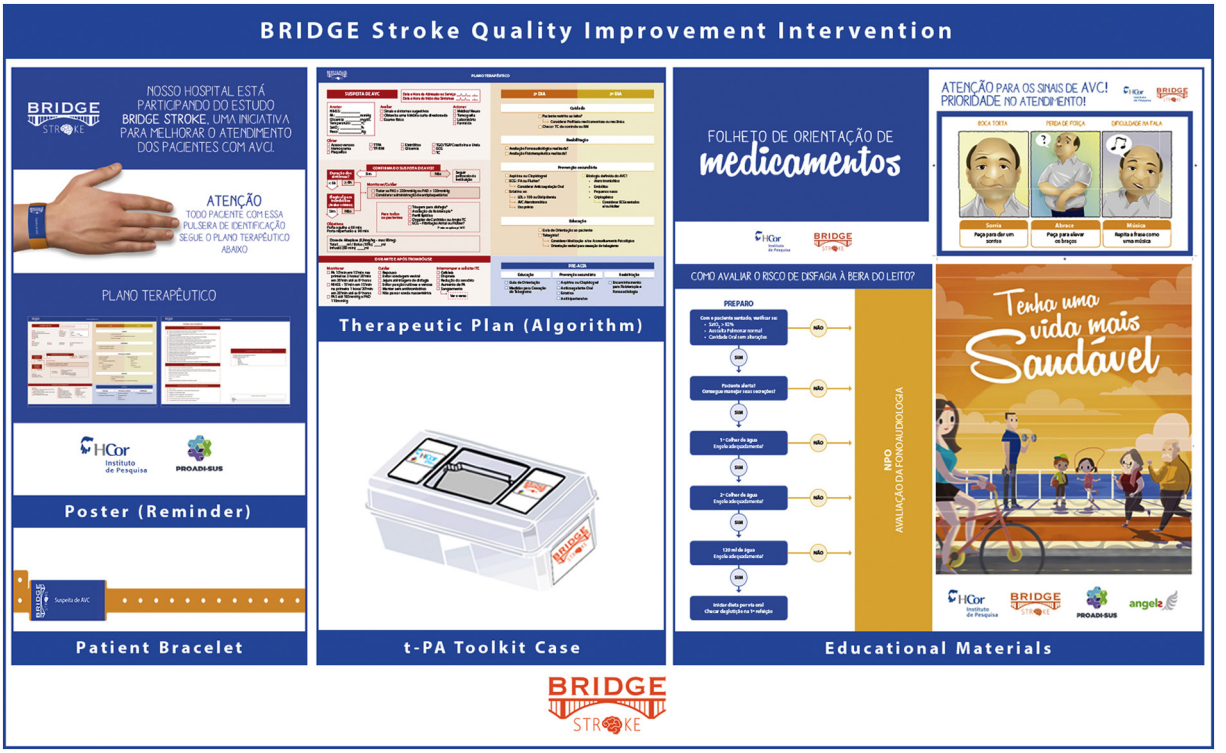
Sample size

We performed a prerandomization cross-sectional study at 45 hospitals and found out that the composite adherence score was 75%. Therefore, considering a control group adherence score of 75%, to detect a 12.5% absolute improvement in the score, considering 80% power, a .05 two-tailed α, and an intracluster correlation coefficient of 0.25, we needed to randomize at least 36 hospitals and approximately 1,440 patients (considering a median of 40 patients per cluster). The distribution of sites between the countries is proportional to each country's population.

Statistical analysis plan

A comprehensive description of the statistical analysis plan is provided in the Supplementary Appendix 1. Quantitative variables will be described by mean and SD whenever there is a normal distribution, or median and/or interquartile amplitude median and interquartile ranges in case of nonparametric distribution. Qualitative variables will be presented as absolute frequencies (number of patients) and relative frequencies

Figure 2



BRIDGE Stroke quality improvement intervention.

