Effect of a Quality Improvement Intervention on Adherence to Therapies for Patients With Acute Ischemic Stroke and Transient Ischemic Attack: A Cluster Randomized Clinical Trial

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**IMPORTANCE** 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.

**OBJECTIVE** To assess the effect of a multifaceted quality improvement intervention on adherence to evidence-based therapies for care of patients with AIS and TIA.

**DESIGN, SETTING AND PARTICIPANTS** This 2-arm cluster-randomized clinical trial assessed 45 hospitals and 2336 patients with AIS and TIA for eligibility before randomization. Eligible hospitals were able to provide care for patients with AIS and TIA in Brazil, Argentina, and Peru. Recruitment started September 12, 2016, and ended February 26, 2018; follow-up ended June 29, 2018. Data were analyzed using the intention-to-treat principle.

**INTERVENTIONS** The multifaceted quality improvement intervention included case management, reminders, a roadmap and checklist for the therapeutic plan, educational materials, and periodic audit and feedback reports to each intervention cluster.

**MAIN OUTCOMES AND MEASURES** The primary outcome was a composite adherence score for AIS and TIA performance measures. Secondary outcomes included an all-or-none composite end point of performance measures, the individual process measure components of the composite end points, and clinical outcomes at 90 days after admission (stroke recurrence, death, and disability measured by the modified Rankin scale).

**RESULTS** A total of 36 hospitals and 1624 patients underwent randomization. Nineteen hospitals were randomized to the quality improvement intervention and 17 to routine care. The overall mean (SD) age of patients enrolled in the study was 69.4 (13.5) years, and 913 (56.2%) were men. Overall mean (SD) composite adherence score for the 10 performance measures in the intervention hospital group compared with control group hospitals was 85.3% (20.1%) vs 77.8% (18.4%) (mean difference, 4.2%; 95% CI, −3.8% to 12.2%). As a secondary end point, 402 of 817 patients (49.2%) at intervention hospitals received all the therapies that they were eligible for vs 203 of 807 (25.2%) in the control hospitals (odds ratio, 2.59; 95% CI, 1.22-5.53; P = .01).

**CONCLUSIONS AND RELEVANCE** A multifaceted quality improvement intervention did not result in a significant increase in composite adherence score for evidence-based therapies in patients with AIS or TIA. However, when using an all-or-none approach, the intervention resulted in improved adherence to evidence-based therapies.

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Stroke represents the second leading cause of death and disability globally.\textsuperscript{1-3} Large-scale randomized evidence has established the efficacy of interventions for acute ischemic stroke (AIS) and transient ischemic attack (TIA), such as intravenous recombinant tissue plasminogen activator (rt-PA),\textsuperscript{4,5} antiplatelet therapy,\textsuperscript{6-8} and anticoagulation for patients with atrial fibrillation.\textsuperscript{9} Nevertheless, the implementation of these therapies in clinical practice remains suboptimal, especially in low- and middle-income countries.\textsuperscript{10-16} To date and to our knowledge, most studies assessing the effect of quality improvement tools such as reminders, audit and feedback, care management, and distribution of educational materials to health care professionals for the care of patients with stroke have been conducted in developed countries.\textsuperscript{17-19} Quality improvement interventions have rarely been rigorously evaluated in lower-resource settings\textsuperscript{20} such as Latin America, where the burden of cerebrovascular diseases remains very high.\textsuperscript{3} Thus, we conducted a cluster randomized trial to assess the effect of a multifaceted quality improvement intervention on the adherence to evidence-based performance measures in patients with AIS or TIA in Brazil, Argentina, and Peru.

Methods

Study Design

The detailed trial methods have been published previously,\textsuperscript{21} and the full protocol and the statistical analysis plan are available in Supplement 1. In brief, the Brazilian Intervention to Increase Evidence Usage in Practice–Stroke (BRIDGE-Stroke) study was a pragmatic international, 2-arm, cluster randomized clinical trial with blinded outcome adjudication. The main objective was to evaluate whether a multifaceted quality improvement intervention could improve the adherence to in-hospital evidence-based therapies for patients with AIS or TIA. All hospitals (clusters) submitted the protocol for approval by their research ethics boards; written informed consent was obtained at the cluster and patient levels. The enrollment period was from September 12, 2016, through February 26, 2018. Follow-up was completed June 29, 2018.

