JAMA Cardiology | Original Investigation

Effect of a Multifaceted Quality Improvement Intervention on the Prescription of Evidence-Based Treatment in Patients at High Cardiovascular Risk in Brazil

The BRIDGE Cardiovascular Prevention Cluster Randomized Clinical Trial

M. Julia Machline-Carrion, MD, MHS, PhD; Rafael Marques Soares, MSc; Lucas Petri Damiani, MSc; Viviane Bezerra Campos, BSc; Bruna Sampaio, BSc; Francisco H. Fonseca, MD, PhD; Maria Cristina Izar, MD, PhD; Celso Amodeo, MD, PhD; Octávio Marques Pontes-Neto, MD, PhD; Juliana Yamashita Santos, BSc; Samara Pinheiro do Carmo Gomes, BSc; José Francisco Kerr Saraiva, MD, PhD; Eduardo Ramacciotti, MD, PhD; Pedro Gabriel de Melo Barros e Silva, MD, PhD; Renato D. Lopes, MD, PhD; Nilton Brandão da Silva, MD, PhD; Hélio Penna Guimarães, MD, PhD; Leopoldo Piegas, MD, PhD; Airton T. Stein, MD, PhD; Otávio Berwanger, MD, PhD; for the BRIDGE Cardiovascular Prevention Investigators

IMPORTANCE Studies have found that patients at high cardiovascular risk often fail to receive evidence-based therapies in community practice.

OBJECTIVE To evaluate whether a multifaceted quality improvement intervention can improve the prescription of evidence-based therapies.

DESIGN, SETTING, AND PARTICIPANTS In this 2-arm cluster randomized clinical trial, patients with established atherothrombotic disease from 40 public and private outpatient clinics (clusters) in Brazil were studied. Patients were recruited from August 2016 to August 2017, with follow-up to August 2018. Data were analyzed in September 2018.

INTERVENTIONS Case management, audit and feedback reports, and distribution of educational materials (to health care professionals and patients) vs routine practice.

MAIN OUTCOMES AND MEASURES The primary end point was prescription of evidence-based therapies (ie, statins, antiplatelet therapy, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) using the all-or-none approach at 12 months after the intervention period in patients without contraindications.

RESULTS Of the 1619 included patients, 1029 (63.6%) were male, 1327 (82.0%) had coronary artery disease (843 [52.1%] with prior acute myocardial infarction), 355 (21.9%) had prior ischemic stroke or transient ischemic attack, and 197 (12.2%) had peripheral vascular disease, and the mean (SD) age was 65.6 (10.5) years. Among randomized clusters, 30 (75%) were cardiology sites, 6 (15%) were primary care units, and 26 (65%) were teaching institutions. Among eligible patients, those in intervention clusters were more likely to receive a prescription of evidence-based therapies than those in control clusters (73.5% [515 of 701] vs 58.7% [493 of 840]; odds ratio, 2.30; 95% CI, 1.14-4.65). There were no differences between the intervention and control groups with regards to risk factor control (ie, hyperlipidemia, hypertension, or diabetes). Rates of education for smoking cessation were higher among current smokers in the intervention group than in the control group (51.9% [364 of 701] vs 18.2% [153 of 840]; odds ratio, 11.24; 95% CI, 2.20-57.43). The rate of cardiovascular mortality, acute myocardial infarction, and stroke was 2.6% for patients from intervention clusters and 3.4% for those in the control group (hazard ratio, 0.76; 95% CI, 0.43-1.34).

CONCLUSIONS AND RELEVANCE Among Brazilian patients at high cardiovascular risk, a quality improvement intervention resulted in improved prescription of evidence-based therapies.

TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT02851732

JAMA Cardiol. 2019;4(5):408-417. doi:10.1001/jamacardio.2019.0649
Published online April 3, 2019.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: Members of the BRIDGE Cardiovascular Prevention Investigators appear at the end of the article.

Corresponding Author: M. Julia Machline-Carrion, MD, MHS, PhD, HCor Research Institute, Hospital do Coração, 250 Abilio Soares St, São Paulo, SP 04005-909, Brazil (mjuliacarrion@gmail.com).

Cardiovascular diseases remain the leading cause of death globally, particularly in low- and middle-income countries, where 80% of the burden resides.[1,2] It is well established that statins,[3,4] antiplatelet therapy,[5] and angiotensin-converting enzyme (ACE) inhibitors[6,7] or angiotensin receptor blockers (ARBs)[8,9] reduce the risk of clinical events in patients with cardiovascular disease. Nevertheless, registries have consistently demonstrated that the implementation of these therapies in practice is suboptimal, especially in low- and middle-income countries.[10,11]

Prior systematic reviews have suggested that certain quality improvement (QI) tools are associated with better quality of care.[12-14] These include reminders, educational outreach visits, audit and feedback, case management, and distribution of educational materials to health care professionals. Combined strategies targeting different barriers are more likely to be effective than single interventions.[15] Nevertheless, trials testing the effects of QI interventions have rarely been conducted in lower-resource settings. To assess the effectiveness of a multifaceted QI intervention in patients at high cardiovascular risk in Brazil, we conducted a cluster randomized clinical trial, the Brazilian Intervention to Increase Evidence Usage (BRIDGE) Cardiovascular Prevention study.

Key Points

Question Can a multifaceted quality improvement intervention increase health care professionals' adherence to prescribing evidence-based therapies for patients at high cardiovascular risk?

Findings In this cluster randomized clinical trial that included 1619 patients from 40 outpatient clinics or primary care units in Brazil, at 12 months, those in intervention clusters were more likely to receive a prescription of all eligible evidence-based therapies than those in control clusters (73.5% [515 of 701] vs 58.7% [493 of 840]).

Meaning Compared with usual care, a multifaceted intervention resulted in improved prescription rates of evidence-based therapies when assessed as an all-or-none measure.

Methods

Study Design

The trial protocol and the statistical analysis plan are available in Supplement 1, and the methods were previously published.[16] Briefly, the BRIDGE Cardiovascular Prevention study was a pragmatic 2-arm, cluster randomized clinical trial. The main objective was to evaluate whether a multifaceted QI intervention could improve the prescription of evidence-based therapies for patients at high cardiovascular risk at 12 months. All clusters submitted the protocol for approval by their research ethics boards; written informed consent was obtained at the cluster and at the patient level. The trial is registered at ClinicalTrials.gov (NCT02851732). The enrollment period was from August 2016 to August 2017. Follow-up was completed in August 2018.

Clusters

Clusters were outpatient clinics from public or private hospitals or primary care units from all regions in Brazil. Details of the Brazilian health care system are provided in eAppendix 1 in Supplement 2. Both teaching and nonteaching units were eligible. We identified clusters through previous registries, our research network, and medical societies.

Patients

We enrolled consecutive male and female patients older than 40 years who had established coronary artery disease, a prior ischemic stroke, or peripheral artery disease. Detailed eligibility criteria are shown in Supplement 1 and in eAppendix 2 in Supplement 2.