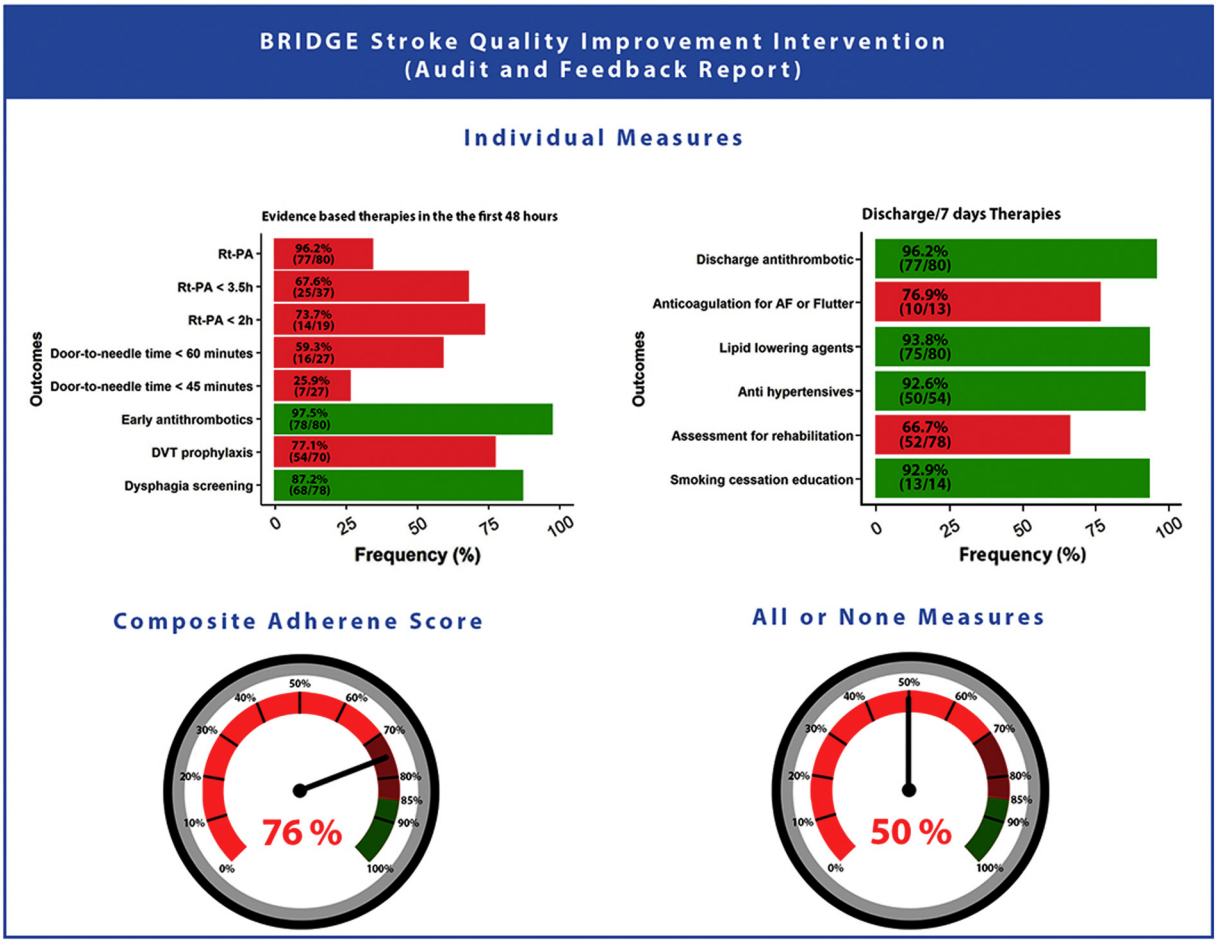
(percentages). An intention-to-treat analysis (main analysis) and a per-protocol analysis (sensitivity analysis) will be performed. The primary outcome will be analyzed using a mixed-effects linear regression model with random effects to account for the correlation of observations within clusters. The components of the primary outcome will be individually evaluated using mixed-effects general linear models considering binomial distribution (logistic regression with random effect at the intercept [cluster adjusted]). All models will be adjusted for the cluster baseline values (obtained during observational phase) and for the group effect (intervention vs control). Treatment effects will be expressed as absolute mean difference or the composite outcome and odds ratio with the respective 95% CIs for the individual components. As a sensitivity analysis, an adjusted analysis for hospital status (teaching vs nonteaching) and presence of a stroke unit will be performed. Pre-specified subgroup analysis, for which interaction is set by group (intervention vs control) will be accessed as follows: teaching hospital (or not), presence of a stroke unit, presence of a neurologist in the emergency department, and final diagnosis (AIS vs TIA). The significance level is set at 5%. Analysis will be performed using R software in its most updated version by the Department of Statistics and the Research Institute HCor.