Clusters and Patients

We included 36 public or private hospitals from Brazil (n = 26), Argentina (n = 6), and Peru (n = 4) offering 24-hour emergency care with at least 1 physician in charge of the emergency care unit for 24 hours, at least 1 on-call neurologist, and available central nervous system imaging and alteplase therapy. At participating sites, we enrolled consecutive patients with AIS or TIA who were admitted within 24 hours from symptom onset as soon as they presented in the emergency department. We excluded patients with hemorrhagic stroke, those with expansive lesions and central nervous system infections, and those for whom presumptive admission diagnosis of AIS or TIA was not confirmed. Detailed eligibility criteria are shown in eMethods 1 in Supplement 2.

Baseline Survey

We conducted a prerandomization survey in all clusters using the same eligibility criteria for patient inclusion. The main objective was to assess whether clusters were comparable with regard to prescription rates of evidence-based therapies and to obtain reliable estimates for our sample size calculation. Methods and results of the survey are presented in eTable 1 in Supplement 2.

Randomization and Allocation Concealment

Hospitals were randomized (1:1) to a quality improvement intervention or to routine practice. Randomization was stratified in tertiles according to baseline performance. The randomization list was generated at once by a statistician (L.P.D.) using a central web-based randomization system before enrollment of the first patient.

Blinding

Patients and investigators were not blinded to the allocation of treatment. Outcome assessors and statisticians were blinded to the nature of the intervention.

Intervention

The quality improvement intervention included care management, reminders, a roadmap and checklist of the therapeutic plan, educational materials, and audit and feedback. Case management was conducted by a physician leader and trained nurses from each cluster. Case managers were responsible for the timely delivery of study materials and for checking the implementation of evidence-based therapies.

Reminders (colored wristbands) and a roadmap of the therapeutic plan were designed to be implemented in sequence during patient management. The wristband helped to promptly identify patients with a potential AIS or TIA. Once the diagnosis was confirmed, the case managers prompted the attending physicians and provided them with a roadmap of the therapeutic plan. This tool guided the physicians from appropriate AIS or TIA diagnosis confirmation to the recommended therapies needed until discharge. The treatment plan also required that the attending physician...
complete a checklist to confirm the implementation of all recommended interventions.

Educational materials included an rt-PA kit case, a bedside dysphagia screening test, the National Institutes of Health Stroke Scale, a medication brochure, and a patient educational brochure. Periodic audit and feedback reports on performance were provided to encourage the teams to seek continuous improvement.

Hospitals randomized to the intervention received on-site training visits complemented by web-based and telephone training. In addition, 2 health care professionals from each of these clusters attended a workshop on how to implement the intervention. The detailed methods of the workshops are provided in eMethods 2 in Supplement 2.

Data Collection
In all hospitals, data were collected prospectively by a trained research coordinator not involved in patient care. Adherence to therapies was assessed by a medical record review, patient files, and medical prescriptions. Quality control was guaranteed by automated data entry checks, on-site monitoring, and central statistical checks.

Outcomes
The primary outcome was as a composite adherence score for evidence-based therapies (early antithrombotic therapy, deep venous thrombosis prophylaxis, intravenous rt-PA among patients with ischemic stroke arriving within 3.5 hours and treated within 4.5 hours, door-to-needle time of 60 minutes or less, dysphagia screening, assessment for rehabilitation, antithrombotics at discharge, statins for patients with low-density lipoprotein levels of 100 mg/dL or higher [to convert to milli-moles per liter, multiply by 0.0259] or not documented, anticoagulants for atrial fibrillation or flutter, and smoking cessation education) in the first 48 hours and at discharge as indicated on the patient diagnosis (AIS or TIA). This outcome consisted of an opportunity score defined as the sum of evidence-based therapies used among the patients’ total eligible opportunities. Secondary outcomes included the proportion of prescription of evidence-based strategies in the first 48 hours and at discharge in an all-or-none approach, individual components of the primary end point, the rt-PA rate among patients with stroke admitted within 24 hours of symptoms, the proportion of use of antihypertensives at discharge, the proportion of patients treated with thrombolysis within a door-to-needle time of no more than 45 minutes, and clinical outcomes at 90 days after admission (stroke recurrence, death, and disability measured by the modified Rankin scale).