Randomization and Allocation Concealment

Clusters were randomized 1:1 to a multifaceted QI improvement strategy or to routine practice. All clusters were randomized at once by a statistician using a central web-based randomization system before enrollment of the first patient. Randomization was stratified according to practice type (specialty vs primary care).

Blinding

Patients and investigators were not blinded to the allocation of treatment. Adjudication of clinical events was performed in a blinded fashion. Statisticians were blinded to the nature of the intervention.

Intervention

The QI intervention included case management, audit and feedback, decision support tools based on current guidelines, and distribution of educational materials (eApppendix 3 in Supplement 2). A nurse trained in the intervention acted as the case manager. The case manager (usually 1 per cluster) was responsible for patient evaluations (lasting 15 to 20 minutes) conducted immediately before and after the physician visit. The prephysician visit evaluations were conducted with a checklist that included information on cardiovascular comorbidities, risk factor control, and current medications. This checklist was organized in 4 colored sections comprehending lipid profile control (red), blood pressure control and use of ACE inhibitors or ARBs (green), glycemic control (blue), and antiplatelet therapy (yellow). The case manager provided the filled checklist to the physician together with the patient medical records and prompted the physician in case any abnormality was detected. After the physician visit, the case manager conducted another patient evaluation to guarantee that each section of the checklist had been addressed. In case actions were not taken, the physician was prompted again to check if further management decisions were needed.

We provided physicians from intervention clusters with a single-page decision support algorithm. The algorithm was also organized in different colored sections comprehending lipid profile control (red), blood pressure control and ACE inhibitor or ARBs usage (green), glycemic control (blue), and antiplatelet therapy (yellow). The decision support system sum-

marized the key recommendations adapted from different guidelines in 1 page.

Monthly audit and feedback reports were provided to both research staff and health care professionals from clusters allocated to the intervention group. These reports contained information on adherence to performance measures, such as prescription of evidence-based therapies and risk factor control, and were periodically discussed during web or telephone conferences with the coordinating center.

Finally, we distributed educational materials to patients (ie, a folder including recommendations on lifestyle modification) and to physicians (ie, a folder with information on how to prescribe evidence-based therapies). Health care professionals from intervention clusters (at least 1 physician who acted as the local leader as well as case managers) were invited to attend a 1-day workshop on cardiovascular prevention and received training on how to implement the quality improvement intervention. In addition, all clusters randomized to the intervention received a 1-day on-site training visit complemented by web-based and telephone training. During visits, we discussed the trial design and how to apply the tools. Visits were attended by leadership, physicians, case managers, and other health care professionals.

End Points

The primary end point was prescription of evidence-based therapies (ie, statins, antiplatelet therapy, and ACE inhibitors or ARBs) using the all-or-none approach at 12 months after the intervention period in patients without contraindications. According to these criteria, to be classified as yes, a patient must have received all therapies; otherwise, the patient was classified as no in the database. We chose to define the primary end point using the all-or-none approach because the all-or-none approach is more conservative than using composite scores, and there is robust evidence from large-scale trials to suggest that these medications reduce major cardiovascular events. In addition, trial data suggest that their effects are additive.

Secondary outcomes were prescription of individual components of the primary end point at 12 months, a combined therapy of statins, antiplatelet therapy, and ACE inhibitors or ARBs at 6 months after the intervention period in patients without contraindications, percentage of eligible patients with low-density lipoprotein cholesterol levels less than 70 mg/dL (to convert to micromoles per liter, multiply by 0.0259) 12 months after the intervention period, and prescription of high-dose statins in patients without contraindications. Clinical events were considered as secondary end points, including a combined end point of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke at 12 months. Outcomes related to prescription patterns and laboratory tests were ascertained by an independent data collector. Clinical events were ascertained during in-person visits by health care professionals who also provided documents for adjudication. In addition, the independent data collector spoke with patients by telephone and reviewed medical records to identify other potential events. Clinical events were centrally adjudicated based on standardized definitions (Supplement 1). In specific prespecified subgroups, we also measured the following end points at 6 and 12 months after the intervention period: prescription of β-blockers in patients with previous myocardial infarction without contraindications; smoking cessation education rates (ascertained by patient interview and medical record review) in current smokers; percentage of patients with hypertension with systolic blood pressure less than 140 mm Hg and diastolic blood pressure less than 90 mm Hg; percentage of patients with hypertension with systolic blood pressure less than 120 mm Hg and diastolic blood pressure less than 80 mm Hg; percentage of patients with diabetes with normal fasting plasma glucose levels (less than 126 mg/dL [to convert to micromoles per liter, multiply by 0.0555]) and less than 110 mg/dL; and percentage of patients with diabetes with hemoglobin A_{1c} less than 7%.

Data Collection

In all clusters, data were collected prospectively by trained data collectors not involved in patient care. To avoid ascertainment bias, only these independent data collectors acquired data. The independent data collectors also assessed adherence to the QI tools by reviewing whether the checklists and decision support tools were filled and whether the visits were registered in medical records. Data quality control was assured by automated data entry checks, central statistical monitoring checks, and on-site monitoring.

Baseline Survey

Baseline performance (prescription rates of evidence-based therapies) was obtained from the Registry of Clinical Practice in High Risk Patients (REACT) Registry,[11] previously conducted in several clusters that have joined the current trial. In clusters that were not part of the REACT Registry, we conducted a prerandomization survey using the same eligibility criteria for patient inclusion. Details are presented in eAppendix 4 and eTable 2 in Supplement 2.

Sample Size

To detect a 20% absolute improvement rate in the primary end point considering a 50% rate in the control group, an intracluster correlation coefficient (ICC) of 0.20[11] with 90% power, and a median of 40 patients per cluster, we needed to randomize at least 21 clusters per group (a total of 42 clusters). A 2-tailed α of 5% was set for statistical significance.

Statistical Analysis

All analyses followed the intention-to-treat principle. Prespecified comparisons between groups were conducted using logistic regression with random effects corrected for the baseline performance. Missing data were not imputed. The effects were presented as odds ratios (ORs) with 95% CIs. A description of how ORs were obtained from logistic regression with random effects is provided in eAppendix 5 in the Supplement 2. Clinical events were compared using Cox regression with random effects, and results are presented as hazard ratios with 95% CIs. Interim analyses were not performed.

We conducted 2 post hoc sensitivity analyses for the primary end point (1) considering multiple imputation for missing data and (2) adjusted for patient age, unit profile (hospital

outpatient clinic vs primary care center), unit status (teaching unit vs nonteaching unit), and general vs specialized unit. We also conducted post hoc analyses using the Benjamini-Hochberg correction for multiple comparisons for secondary outcomes at 12 months.[17] The effect of the intervention was compared in the following prespecified subgroups: hospital outpatient clinics vs primary care units, teaching vs nonteaching institutions, general vs specialized unit, and presence or not of polyvascular disease.

All analyses were performed using R version 3.5.1 (The R Foundation). A 2-sided *P* value less than .05 was established as the level of significance for all tests. *P* values for ORs were calculated using the Wald test and for hazard ratios using normal approximation to the distribution of the restricted maximum likelihood estimators. The Benjamini-Hochberg procedure was also applied to the *P* values regardless of the model to control for false discovery rate.