Organizational structure

Study oversight

The BRIDGE Stroke Trial Steering Committee is led by 2 Co-Chairs. This committee provided scientific direction and input, addressed policy issues regarding the protocol, and periodically assessed the trial progress. The Executive Committee is composed by a subset of senior leaders from the Steering Committee and is responsible for overseeing the trial daily activities. The Quality Improvement Committee is composed of clinical and management experts from the Steering Committee and is responsible for overseeing the current adherence of the intervention and the key performance measures, analyzing the potential causes for low implementation rates, setting new goals for improvement, and conducting conference calls with the quality improvement team at every cluster. The Clinical Events Classification Committee is composed by experts in events adjudication and is responsible for drafting the Clinical Events Classification charter and reviewing clinical events.

Figure 3



BRIDGE Stroke audit and feedback report.

The trial is being conducted by an international coordinating center, Research Institute HCor, responsible for the study global coordination and by 2 regional coordinating centers: ACRG in Argentina and Hospital Cayetano Heredia in Peru. Some of the international coordinating center activities include site selection and training, assisting trial centers with regulatory submissions, distributing and supplying study sites with the tools and forms, monitoring recruitment and data quality, data management, data capture system, and data analysis. The trial organization and participating sites are listed in the Supplementary Appendix 2.

Funding

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Ethical considerations

This study is being conducted in accordance with the Declaration of Helsinki, the Ottawa Statement,[32] local regulatory guidelines, and good clinical practices. All participating clusters submitted the protocol for approval by their ethics research board; written consent was obtained at the cluster level. This is a common and well-accepted approach; the objective of such an approach is to avoid selection bias that may arise from different consent refusals rates between clusters. Additionally, written consent at the patient level was also obtained with the sole purpose of obtaining information at the 90-day follow up by a telephone call.

Data collection, quality control, and clinical data management system

In all participating clusters, data are collected prospectively by a trained independent health professional not involved in the care of AIS or TIA patients. Data are entered

using an electronic Web-based data capture system (ACT Clinic) developed on a Microsoft SQL System (Microsoft Corp, Redmond, WA) platform by team programmers at the Research Institute HCor. Data quality control is guaranteed by automated data entry checks, weekly contact with investigators, central statistical monitoring, and on-site monitoring for medical records checking. Additionally, the data management team at the coordinating center is also responsible for providing the audit feedback report to the clusters allocated to the intervention group. Global feedback is provided in periodic newsletters. The authors are solely responsible for the design and conduct of this study, all study analysis, the drafting and editing this manuscript, and its final contents.

Discussion

Previous studies using a before-and-after or multiple temporal series designs suggested improvements in the uptake of evidence-based therapies in stroke patients in developed countries. The Get With The Guidelines–Stroke program, for example, developed as a national stroke quality improvement initiative to address the treatment quality of care for AIS and TIA in United States, has shown a significant improvement in quality of care from 2003 and 2009 as reflected by the 40.3% absolute increase in "all or none" measures adherence.[27] Conversely, studies conducted in low- and middle-income countries documenting consistent effects on quality measures, clinical outcomes, and sustainability of changes are still limited.[33] In nonrandomized studies, the intervention effects might be confounded by several factors including (*a*) the availability of evidence and knowledge that might influence health care providers, (*b*) secular trends, and (*c*) the Hawthorne effect.[34] To prevent such types of bias, cluster-randomized trials are recommended as the ideal design for evaluating quality improvement interventions. In addition, cluster-randomized trials allow adequate control of contamination, which would be challenging in a trial with randomization at the patient level. Finally, in cluster-randomized trials, bias can be prevented by using concealed allocation, blinding adjudication of clinical outcomes, and avoiding different consent refusal rates between clusters[30,35]

Cluster-randomized trials assessing the effect of different quality improvement interventions have been proved to be successful in emerging economies. The quality improvement intervention assessed at the BRIDGE ACS trial, a study conducted in 34 Brazilian public hospitals and assessing the quality of care for acute coronary syndrome patients, increased in 18% the uptake of evidence-based therapies during the first 24 hours, mainly driven by increased prescription rates of antithrombotic therapies and statins.[30] Additionally, the multilevel and multifaceted educational intervention proposed by the IMPACT trial, conducted in 48 centers from Argentina, Brazil, China, India, and Romania, resulted in a 9.1% difference in the use of oral anticoagulants for atrial fibrillation patients between intervention and control groups after 12 months.[36] Recently, the Golden Bridge Study, aiming to improve the quality of care for AIS patients in China, also showed a 3.54% absolute increase in the use of evidence-based therapies.[29,35]

To the best of our knowledge, BRIDGE Stroke represents the first international cluster-randomized trial developed in Latin American countries and evaluating the effect of a quality improvement intervention on the composite adherence score (comprising the multidisciplinary nature of stroke care), "all or none" measures, and clinical outcomes in patients with AIS or TIA.