Statistical Analysis
Considering a control group composite adherence score of 75% and an intraclass correlation coefficient (ICC) of 0.25 (both based on our baseline survey), we needed to randomize at least 36 clusters and 1440 patients (mean of 40 patients per cluster) to detect a 12.5% absolute improvement in the score with 80% power, 2-tailed α = .05, and an ICC of 0.25. Main analysis followed the intention-to-treat principle. The primary outcome was analyzed using a mixed-effects regression model with random effects to account for the correlation of observations within clusters. Components of the primary outcome were individually evaluated using mixed-effects general linear models considering binomial distribution (logistic regression with random effects at the intercept per cluster). All models were adjusted for the cluster baseline values (obtained during the observational phase). Treatment effects are expressed as absolute mean difference for the composite outcome and odds ratio (OR) for binary outcomes with their respective 95% CIs. We also compared the effects of our intervention in the following subgroups: teaching vs nonteaching hospitals, hospitals with or without stroke units, hospitals with or without a neurologist in the emergency department, final diagnosis (AIS vs TIA), and country. Clinical events were compared using frailty Cox proportional hazards regression models with health care center as the random effect. We performed the following sensitivity analyses: including only patients with AIS diagnosis, including only patients with TIA diagnosis, and an adjusted analysis for hospital status and presence of a stroke unit. The significance level was set at 5% as 2-sided P < .05. Analyses were conducted using R software, version 3.5.1 (R Foundation for Statistical Computing).

Results
Of 117 potentially eligible hospitals that were invited, 72 were excluded (65 could not undergo start-up procedures, 4 were excluded owing to operational constraints, and 3 did not meet inclusion criteria). From the remaining 45 hospitals that confirmed interest and completed the baseline survey, 9 were excluded before the randomization phase (3 declined participation, 5 had insufficient enrollment, and 1 had operational constraints), leaving 36 sites. From these randomized hospitals that completed the trial, a total of 1624 patients were enrolled prospectively (Figure 1).

Hospital and Patient Characteristics
Baseline hospital and patient characteristics were generally similar in each group (Table 1). From the included clusters, 17 (47.2%) had stroke units, 32 (88.9%) had intra-arterial thrombolysis capabilities available 24 hours per day, 28 (77.8%) were teaching hospitals, and the median volume of patients seen in the ED was about 1500 patients per month (interquartile range, 500-3700). Among enrolled patients, the mean (SD) age was 69.4 (13.5) years, 913 (56.2%) were men, 456 (28.1%) had prior stroke, 1219 (75.1%) had hypertension, and 484 (29.8%) had diabetes. From the included patients, 1434 (88.3%) had a final diagnosis of AIS and 190 (11.7%) of TIA. The mean number of patients in each hospital was 43 (range, 9-85).

Adherence to the Quality Improvement Intervention
In the intervention group, health care professionals acted as case managers in 18 of 19 hospitals (94.7%), the audit and feedback system was adhered to by 18 of 19 clusters (94.7%), and adherence to a therapeutic plan roadmap occurred during the...
first 48 hours in 539 of 817 patients (66.0%) and at discharge in 519 of 817 (63.5%) (eTable 2 in Supplement 2). One hospital did not adhere to any of the quality improvement tools from our intervention.

Effects on Evidence-Based Therapies
The effects of the quality improvement intervention on prescription rates of evidence-based therapies are shown in Table 2. The overall mean (SD) composite adherence score was not significantly higher in the intervention than in the control groups (85.3% [20.1%] vs 77.8% [18.4%]; mean difference, 4.2%; 95% CI, −3.8% to 12.2%; ICC, 0.332; P = .29). As a prespecified secondary end point, patients in the intervention hospitals were more likely to receive all acute therapies during hospitalization than those in control hospitals (402 of 817 [49.2%] vs 203 of 807 [25.2%]; OR, 2.59; 95% CI, 1.22-5.53; ICC, 0.251; P = .01). These results were mainly driven by the following individual components that were more likely to be provided to the intervention group patients: intravenous rt-PA within the therapeutic window (122 of 222 [55.0%] vs 107 of 268 [39.9%]; OR, 2.77; 95% CI, 1.31-5.82; ICC, 0.169; P = .01) and smoking cessation education (93 of 129 [72.1%] vs 82 of 169 [48.5%]; OR, 3.22; 95% CI, 1.05-9.88; ICC, 0.278; P = .04) (Table 2).