Results

From 123 potentially eligible clusters that were invited, 83 were excluded (63 did not answer the invitation despite at least 2 attempts, 15 declined participation, and 2 did not meet inclusion criteria). From the remaining 43 clusters that confirmed interest, 3 withdrew postrandomization but prior to intervention because they were unable to send any research staff to attend training sessions. The characteristics of the 3 clusters excluded postrandomization are presented in eTables 1 and 2 in Supplement 2. From the 40 randomized clusters that completed the study, a total of 1619 patients were enrolled prospectively (**Figure 1**).

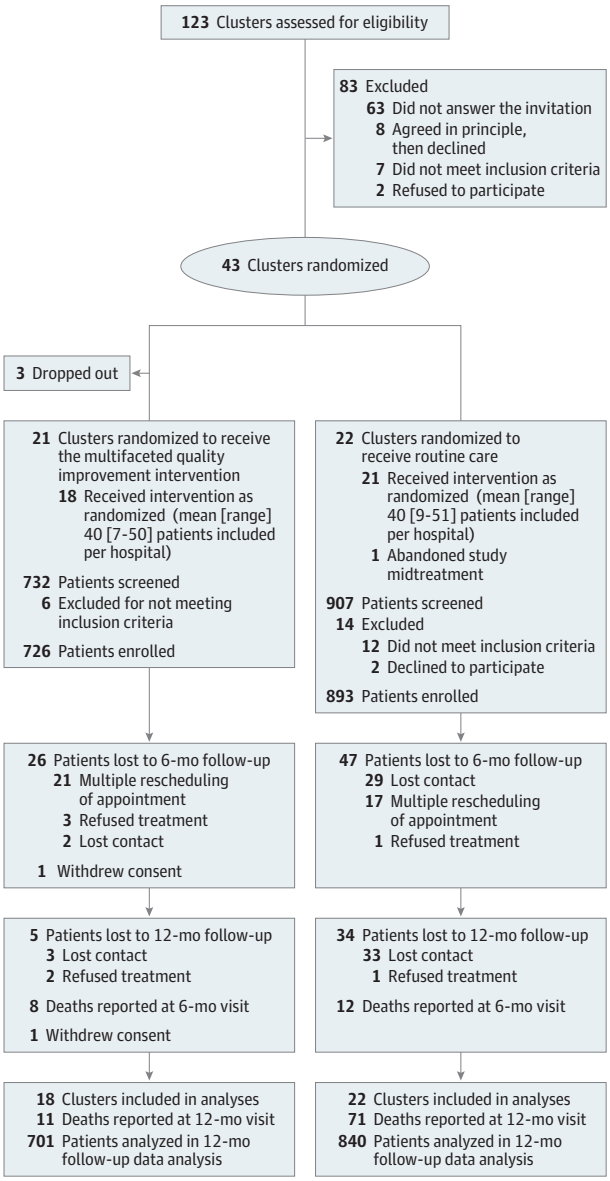
Baseline Characteristics

Baseline cluster and patient characteristics were generally similar in each group (**Table 1**). From the included clusters, 30 (75%) were cardiology sites, 6 (15%) were primary care units, 26 (65%) were teaching hospitals, and the median volume of patients seen was approximately 240 patients per month. The mean (SD) age of the patients enrolled was 65.6 (10.5) years, and 1029 (63.6%) were male, 1327 (82.0%) had coronary artery disease (843 [52.1%] with prior myocardial infarction), 355 (21.9%) had prior ischemic stroke or transient ischemic attack, 197 (12.2%) had peripheral vascular disease, 1431 (84.4%) had a history of hypertension, and 624 (38.5%) had diabetes. The mean (range) number of patients in each cluster was 40 (7-51).

Adherence to the QI Intervention

In the intervention group, nurses were able to act as case managers for 654 of 713 included patients (91.7%; prephysician and postphysician evaluation visits were completed in 652 patients [91.4%]), adherence to the decision support tools by physicians occurred in 658 cases (92.3%), and lifestyle recommendations brochures were distributed to 637 patients (89.3%) (eTable 3 in the Supplement). All clusters from the intervention group received monthly audit and feedback reports.

Figure 1. Study Flow Diagram



Effects on Prescription of Evidence-Based Therapies

The effects of the QI intervention on prescription rates of evidence-based therapies at 12 months are shown in **Table 2**. Effects of the intervention on prescription rates at admission and at 6 months are shown in eTables 4 and 5 in Supplement 2.

Among eligible patients, those in intervention clusters were more likely to receive a prescription of all eligible evidence-based therapies (ie, statins, antiplatelet therapy and ACE inhibitors or ARBs) than those in control clusters (73.5% [515 of 701] vs 58.7% [493 of 840]; OR, 2.30; 95% CI, 1.14-4.65; ICC, 0.17). Post hoc sensitivity analyses for the primary end point yielded similar results (eTable 6 in Supplement 2).

Prescription of statins among 801 of 1150 eligible patients (69.7%) at 12 months was higher in intervention clusters vs control clusters (93.6% [656 of 701] vs 81.7% [686 of 840];

Table 1. Baseline Characteristics of Participating Clusters and Patients

Baseline Characteristic	No. (%)	
	Intervention	Control
Cluster		
Total, No.	18	22
Predominant clinical specialty		
Cardiology	14 (78)	16 (73)
Neurology	0	1 (5)
Vascular surgery	1 (6)	1 (5)
Internal medicine	1 (6)	0
Primary care unit	2 (11)	4 (18)
Previous participation in clinical trials	16 (89)	16 (73)
Teaching unit	13 (72)	13 (59)
Volume of patients seen in ambulatory per mo, median (IQR)	285 (150- 550)	200 (100-489)
Public units	9 (50)	11 (50)
Structured protocol for care and management of patients at high cardiovascular risk	7 (39)	11 (50)
Patient		
Total, No.	726	893
Male	462 (63.6)	567 (63.5)
Age, mean (SD), y	65.9 (10.4)	65.4 (10.7)
Previous CAD	612 (84.3)	715 (80.1)
Previous acute myocardial infarction	370 (51.0)	473 (53.0)
Previous stroke or TIA	146 (20.1)	209 (23.4)
Peripheral arterial disease	83 (11.4)	114 (12.8)
Systemic arterial hypertension	662 (91.2)	769 (86.1)
Diabetes	308 (42.4)	316 (35.4)
Dyslipidemia	535 (73.7)	563 (63.0)
Diabetic nephropathy	25 (3.4)	23 (2.6)
Asymptomatic carotid disease	40 (5.5)	86 (9.6)
Family history of CAD	272 (37.5)	333 (37.3)
Heart failure	110 (15.2)	161 (18.0)
Renal insufficiency	26 (3.6)	24 (2.7)
Valvular heart disease	10 (1.4)	45 (5.0)
COPD	30 (4.1)	35 (3.9)
Bronchial asthma	18 (2.5)	24 (2.7)
Body mass index >30, No./total No. (%)[a]	231/725 (31.9)	274/892 (30.7)
Current smoker	74 (10.2)	108 (12.1)
Blood pressure, mean (SD), mm Hg		
Systolic	131 (20.2)	131.7 (20.3)
Diastolic	76.7 (11.2)	79.7 (11.1)

Abbreviations, CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; TIA, transient ischemic attack.