Conclusions

In summary, quality improvement initiatives may provide a crucial way to bridge the gap between guideline-based recommendation and real-world clinical practice in acute stroke care. If proven effective, the multifaceted quality improvement intervention tested in our trial might be useful to other regions of the world as a method of promoting optimal use of evidence-based interventions for the management of AIS and TIA.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.09.009.

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Conflict of interests

The authors report no potential conflict of interest relevant to this article except for the following:

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Author contributions

Maria Julia Machline-Carrion: conceptualization, methodology, writing original draft, writing–review and editing, supervision, validation, funding acquisition; Eliana Vieira Santucci: methodology, software, validation, data curation, writing original draft, writing–review and editing; Lucas Petri Damiani: methodology, software, formal analysis, writing original draft, writing–review and editing; Cecilia Bahit: methodology, project administration, validation, writing–review and editing; Germán Málaga: methodology, project administration, validation, writing–review and editing; Octávio Marques Ponte-Neto: methodology, writing–review and editing; Sheila Cristina Ouriques Martins: methodology, investigation; Viviane Flumignan Zétola: investigation, writing–review and editing; Karina Normilio-Silva: project administration, investigation, writing–review and editing; Gabriel Rodrigues de Freitas: methodology, writing–review and editing; Alessandra Gorgulho: methodology, writing–review and editing; Antônio De Salles: methodology, writing–review and editing; Beatriz Gonzales Pacheco da Silva: investigation; resources; Juliana Yamashita Santos: investigation; resources; Isabella de Andrade Jesuíno: investigation, visualization, resources; Priscila Regina Torres Bueno: investigation, visualization, project administration; Alexandre Biasi Cavalcanti: methodology, supervision, writing–review and editing; Hélio Penna Guimarães: methodology, supervision, writing–review and editing; Ying Xian: methodology, supervision, writing–review and editing; Janet Prvu Bettger: methodology, supervision, writing–review and editing; Renato D. Lopes: methodology, supervision, writing–review and editing, Eric D. Peterson: methodology, supervision, writing–review and editing; Otávio Berwanger: conceptualization, methodology, writing original draft, writing–review and editing, supervision, validation, funding acquisition.

References

1. DALYs GBD, Collaborators H. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390(10100):1260-344.
2. Franca EB, Passos VMA, Malta DC, et al. Cause-specific mortality for 249 causes in Brazil and states during 1990-2015: a systematic analysis for the global burden of disease study 2015. Popul Health Metr 2017;15(1):39.
3. Lotufo PA, Goulart AC, Passos VMA, et al. Cerebrovascular disease in Brazil from 1990 to 2015: Global Burden of Disease 2015. Rev Bras Epidemiol 2017;20 Suppl 01(Suppl 01):129-41.
4. Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 2010;375(9727):1695-703.
5. Emberson J, Lees KR, Lyden P, et al. 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(9958):1929-35.
6. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med 2018;378(1):11-21.
7. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372(24):2285-95.
8. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372(11):1009-18.
9. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke CAST (Chinese Acute Stroke Trial) Collaborative GroupLancet 1997;349(9066):1641-9.
10. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke International Stroke Trial Collaborative GroupLancet 1997;349(9065):1569-81.
11. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 2013;369(1):11-9.
12. Lopez-Lopez JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ 2017;359, j5058.
13. Collaboration CTDennis M, Sandercock PA, et al. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. Lancet 2009;373(9679):1958-65.
14. Sherman DG, Albers GW, Bladin C, et al. The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL Study): an open-label randomised comparison. Lancet 2007;369(9570):1347-55.
15. Perry L, Love CP. Screening for dysphagia and aspiration in acute stroke: a systematic review. Dysphagia 2001;16(1):7-18.
16. Ramsey DJ, Smithard DG, Kalra L. Early assessments of dysphagia and aspiration risk in acute stroke patients. Stroke 2003;34(5):1252-7.
17. Amarenco P, Bogousslavsky J, Callahan III A, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355(6):549-59.
18. Alves MB, Silva GS, Miranda RCA, et al. Patterns of care and temporal trends in ischemic stroke management: a Brazilian perspective. J Stroke Cerebrovasc Dis 2017;26(10):2256-63.
19. Lange MC, Braga GP, Novak EM, et al. Key performance indicators for stroke from the Ministry of Health of Brazil: benchmarking and indicator parameters. Arq Neuropsiquiatr 2017;75(6):354-8.
20. de Carvalho JJ, Alves MB, Viana GA, et al. Stroke epidemiology, patterns of management, and outcomes in Fortaleza, Brazil: a