Effects on Clinical Events
The effects of our intervention on clinical events are shown in Table 3. Total mortality rates in 90 days were 12.6% (103 of 817 patients) in the intervention group and 11.8% (95 of 807 patients) in the control group (hazard ratio, 1.16; 95% CI, 0.68-2.01; P = .58). The rates of in-hospital hemorrhagic transformation were 5.1% (42 of 817 patients) in the intervention group and 2.5% (20 of 804 patients) in the control group (OR, 2.11; 95% CI, 1.13-3.94; P = .02).

Subgroup Analysis
Subgroup analysis is shown in Figure 2. The effect of our intervention on the primary outcome was greater in patients with AIS (mean [SD] composite adherence score, 84.6% [19.8%] vs 76.7% [17.8%]; mean difference, 5.0%; 95% CI, −2.6% to 12.7%) compared with patients with TIA (mean [SD], 90.3% [21.3%] vs 87.1% [20.7%]; mean difference, −1.3%; 95% CI, −10.1% to
Table 1. Baseline Characteristics of Clusters (Hospitals) and Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study Groupa</th>
<th>-control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>441/817 (54.0)</td>
<td>472/807 (58.5)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>70.3 (13.6)</td>
<td>68.4 (13.4)</td>
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<tr>
<td>Hypertension</td>
<td>252/817 (30.8)</td>
<td>232/806 (28.8)</td>
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<td>Dyslipidemia</td>
<td>627/817 (76.7)</td>
<td>592/807 (73.4)</td>
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<td>Current smoking</td>
<td>129/817 (15.8)</td>
<td>169/807 (20.9)</td>
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<tr>
<td>Family history of stroke</td>
<td>62/817 (7.6)</td>
<td>116/807 (14.4)</td>
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<td>Family history of CAD</td>
<td>53/817 (6.5)</td>
<td>121/807 (15.0)</td>
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<td>Prior stroke</td>
<td>243/817 (29.7)</td>
<td>213/807 (26.4)</td>
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<td>Atrial fibrillation</td>
<td>120/817 (14.7)</td>
<td>74/807 (9.2)</td>
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<td>Renal failure</td>
<td>25/817 (3.1)</td>
<td>32/807 (4.0)</td>
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<td>Use of aspirin in the past month</td>
<td>211/817 (25.8)</td>
<td>201/807 (24.9)</td>
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<td>Use of anticoagulants in the past month</td>
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<td>68/807 (8.4)</td>
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<td>Use of statins in the past month</td>
<td>207/817 (25.3)</td>
<td>190/807 (23.5)</td>
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<td>Final diagnosis</td>
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<td>723/807 (89.6)</td>
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<td>AIS</td>
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<td>84/807 (10.4)</td>
</tr>
<tr>
<td>TIA</td>
<td>711/817 (87.0)</td>
<td>723/807 (89.6)</td>
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Clusters

<table>
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<tr>
<th>Characteristic</th>
<th>Study Group</th>
<th>Control</th>
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<tr>
<td>Neurologist available at ED</td>
<td>13/19 (68.4)</td>
<td>9/17 (52.9)</td>
</tr>
<tr>
<td>Mechanical thrombectomy capabilities</td>
<td>17/19 (89.5)</td>
<td>15/17 (88.2)</td>
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<td>Stroke unit</td>
<td>10/19 (52.6)</td>
<td>7/17 (41.2)</td>
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<td>Stroke protocol available at ED</td>
<td>17/19 (89.5)</td>
<td>17/17 (100)</td>
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<td>Stroke protocol available at hospital</td>
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<td>17/17 (100)</td>
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<td>JCI accreditation</td>
<td>1/19 (5.3)</td>
<td>3/17 (17.6)</td>
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<td>Teaching hospital</td>
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<td>15/17 (88.2)</td>
</tr>
<tr>
<td>Prior participation in multicenter clinical trial</td>
<td>17/19 (89.5)</td>
<td>15/17 (88.2)</td>
</tr>
<tr>
<td>Patients seen in ED per mo, median (IQR), No.</td>
<td>1600 (425–3000)</td>
<td>1400 (800–4000)</td>
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<td>Baseline rate of composite adherence score, median (IQR)b</td>
<td>77.1 (67.7–82.5)</td>
<td>75.3 (66.2–79.8)</td>
</tr>
</tbody>
</table>