[a] Calculated as weight in kilograms divided by height in meters squared.

OR, 4.04; 95% CI, 1.50-10.89; ICC, 0.28). Overall prescription of antiplatelet therapy was higher in patients from clusters in the intervention group than in patients from the control group (94.0% [659 of 701] vs 86.3% [725 of 840]; OR, 3.13; 95% CI, 1.29-7.60; ICC, 0.21), mainly driven by increased prescription of aspirin in patients from intervention clusters vs control clusters (92.1% [637 of 692] vs 81.6% [682 of 836]; OR, 3.15; 95% CI, 1.37-7.26; ICC, 0.20). Prescription of ACE inhibitors or ARBs were also higher in QI intervention clusters than in control clusters (80.3% [561 of 699] vs 74.4% [625 of 840]; OR, 1.44; 95% CI, 0.88-2.36; ICC, 0.07), but the difference was not statistically significant.

Effects on Risk Factors Control

Table 2 shows the effects of the intervention on risk factor control at 12 months. There were no differences between the intervention and control groups with regards to the proportion of patients who achieved low-density lipoprotein cholesterol levels less than 70 mg/dL.

Among patients with hypertension, the intervention had no effects on the rate of patients who achieved systolic blood pressure levels less than 140 mm Hg or diastolic blood pressure levels less than 90 mm Hg (67.9% [433 of 638] vs 59.8% [432 vs 722]; OR, 1.37; 95% CI, 0.87-2.18; ICC, 0.07). Similarly, there was no difference between groups in the proportion of patients who achieved systolic blood pressure less than 120 mm Hg.

Education for smoking cessation rates were higher in the intervention than in the control group (51.9% [364 of 701] vs 18.2% [153 of 840]; OR, 11.24; 95% CI, 2.20-57.43; ICC, 0.56). There were no differences between groups regarding diabetes control.

Effects on Clinical Events

Table 3 shows the effects of our intervention on clinical events at 12 months. A total of 19 of 705 patients (2.7%) in the intervention group and 30 of 844 (3.6%) in the control group experienced major cardiovascular events, without a statistically significant difference (hazard ratio, 0.76; 95% CI, 0.43-1.34; ICC, 0).

Subgroup Analysis

The subgroup analysis is shown in **Figure 2**. The effect of the intervention on the primary end point was greater in teaching vs nonteaching clusters. Despite the fact that testing for interaction did not suggest evidence of other subgroup effects, these findings should be interpreted with caution.

Discussion

In this cluster randomized clinical trial, a QI intervention including case management, audit and feedback reports, decision support tools, and distribution of educational materials was effective in improving prescription rates of evidence-based therapies at 12 months. Results were consistent for the components of the primary end point, particularly statins and antiplatelet therapies, among different subgroups but with greater effect in clusters with teaching units. In addition, our intervention also improved education for smoking cessation rates. The intervention had no effect on risk factor control or clinical events.

Previous trials aimed at improving the care of patients with or at risk for cardiovascular diseases conducted in developed countries have had mixed results. The Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion (TORPEDO) trial[18] involved

Table 2. Effects of a Quality Improvement Intervention on Prescription of Evidence-Based Therapies and Risk Factor Control at 12-Month Follow-up

Outcome	No./Total No. (%)		OR (95% CI)		ICC	*P* Value	*P* Value[a]
	Intervention	Control	Unadjusted	Adjusted			
Adherence to evidence-based therapies[b]							
Admission	492/726 (67.8)	547/893 (61.3)	1.33 (1.06-1.67)	1.49 (0.86-2.60)	0.11	.10	NA
12 mo	515/701 (73.5)	493/840 (58.7)	1.95 (1.53-2.48)	2.30 (1.14-4.65)	0.18	.01	NA
Statins	656/701 (93.6)	686/840 (81.7)	3.27 (2.21-4.85)	4.04 (1.50-10.89)	0.28	<.001	.01
High-dose statins[c]	74/701 (10.6)	59/840 (7.0)	1.56 (1.05-2.32)	2.64 (0.80-8.72)	0.34	.06	.34
Antiplatelet therapy	659/701 (94.0)	725/840 (86.3)	2.49 (1.64-3.77)	3.13 (1.29-7.60)	0.21	<.001	.02
Aspirin	637/692 (92.1)	682/836 (81.6)	2.62 (1.81-3.78)	3.15 (1.37-7.26)	0.21	<.001	.01
Clopidogrel	118/701 (16.8)	159/838 (19.0)	0.86 (0.64-1.16)	0.95 (0.48-1.87)	0.15	.86	.97
Ticagrelor	7/701 (1.0)	9/840 (1.1)	0.93 (0.31-2.82)	1.12 (0.16-8.00)	0.43	.89	.97
Prasugrel	0	2/840 (0.2)	NA	NA	NA	NA	NA
ACEi or ARB	561/699 (80.3)	625/840 (74.4)	1.40 (1.07-1.83)	1.44 (0.88-2.36)	0.08	.09	.35
ACEi	273/699 (39.1)	347/840 (41.3)	0.91 (0.72-1.14)	1.02 (0.57-1.82)	0.12	.94	.97
ARB	303/700 (43.3)	290/840 (34.5)	1.45 (1.15-1.82)	1.35 (0.77-2.37)	0.11	.21	.58
β-Blockers in patients with MI	281/358 (78.5)	332/456 (72.8)	1.36 (0.95-1.96)	1.37 (0.58-3.22)	0.21	.40	.77
Smoking cessation education	364/701 (51.9)	153/840 (18.2)	4.85 (3.76-6.25)	11.24 (2.20-57.43)	0.56	<.001	.01
Risk factor control							
LDL-C level, mg/DL							
Mean (SD)	81.5 (32.7)	86.4 (36.5)	−4.88 (−13.78 to 4.02)[d]	−5.19 (−14.28 to 3.91)[e]	0.09	.25	.58
<100	330/432 (76.4)	272/380 (71.6)	1.28 (0.91-1.82)	1.23 (0.67-2.26)	0.09	.43	.77
<70	177/432 (41.0)	146/380 (38.4)	1.11 (0.81-1.52)	1.12 (0.60-2.09)	0.11	.67	.90
BP in patients with hypertension, mm Hg							
Systolic BP, mean (SD)	124.3 (32.8)	126.7 (34.9)	−2.37 (−14.78 to 10.04)[d]	−2.05 (−14.92 to 10.80)[e]	0.27	.75	.95
Diastolic BP, mean (SD)	74.1 (19.1)	75.1 (20.4)	−1.00 (−8.23 to 6.23)[d]	−0.46 (−7.91 to 7.00)[e]	0.27	.90	.97
<140/90	433/638 (67.9)	432/722 (59.8)	1.42 (1.11-1.82)	1.37 (0.87-2.18)	0.07	.11	.35
<120/80	132/638 (20.7)	134/722 (18.6)	1.14 (0.85-1.54)	1.22 (0.58-2.57)	0.19	.54	.87
Systolic BP <120	158/638 (24.8)	166/722 (23.0)	1.10 (0.83-1.46)	1.00 (0.51-1.94)	0.14	.99	.99
Fasting glucose levels in patients with diabetes, mg/dL							
≤110	68/202 (33.7)	53/155 (34.2)	0.98 (0.60-1.59)	1.12 (0.60-2.11)	0	.67	.90
≤126	110/202 (54.5)	82/155 (52.9)	1.06 (0.67-1.69)	1.13 (0.60-2.16)	0	.65	.90
Hemoglobin A_{1c} level ≤7.0% in patients with diabetics	83/165 (50.3)	67/139 (48.2)	1.09 (0.66-1.79)	1.37 (0.52-3.60)	0.03	.44	.77