hospital-based multicenter prospective study. Stroke 2011;42(12):3341-6.
21. Sposato LA, Esnaola MM, Zamora R, et al. Quality of ischemic stroke care in emerging countries: the Argentinian National Stroke Registry (ReNACer). Stroke 2008;39(11):3036-41.
22. Conforto AB, Paulo RB, Patroclo CB, et al. Stroke management in a university hospital in the largest South American city. Arq Neuropsiquiatr 2008;66(2B):308-11.
23. de Carvalho FA, Schwamm LH, Kuster GW, et al. Get with the guidelines stroke performance indicators in a brazilian tertiary hospital. Cerebrovasc Dis Extra 2012;2(1):26-35.
24. Kuster GW, Dutra LA, Brasil IP, et al. Outcome determinants of stroke in a Brazilian primary stroke center. Stroke Res Treat 2014;2014:194768.
25. Grimshaw J, Eccles M, Thomas R, et al. Toward evidence-based quality improvement. Evidence (and its limitations) of the effectiveness of guideline dissemination and implementation strategies 1966–1998. J Gen Intern Med 2006;21(Suppl 2):S14-20.
26. Grimshaw JM, Shirran L, Thomas R, et al. Changing provider behavior: an overview of systematic reviews of interventions. Med Care 2001;39(8 Suppl 2):II2-II45.
27. Fonarow GC, Reeves MJ, Smith EE, et al. Characteristics, performance measures, and in-hospital outcomes of the first one million stroke and transient ischemic attack admissions in get with the guidelines-stroke. Circ Cardiovasc Qual Outcomes 2010;3(3):291-302.
28. Middleton S, McElduff P, Ward J, et al. Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. Lancet 2011;378(9804):1699-706.
29. Wang Y, Li Z, Zhao X, et al. Effect of a multifaceted quality improvement intervention on hospital personnel adherence to performance measures in patients with acute ischemic stroke in China: a randomized clinical trial. JAMA 2018;320(3):245-54.
30. Berwanger O, Guimaraes HP, Laranjeira LN, et al. Effect of a multifaceted intervention on use of evidence-based therapies in patients with acute coronary syndromes in Brazil: the BRIDGE-ACS randomized trial. JAMA 2012;307(19):2041-9.
31. Peterson ED, DeLong ER, Masoudi FA, et al. ACCF/AHA 2010 position statement on composite measures for healthcare performance assessment: a report of American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures (Writing Committee to Develop a Position Statement on Composite Measures). J Am Coll Cardiol 2010;55(16):1755-66.
32. Taljaard M, Weijer C, Grimshaw JM, et al. The Ottawa Statement on the ethical design and conduct of cluster randomised trials: precis for researchers and research ethics committees. BMJ 2013;346:f2838.
33. Pandian JD, William AG, Kate MP, et al. Strategies to improve stroke care services in low- and middle-income countries: a systematic review. Neuroepidemiology 2017;49(1–2):45-61.
34. Grimshaw J, Campbell M, Eccles M, et al. Experimental and quasi-experimental designs for evaluating guideline implementation strategies. Fam Pract 2000;17(Suppl 1):S11-6.
35. Wang Y, Li Z, Xian Y, 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 2015;169(6):767-774.e2.
36. Vinereanu D, Lopes RD, Bahit MC, et al. A multifaceted intervention to improve treatment with oral anticoagulants in atrial fibrillation (IMPACT-AF): an international, cluster-randomised trial. Lancet 2017;390(10104):1737-46.