Abbreviations: AIS, acute ischemic stroke; CAD, coronary artery disease; ED, emergency department; IQR, interquartile range; JCI, Joint Commission International; TIA, transient ischemic attack.

a Unless otherwise indicated, data are expressed as number/total number (percentage) of patients or clusters.
b Indicates primary outcome.

7.6%; \( P = .02 \) for interaction) and in hospitals with a stroke unit (mean [SD] score, 90.6% [14.0%] vs 77.5% [17.5%]; mean difference, 11.1%; 95% CI, 0.7%-21.4%) compared with clusters without a stroke unit (mean [SD] score, 78.6% [24.3%] vs 78.2% [19.1%]; mean difference, −3.7%; 95% CI, −13.4% to 6.2%; \( P = .05 \) for interaction).

Sensitivity Analysis

A sensitivity analysis including only patients with AIS diagnosis is shown in eTable 3 in Supplement 2. Overall composite adherence scores were higher in the intervention group than in the control group (mean [SD], 84.6% [19.8%] vs 76.7% [17.8%]; mean difference, 5.2%; 95% CI, −2.9% to 13.4%; ICC, 0.363; \( P = .20 \)). An analysis including only patients with TIA diagnosis (eTable 4 in Supplement 2) and an analysis adjusted for hospital status and presence of a stroke unit (eTable 5 in Supplement 2) showed similar results.

Discussion

In this cluster randomized trial, a quality improvement intervention that included case management, reminders, a therapeutic plan and checklist, educational materials, and audit and feedback was not effective in the care of patients with AIS and TIA as assessed by a composite adherence score. However, as assessed by a dichotomous all-or-none approach, the study presents hypothesis-generating findings of improved uptake of in-hospital evidence-based therapies. These findings were driven by increased prescription rates of rt-PA within a therapeutic window in intervention hospitals. The results were consistent among different subgroups, but with greater effect in hospitals with stroke units and in patients with AIS.

Previous nonrandomized quality improvement initiatives have demonstrated improvement in stroke quality of care. A study on the Get With the Guidelines–Stroke program showed a 40.3% absolute increase in evidence-based therapies (all-or-none measures) and a 10.72% absolute increase in the composite adherence score associated with use of the program. In our trial, we observed a 25% absolute increase in all-or-none measures adherence and an 8% increase in the composite adherence score. In another study, a quality improvement strategy was associated with increased uptake of rt-PA, which is also similar to our results.

Previous quality improvement cluster randomized clinical trials were predominantly conducted in high-income countries. Trials testing the use of critical pathways and therapeutic plans demonstrated increased use of evidence-based management procedures such as early aspirin prescription and dysphagia screening. In addition, cluster trials testing multidimensional implementation strategies conducted in the Netherlands and in the United Kingdom found small to moderate improvements in the proportion of patients with AIS treated with thrombolsys within 4 hours from onset, which is in line with our findings. Conversely, the Project for the Improvement of Stroke Care Management in Minnesota (PRISMM) failed to identify an intervention effect on 10 quality measures of stroke care. The neutral results may be related to suboptimal adherence to quality improvement tools (stroke care order sets, protocols, and patient educational materials) and to large secular trends.

We believe that our trial adds complementary information to studies conducted in higher-resource settings. To our knowledge, the BRIDGE-Stroke study constitutes the first randomized clinical trial aimed at improving stroke care conducted in Latin America. In this region, additional barriers to implementing evidence-based care include overcrowding, heavier individual clinical workloads, and fewer personnel devoted to continuing educational activities. Despite the neutral finding in our primary outcome, our results suggest that quality improvement interventions might be feasible in...
these settings, and we generated the hypothesis that the interventions might improve some performance measures. Therefore, we consider that the BRIDGE-Stroke findings represent an initial step to improve stroke care in the region, and the quality improvement tools developed for our trial need to be further improved and tested in future larger projects.