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; ICC, intracluster correlation coefficient; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NA, not applicable; OR, odds ratio.

SI conversion factors: To convert LDL-C to micromoles per liter, multiply by 0.0259; to convert glucose to micromoles per liter, multiply by 0.0555.

[a] *P* value adjustment for multiple testing (Benjamini–Hochberg procedure).

[b] Complete adherence to statins, antiplatelet therapy (in patients with MI up to 12 months, dual antiplatelet therapy is considered), and ACEi or ARBs.

[c] High doses defined as 80 mg of simvastatin, 80 mg of pravastatin, 80 mg of atorvastatin, 40 mg of rosuvastatin, 80 mg of fluvastatin, or 4 mg of pitavastatin.

[d] Mean difference and 95% CI estimated by mixed-effect regression model using the center as the random intercept.

[e] Mean difference and 95% CI estimated by mixed-effect regression model using the center as the random intercept and corrected for the baseline survey values as a fixed effect.

more than 38 000 people and 60 clusters in Australia and tested a decision support system combined with audit and feedback. The intervention resulted in a 10% absolute improvement in screening for cardiovascular disease risk. However, there were no significant improvements in prescribing recommended medicines to people at high cardiovascular risk.[18] As opposed to this trial, in the TORPEDO trial, there were no adjustments for baseline care.

The Improved Delivery of Cardiovascular Care (IDOCC) project[19] was a cluster randomized clinical trial designed to im-

Table 3. Effects of a Quality Improvement Intervention on Major Cardiovascular Events at 12-Month Follow-up

Outcome	No. of Events/Person-Years (Incidence Rate per 100 Person-Years)		Hazard Ratio (95% CI)[a]	ICC	*P* Value	*P* Value[b]
	Intervention	Control				
MACE[c]	19/705 (2.69)	30/844 (3.56)	0.76 (0.43-1.34)	NA	.34	.73
Cardiovascular mortality	10/710 (1.41)	13/851 (1.53)	0.92 (0.41-2.11)	0	.85	.97
Stroke	7/707 (0.99)	18/844 (2.13)	0.46 (0.18-1.18)	0.05	.11	.35
Myocardial infarction	7/708 (0.99)	4/851 (0.47)	2.10 (0.61-7.17)	0	.24	.58
Total mortality	19/710 (2.68)	19/851 (2.23)	1.21 (0.64-2.28)	0	.56	.87

Abbreviations: ICC, intracluster correlation coefficient; MACE, major cardiovascular events.

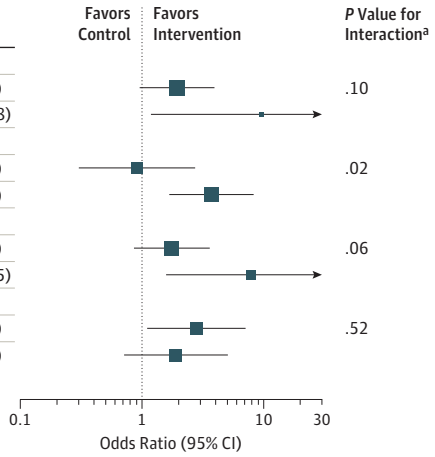
[a] Presented as hazard ratio estimates from unadjusted frailty Cox proportional hazard models with random effect by cluster.

[b] *P* value adjustment for multiple testing (Benjamini–Hochberg procedure).

[c] Combined occurrence of a first cardiovascular event (ie, cardiovascular mortality, acute myocardial infarction, and stroke).

Figure 2. Primary End Point According to Specified Subgroups

Subgroup	Prescription of Statins, Antiplatelet Therapy, and ACEi or ARB		Odds Ratio (95% CI)	*P* Value for Interaction[a]
	Intervention Group No./Total No. (%)	Control Group No./Total No. (%)		
Unit profile				
Hospital outpatient clinic	479/658 (72.8)	424/702 (60.4)	1.93 (0.95-3.93)	.10
Primary care unit	36/43 (84.0)	69/138 (50.0)	9.51 (1.18-76.38)	
Unit status				
Nonteaching unit	115/184 (62.5)	228/375 (60.8)	0.91 (0.30-2.71)	.02
Teaching unit	400/517 (77.4)	265/465 (57.0)	3.68 (1.66-8.18)	
Patient admission				
Specialty unit	440/608 (72.4)	422/693 (60.9)	1.75 (0.85-3.59)	.06
General unit	75/93 (81.0)	71/147 (48.3)	7.87 (1.56-39.55)	
Polyvascular disease				
No	296/412 (71.8)	191/349 (54.7)	2.79 (1.10-7.04)	.52
Yes	219/289 (75.8)	302/491 (61.5)	1.89 (0.71-5.07)	



ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

prove the delivery of evidence-based cardiovascular care in 48 primary care practices in Canada. Participants were randomly assigned by region to one of 3 steps. Practice facilitators were intended to visit practices every 3 to 4 weeks (year 1—intensive phase) or 6 to 12 weeks (year 2—sustainability phase) to support changes in practice behavior. The primary outcome was adherence to indicators of evidence-based care measured at the patient level. After adjustment for patient and health care professional characteristics, the intervention did not improve adherence to best practices.[19] Similar efforts are currently being conducted in the United States, such as the HealthyHearts NYC trial.[20]

The main differences between our trial and these studies are (1) inclusion of a broader range of clusters, including outpatient clinics of different specialties from teaching and nonteaching hospitals as well as primary care units; (2) focus on patients with established atherothrombotic disease; and (3) use of a multifaceted intervention, including case management, audit and feedback reports, decision support tools, and distribution of educational materials for health care professionals and patients. To our knowledge, the BRIDGE Cardiovascular Prevention study represents one of the first trials testing a QI intervention in patients with established atherothrombotic disease conducted in a middle-income country. Our results suggest that QI interventions may be feasible in these settings, especially using interventions such as the one shown in this study, which is simple and does not rely on expensive information technology or on complex human interventions. Further trials are needed in lower resource settings.[13] An ongoing trial from China (31 708 high-risk patients from 67 clusters)[21] is testing a package of interventions to increase adherence to lifestyle modifications and prescription of evidence-based therapies. The primary outcome is the 24-month incidence of cardiovascular events. Finally, the Cardiovascular Risk Reduction in South Asia (CARRS) trial[22] is testing a multifactorial diabetes care delivery strategy aimed at improving risk factor control and treatment plans in South Asia.