Recently, the Intervention to Bridge the Evidence-Based Gap in Stroke Care Quality (Golden-Bridge) trial, which included 40 clusters in China, showed a statistically significant improvement in the composite adherence score of 3.5% and a nonsignificant improvement of 6.7% with an all-or-none approach. These results are directionally similar to those seen in the BRIDGE-Stroke study, in which we observed an 8% nonsignificant improvement in the composite adherence score and a significant 25% improvement in the all-or-none measure. The Golden-Bridge study included only patients with AIS, whereas the BRIDGE-Stroke study included patients with AIS and TIA, and we found evidence of the interaction favoring patients with stroke; second, the BRIDGE-Stroke study assessed an international cluster assembly that expresses a stronger cluster effect as denoted by the larger ICC. Also, the BRIDGE-Stroke study assessed quality measures referring to the multidisciplinary stroke care pathway and was not restricted to medical prescriptions.

Owing to the nonpowered sample size for clinical outcomes and the observed low number of events with wide CIs, our results on clinical outcomes are exploratory. Nevertheless, we observed an increased incidence of hemorrhagic transformation events in clusters randomized to the intervention, probably owing to the increased use of rt-PA in patients with AIS. This finding is consistent with the higher hemorrhagic transformation incidence observed in large-scale trials of thrombolysis. Despite this finding, major bleeding and all-cause mortality (in-hospital and at 90 days) were similar between groups.
Strengths and Limitations

Our trial had specific strengths. The cluster-randomized design using the hospitals as the unit of randomization reduced the possibility of contamination. We prevented bias by using concealed allocation and blinded adjudication of outcomes. We analyzed data according to the intention-to-treat principle and took the cluster randomized trial design into account. We monitored screening logs from all sites to guarantee that clusters randomized a consecutive sample. Data were collected by independent research coordinators at each site, minimizing the risk of selective reporting of outcomes. Independent data collection was complemented by on-site monitoring and central statistical checks. The multifaceted intervention targeted 10 different quality indicators comprehending not only medical prescriptions but also assessment for rehabilitation and smoking cessation education.

Our trial has several limitations. First, for the intervention we had a hospital that did not adhere to the intervention because of dramatic changes in the leadership and management of the hospital, which could have influenced the general results of the study and certainly influenced the subgroup analysis per country as observed in Figure 2. Second,
we found evidence of interaction in the subgroup analysis for clusters with vs without stroke units. Thus, our intervention may be best suited for hospitals that are more motivated and that are better organized to provide stroke care. Third, the observed effect size was lower and the ICC for our primary outcome was greater than the variables used to calculate our sample size, which may have limited our power to detect a positive finding on the primary outcome. Fourth, our study is underpowered to detect meaningful differences in clinical outcomes, and the losses observed in the 90-day follow-up might also limit the interpretation of these findings. Fifth, cluster randomized clinical trials are prone to additional limitations, such as lesser statistical power and the variation within or between clusters, compared with trials with randomization at the individual level. Nevertheless, clustering was considered in all reported analyses using appropriate methods.

Conclusions

A multifaceted quality improvement intervention did not result in a significantly increased composite adherence score for evidence-based therapies in patients with AIS or TIA. These findings do not support the routine use of our intervention among unselected institutions. However, our results generate the hypothesis that the intervention might improve adherence to evidence-based therapies using an all-or-none approach and might improve the use of thrombolysis in eligible patients. Therefore, our intervention might be particularly useful for patients with AIS and for hospitals that have stroke units and in which staff is motivated to adhere to the quality improvement tools. Further trials conducted in lower-resource settings and adequately powered to assess the impact of quality improvement interventions on clinical outcomes are warranted.

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**Data Sharing Statement:** See Supplement 3.

**REFERENCES**


Quality Improvement Intervention for Hospital Adherence to Therapies for Patients With Stroke