Limitations

Our trial had several limitations. Most participating sites were cardiovascular clinics, which may limit the external validity of our results. Additionally, our trial did not assess the cost-

effectiveness of the intervention, which may limit its widespread utilization owing to costs associated with case management and audit and feedback. Although centers were requested to enroll consecutive patients, we did not implement a system of registration of potentially eligible patients to confirm whether that actually happened. Our intervention was delivered over 12 months, and this may be too short to detect changes in practice and in clinical end points. Our trial did not detect differences in risk factor control, as reflected by the neutral results in blood pressure and lipid control, suggesting that the increase in drugs prescribed was not followed by an increase in drugs actually taken. There is evidence that patient-directed interventions combined with physician-focused strategies may be more effective than the latter alone.[23] Thus, the full implementation of evidence-based therapies and translation to improved health outcomes depends on combined strategies. In addition, our study was underpowered to detect differences in clinical outcomes. However, we consider that improving the prescription of statins, antiplatelet therapy, and ACE inhibitors or ARBs represents a valid end point, since it is well established that these therapies have additive effects in reducing major cardiovascular events.[24] Our trial is prone to recruitment bias since there were baseline differences in the primary end point between the groups. Additionally, we had more teaching units in the intervention group. We attempted to correct for this limitation by performing our main analyses adjusted for baseline performance.

Conclusions

In conclusion, in patients at high cardiovascular risk, a multifaceted QI intervention resulted in significant improvement in the prescription of evidence-based therapies. The tools tested in our trial can become the starting point for developing future programs to maximize the use of evidence-based interventions for the management of patients with established cardiovascular disease, especially in settings with limited resources.

ARTICLE INFORMATION

Accepted for Publication: February 7, 2019.

Published Online: April 3, 2019. doi:10.1001/jamacardio.2019.0649

Author Affiliations: HCor Research Institute, Hospital do Coração, São Paulo, São Paulo, Brazil (Machline-Carrion, Soares, Damiani, Campos, Sampaio, Santos, Gomes, Barros e Silva, Guimarães, Berwanger); Federal University of São Paulo, São Paulo, São Paulo, Brazil (Fonseca, Izar); Instituto Dante Pazzanese de Cardiologia, São Paulo, São Paulo, Brazil (Amodeo); Ribeirão Preto Medical School, University of São Paulo, São Paulo, São Paulo, Brazil (Pontes-Neto); Hospital e Maternidade Celso Pierro, Campinas, São Paulo, Brazil (Saraiva); Hospital e Maternidade Christóvão da Gama, Santo André, São Paulo, Brazil (Ramacciotti); Brazilian Clinical Research Institute, São Paulo, São Paulo, Brazil (Barros e Silva, Lopes); Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina (Lopes); Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil (Brandão da Silva, Stein); Hospital do Coração, São Paulo, São Paulo, Brazil (Piegas).

Authors Contribution: Drs Machline-Carrion and Damiani had full access to all data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.
Study concept and design: Machline-Carrion, Soares, Damiani, Campos, Amodeo, Pontes-Neto, Saraiva, Brandão da Silva, Guimarães, Piegas, Stein, Berwanger.
Acquisition, analysis, or interpretation of data: Machline-Carrion, Damiani, Sampaio, Fonseca, Izar, Santos, Gomes, Saraiva, Ramacciotti, Barros e Silva, Lopes, Brandão da Silva, Berwanger.
Drafting of the manuscript: Machline-Carrion, Campos, Sampaio, Amodeo, Santos, Gomes, Saraiva, Ramacciotti, Brandão da Silva, Berwanger.
Critical revision of the manuscript for important intellectual content: Machline-Carrion, Soares, Damiani, Fonseca, Izar, Pontes-Neto, Saraiva, Ramacciotti, Barros e Silva, Lopes, Brandão da Silva, Guimarães, Piegas, Stein, Berwanger.
Statistical analysis: Machline-Carrion, Damiani, Brandão da Silva, Berwanger.
Obtained funding: Machline-Carrion, Brandão da Silva, Berwanger.
Administrative, technical, or material support: Machline-Carrion, Soares, Campos, Sampaio, Santos, Gomes, Saraiva, Barros e Silva, Brandão da Silva, Guimarães, Stein, Berwanger.
Study supervision: Machline-Carrion, Fonseca, Amodeo, Saraiva, Ramacciotti, Brandão da Silva, Guimarães, Piegas, Stein, Berwanger.

Conflict of Interest Disclosures: Drs Machline-Carrion, Soares, Damiani, Campos, Sampaio, Santos, Gomes, Lopes, and Berwanger have received grants from Amgen during the conduct of the study. Dr Machline-Carrion has received personal fees from Boehringer Ingelheim. Dr Pontes-Neto has received grants from the National Council for Scientific and Technological Development as well as personal fees from Boehringer Ingelheim, Medtronic, and Pfizer. Dr Barros e Silva has received grants from Bayer and personal fees from Pfizer. Dr Lopes has received grants from Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, and Sanofi-Aventis as well as personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Pfizer, and Portola Pharmaceuticals. Dr Berwanger has received grants and personal fees from AstraZeneca, Bayer, and Novartis; personal fees from NovoNordisk and Servier; nonfinancial support from AstraZeneca; and educational support from Boehringer Ingelheim. No other disclosures were reported.

Funding/Support: This study is funded by Amgen as an investigator-initiated trial.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The BRIDGE Cardiovascular Prevention Investigators include the following members: *Steering Committee*: Principal Investigator: M. Julia Machline-Carrion, MD, MHS, PhD (HCor Research Institute, Hospital do Coração, São Paulo, São Paulo, Brazil); Chair: Otávio Berwanger, MD, PhD (HCor Research Institute, Hospital do Coração); Airton Stein, MD, PhD (Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil); Francisco H. Fonseca, MD, PhD (Federal University of São Paulo, São Paulo, São Paulo, Brazil); Maria Cristina Izar, MD, PhD (Federal University of São Paulo); Octávio Marques Pontes-Neto, MD, PhD (Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil); Celso Amodeo, MD, PhD (Instituto Dante Pazzanese de Cardiologia, São Paulo, São Paulo, Brazil); Leopoldo Piegas, MD, PhD (Hospital do Coração, São Paulo, São Paulo, Brazil); Hélio Penna Guimarães, MD, PhD (HCor Research Institute, Hospital do Coração); Renato Delascio Lopes, MD, PhD (Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina); and Nilton Brandão da Silva, MD, PhD (Universidade Federal de Ciências da Saúde de Porto Alegre); *Coordinating Center (HCor Research Institute, Hospital do Coração)*: site management: Rafael Marques Soares, MSc; data management: Viviane Bezerra Campos, BSc, and Bruna Sampaio, BSc; regulatory affairs: Beatriz Pacheco Gonzales, BSc, and Juliana Yamashita Santos, BSc; electronic case report form management: Alessandra Kodama, BSc, and Bruna Sampaio, BSc; clinical events adjudication: Hélio Penna Guimarães, MD, PhD; Pedro Gabriel de Melo Barros e Silva, MD, PhD; and Samara Pinheiro, BSc (documents management); and statistical analysis: Lucas Petri Damiani, MSc, and Renato Hideo Nakagawa, BSc; participating sites: *Hospital Santa Casa de Curitiba, Curitiba, Paraná, Brazil*: José Augusto Ribas Fortes, MD; Juliane Woehl, MD; and Juliana Barbosa do Carmo, BSc; *Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil*: Paulo Ernesto Leães, PhD; Vanessa Baldissera, BSc; and Raquel Osório Luiz, BSc; *Unidade Básica de Saúde Santa Cecilia, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil*: Marcelo Rodrigues Gonçalves, MD, and Shayanne Santos da Silva, BSc; *Grupo Hospitalar Conceição, Porto Alegre, Rio Grande do Sul, Brazil*: Sergio Antonio Sirena, PhD;

Luciane Kopittke, BSc; and Lia Paulina Wawrzyniak Silva, BSc; *Hospital São José, Antônio Prado, Rio Grande do Sul, Brazil*: Guilherme Brasil Grezzana, MD, and Danusa Conte, BSc; *Universidade de Santa Cruz do Sul, Santa Cruz do Sul, Rio Grande do Sul, Brazil*: Luciano Nunes Duro, MD, and Maurício Winck Esteves, MD; *Secretaria Municipal de Saúde de Montenegro, Montenegro, Rio Grande do Sul, Brazil*: Mario Jose do Canto Filho, MD, and Laila da Silveira, BSc; *Hospital Celso Ramos, Florianópolis, Santa Catarina, Brazil*: Gladys Lentz Martins, PhD, and Carla Pauli, BSc; *Universidade Estadual do Rio de Janeiro–Clínica de Hipertensão Arterial e Doenças Metabólicas Associadas, Rio de Janeiro, Rio de Janeiro, Brazil*: Mario Fritsch Neves, PhD, and Claudia Deolinda Lopes, BSc; *Hospital e Maternidade Santa Lucia de Poços de Caldas, Poços de Caldas, Minas Gerais, Brazil*: Ricardo Reinaldo Bergo, MD; Frederico Toledo Campo Dall Orto, MD; and Gislayne Rogante Ribeiro, BSc; *Hospital Regional São Sebastião, Lavras, Minas Gerais, Brazil*: Ernesto Lippi Neto, MD, and Patrícia Duarte Santos, BSc; *CARDIOPED, Colatina, Espírito Santo, Brazil*: João Miguel Malta Dantas, MD, and Luanna de Oliveira Silva, BSc; *Hospital das Clinicas da Universidade Federal de Goiás, Goiás, Goiás, Brazil*: Paulo César Brandão Veiga Jardim, MD, and Ana Luiza Lima Sousa, MD; *Fundação Universidade Federal Sergipe, Aracajú, Sergipe, Brazil*: José Augusto Soares Barreto Filho, MD, and Andreza Santos Almeida, BSc; *Centro de Pesquisa Clínica do Coração, Aracajú, Sergipe, Brazil*: Fábio Serra Silveira, MD; Maelyn Goeking de Oliveira Silveira, BSc; and Kívia Camilla Cardoso da Silva Serra, BSc; *Hospital Agamenon Magalhães, Recife, Pernambuco, Brazil*: João Batista de Moura Xavier de Moraes Jr, MD; Fernanda Freire Wanderley, BSc; and Sheylla de Andrade Ribeiro Souza, BSc; *Hospital e Maternidade Celso Pierro, Campinas, São Paulo, Brazil*: José Francisco Kerr Saraiva, PhD; Carla Cristina Vicente, BSc; Larissa Miranda Trama, BSc; Camila Ormundo, BSc; and Talita Pereira Silva, BSc; *Instituto de Cardiologia do Valle do Paraíba, São José dos Campos, São Paulo, Brazil*: Raphael Kazuo Osugue, MD, and Silvio Delfini Guerra, MD; *Clínica Villela Martin, São José do Rio Preto, São Paulo, Brazil*: José Fernando Vilela Martin, PhD, and Letícia Aparecida Barufi Fernandes, BSc; *Prevent Senior, São Paulo, São Paulo, Brazil*: Rodrigo Barbosa Esper, MD; *Luiz Phellipe Dell'aquila Hospital São Francisco de Ribeirão Preto, Ribeirão Preto, São Paulo, Brazil*: Fernando Nobre, PhD, and Viviane de Fátima Neves da Veiga, BSc; *Hospital das Clínicas da Hospital Universitário da Universidade Federal do Maranhão, São Luís, Maranhão, Brazil*: José Albuquerque Figueiredo Neto, MD; Joilma Silva Prazeres Tobias, BSc; Renata Melo de Assis, BSc; Josete Costa dos Santos, BSc; Maria Jozélia Diniz Moraes, BSc; and Maria de Fátima Rocha, BSc; *Clinica da Família Teewald, Santa Maria do Herval, Rio Grande do Sul, Brazil*: Enrique Falceto de Barros, MD; Joice Valquiria Ziebell, BSc; and Leonice Werle, BSc; *Instituto Municipal de Estratégia de Saúde da Família, Jardim Protásio Alves, Porto Alegre, Rio Grande do Sul, Brazil*: André Luiz Silva, PhD; Graciela de Oliveira Antunes Marcela, MD; and Ana Paula Feier, BSc; *Ambulatório de Clinica Medica Santa Casa De Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil*: Nilton Brandão da Silva, PhD; Giovana Caroline Marx Becke, MD; Jessica Carolina Matos D'Almeida Santo, MD; and Edna Vieira dos Santos, BSc; *Instituto de Pesquisas e Ensinos Médicos de Itajaí, Itajaí, Santa Catarina, Brazil*: Sidney Lourenço, MD; Vivian Caron, BSc; and Luis Henrique Domingues, BSc; *Sociedade Hospitalar Angelina Caron, Campina Grande do Sul, Paraná, Brazil*: Dalton Bertolim Precoma, PhD; João Vitor Simas Corrêa, BSc; Janaina Andreatta Bernardi Baréa, BSc; and Eliane Sehnem, BSc; *Instituto Dante Pazzanese de Cardiologia, São Paulo, São Paulo, Brazil*: Clarisse Kaoru Ogawa Indio do Brasil, PhD; Maria Isabel del Monaco, BSc; Simone Lopes Barroso, BSc; and Nilza Tamashiro, BSc; *Instituto de Moléstias Cardiovasculares, São José do Rio Preto, São Paulo, Brazil*: Elzo Thiago Brito Mattar, PhD; Clotildes Santiago Prates Queirantes, BSc; and Thamyres Santini Arroyo Cruz, BSc; *Hospital Regional de Presidente Prudente, Universidade do Oeste Paulista, Presidente Prudente, São Paulo, Brazil*: Margaret Assad Cavalcante, PhD; Gabriel Oliveira Silva, MD; Lucas Lima de Moraes, MD; and Vinícius Encenha Lanza, MD; *Hospital Naval Marcílio Dias, Instituto de Pesquisa Biomédica, Rio de Janeiro, Rio de Janeiro, Brazil*: Paulo Henrique Godoy, MD; Mônica Medeiros Luna, MD; and Evandro Ferreira de Lima, BSc; *Hospital Lifecenter, Belo Horizonte, Minas Gerais, Brazil*: Estêvão Lanna Figueiredo, PhD; Gustavo Fonseca Werner, BSc; Bruna Edilena, BSc; and Samara Bianca Rodrigues de Campos, BSc; *Santa Casa de Misericórdia de Vitória, Vitória, Espírito Santo, Brazil*: Roberto Ramos Barbosa, MD; Andressa Corteletti, BSc; Camila Carone, BSc; and Jocyley Emerick Padilha Jr, BSc; *Hospital da Bahia, Salvador, Bahia, Brazil*: Marianna Andrade, PhD; Natália Oliveira, BSc; and Rafaela Souza Hasselmann, BSc; *Hospital do Coração de Aracaju, Rodolfo Neirotti, Aracajú, Sergipe, Brazil*: Thiago Augusto do Nascimento, MD; Katharina Kelly de Oliveira Gama Silva, BSc; and Marina Provinciali Mendonça Vieira, BSc; *Pronto-Socorro Cardiológico Universitário de Pernambuco–Prof. Luiz Tavares, Recife, Pernambuco, Brazil*: Sérgio Tavares Montenegro, PhD; Dario Celestino Sobral Filho, PhD; Antônio Fernandes Brunet, BSc; and Eveline Lustosa Pires Almeida, BSc; *CARDIOLIMA, Teresina, Piauí, Brazil*: Carlos Eduardo Batista de Lima, PhD; Alysson Victor de Oliveira Castro, BSc; Pedro Victor, BSc; Luís Fernando Cunha Gomes, BSc; and Igor Leonardo Vieira Caetano, BSc; *Hospital e Maternidade Christóvão da Gama, Santo Andre, São Paulo, Brazil*: Eduardo Ramacciotti, PhD; Leandro Barile Agati, PhD; Rogerio Krakauer, PhD; Jessica Bonucci, BSc; and Marina Rosa Cassandra, BSc; and *Hospital São Paulo, Federal University of São Paulo, São Paulo, São Paulo, Brazil*: Francisco Antonio Helfenstein Fonseca, PhD; Maria Cristina de Oliveira Izar, PhD; and Simone Pinto Matheus Fischer, BSc.

Data Sharing Statement: See Supplement 3.

REFERENCES

1. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390(10100):1151-1210. doi:10.1016/S0140-6736(17)32152-9

2. França 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. doi:10.1186/s12963-017-0156-y

3. Baigent C, Keech A, Kearney PM, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366(9493):1267-1278. doi:10.1016/S0140-6736(05)67394-1

4. Baigent C, Blackwell L, Emberson J, et al; Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670-1681. doi:10.1016/S0140-6736(10)61350-5

5. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324(7329):71-86. doi:10.1136/bmj.324.7329.71

6. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G; Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342(3):145-153.

7. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001;358(9287):1033-1041. doi:10.1016/S0140-6736(01)06178-5

8. Yusuf S, Diener HC, Sacco RL, et al; PRoFESS Study Group. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med*. 2008;359(12):1225-1237. doi:10.1056/NEJMoa0804593

9. Yusuf S, Teo KK, Pogue J, et al; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358(15):1547-1559. doi:10.1056/NEJMoa0801317

10. Yusuf S, Islam S, Chow CK, et al; Prospective Urban Rural Epidemiology (PURE) Study Investigators. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. *Lancet*. 2011;378(9798):1231-1243. doi:10.1016/S0140-6736(11)61215-4

11. Berwanger O, Piva e Mattos LA, Martin JF, et al. Evidence-based therapy prescription in high-cardiovascular risk patients: the REACT study. *Arq Bras Cardiol*. 2013;100(3):212-220. doi:10.5935/abc.20130062

12. 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.

13. Rowe AK, Rowe SY, Peters DH, Holloway KA, Chalker J, Ross-Degnan D. Effectiveness of strategies to improve health-care provider practices in low-income and middle-income countries: a systematic review. *Lancet Glob Health*. 2018;6(11):e1163-e1175. doi:10.1016/S2214-109X(18)30398-X

14. Viswanathan M, Golin CE, Jones CD, et al. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. *Ann Intern*

Med. 2012;157(11):785-795. doi:10.7326/0003-4819-157-11-201212040-00538

15. 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-S20.

16. Machline-Carrion MJ, Soares RM, Damiani LP, et al. Rationale and design for a cluster randomized quality-improvement trial to increase the uptake of evidence-based therapies for patients at high cardiovascular risk: the BRIDGE-Cardiovascular Prevention trial. *Am Heart J*. 2019;207:40-48. doi:10.1016/j.ahj.2018.10.001

17. Benjamini Y, Hochbeg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol*. 1995;57(1):289-300.

18. Peiris D, Usherwood T, Panaretto K, et al. Effect of a computer-guided, quality improvement program for cardiovascular disease risk management in primary health care: the treatment of cardiovascular risk using electronic decision support cluster-randomized trial. *Circ Cardiovasc Qual Outcomes*. 2015;8(1):87-95. doi:10.1161/CIRCOUTCOMES.114.001235

19. Liddy C, Hogg W, Singh J, et al. A real-world stepped wedge cluster randomized trial of practice facilitation to improve cardiovascular care. *Implement Sci*. 2015;10:150. doi:10.1186/s13012-015-0341-y

20. Shelley DR, Ogedegbe G, Anane S, et al. Testing the use of practice facilitation in a cluster randomized stepped-wedge design trial to improve adherence to cardiovascular disease prevention guidelines: HealthyHearts NYC. *Implement Sci*. 2016;11(1):88. doi:10.1186/s13012-016-0450-2

21. Wei X, Zou G, Gong W, et al. Cardiovascular disease risk reduction in rural China: a clustered randomized controlled trial in Zhejiang. *Trials*. 2013;14:354. doi:10.1186/1745-6215-14-354

22. Shah S, Singh K, Ali MK, et al; CARRS Trial Writing Group. Improving diabetes care: multi-component cardiovascular disease risk reduction strategies for people with diabetes in South Asia—the CARRS multi-center translation trial. *Diabetes Res Clin Pract*. 2012;98(2):285-294. doi:10.1016/j.diabres.2012.09.023

23. Tricco AC, Ivers NM, Grimshaw JM, et al. Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis. *Lancet*. 2012;379(9833):2252-2261. doi:10.1016/S0140-6736(12)60480-2

24. Yusuf S. Two decades of progress in preventing vascular disease. *Lancet*. 2002;360(9326):2-3. doi:10.1016/S0140-6736(02)09358-3