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# Effect of a Multifaceted Intervention on Use of Evidence-Based Therapies in Patients With Acute Coronary Syndromes in Brazil

## The BRIDGE-ACS Randomized Trial

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**Context** Studies have found that patients with acute coronary syndromes (ACS) often do not receive evidence-based therapies in community practice. This is particularly true in low- and middle-income countries.

**Objective** To evaluate whether a multifaceted quality improvement (QI) intervention can improve the use of evidence-based therapies and reduce the incidence of major cardiovascular events among patients with ACS in a middle-income country.

**Design, Setting, and Participants** The BRIDGE-ACS (Brazilian Intervention to Increase Evidence Usage in Acute Coronary Syndromes) trial, a cluster-randomized (concealed allocation) trial conducted among 34 clusters (public hospitals) in Brazil and enrolling a total of 1150 patients with ACS from March 15, 2011, through November 2, 2011, with follow-up through January 27, 2012.

**Intervention** Multifaceted QI intervention including educational materials for clinicians, reminders, algorithms, and case manager training, vs routine practice (control).

**Main Outcome Measures** Primary end point was the percentage of eligible patients who received all evidence-based therapies (aspirin, clopidogrel, anticoagulants, and statins) during the first 24 hours in patients without contraindications.

**Results** Mean age of the patients enrolled was 62 (SD, 13) years; 68.6% were men, and 40% presented with ST-segment elevation myocardial infarction, 35.6% with non–ST-segment elevation myocardial infarction, and 23.6% with unstable angina. The randomized clusters included 79.5% teaching hospitals, all from major urban areas and 41.2% with 24-hour percutaneous coronary intervention capabilities. Among eligible patients (923/1150 [80.3%]), 67.9% in the intervention vs 49.5% in the control group received all eligible acute therapies (population average odds ratio [$OR_{PA}$], 2.64 [95% CI, 1.28-5.45]). Similarly, among eligible patients (801/1150 [69.7%]), those in the intervention group were more likely to receive all eligible acute and discharge medications (50.9% vs 31.9%; $OR_{PA}$, 2.49 [95% CI, 1.08-5.74]). Overall composite adherence scores were higher in the intervention clusters (89% vs 81.4%; mean difference, 8.6% [95% CI, 2.2%-15.0%]). In-hospital cardiovascular event rates were 5.5% in the intervention group vs 7.0% in the control group ($OR_{PA}$, 0.72 [95% CI, 0.36-1.43]); 30-day all-cause mortality was 7.0% vs 8.4% ($OR_{PA}$, 0.79 [95% CI, 0.46-1.34]).

**Conclusion** Among patients with ACS treated in Brazil, a multifaceted educational intervention resulted in significant improvement in the use of evidence-based therapies.

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CARDIOVASCULAR DISEASES, especially acute coronary syndromes (ACS), are the leading cause of morbidity and mortality globally.[1,2] Large-scale randomized trials have established the efficacy of several interventions for the care of patients with ACS, including antiplatelet therapy, anticoagulation, reperfusion for patients with ST-segment elevation myocardial infarction (STEMI), and secondary prevention with aspirin, β-blockers, statins, and angiotensin-converting enzyme inhibitors.[3-8] Nevertheless, registries have consistently demonstrated that the translation of research findings into practice is suboptimal[9-11] and that these care gaps are even greater in low- and middle-income countries.[12-15]

Changing clinical behavior to improve quality of care is challenging. Prior systematic reviews have suggested that certain quality improvement (QI) tools are associated with better quality of care.[16] These include reminders, educational outreach visits, audit and feedback, case management, and distribution of edu-

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cational materials to health professionals.[17] Combined strategies targeting different barriers are more likely to be effective than single interventions.[18] However, QI interventions have rarely been rigorously evaluated, especially in low- and middle-income countries, which account for up to 80% of the global burden of cardiovascular diseases.[19,20]

To assess the effectiveness of a QI initiative in patients with ACS from public hospitals in an emerging economy setting, we designed and conducted a cluster-randomized trial, BRIDGE-ACS (Brazilian Intervention to Increase Evidence Usage in Acute Coronary Syndromes).

## METHODS

### Study Design

The trial methods and design have been published previously.[21] In brief, BRIDGE-ACS was a pragmatic 2-group, cluster-randomized controlled trial with blinded adjudication of outcomes and intention-to-treat analysis. The main objectives were to evaluate the effect of a multifaceted QI intervention on the prescription of therapies proven efficacious for patients with ACS within the first 24 hours and at hospital discharge as well as on the incidence of major cardiovascular events.

All clusters submitted the study protocol for approval by their institutional research ethics board; written informed consent was obtained at the cluster level from the hospital medical director. The objective of such an approach was to avoid selection bias that may arise from different consent refusal rates between clusters.[21] The enrollment period was from March 15, 2011, through November 2, 2011. Follow-up was completed on January 27, 2012.

### Hospitals

We enrolled hospitals from major urban areas in Brazil; all were general public hospitals with emergency departments (EDs) that receive patients with ACS. We excluded private hospitals, cardiology institutes, and hospitals in rural areas. A list of potential eligible clusters (hospitals) was provided by the Brazilian Ministry of Health.

### Patients

At participating clusters, we enrolled consecutive patients as soon as they presented in the ED with ACS according to standardized definitions[7,8]; patients with STEMI, non–ST-segment elevation myocardial infarction (NSTEMI), and unstable angina were included. We excluded patients transferred from other hospitals after 12 hours or longer, patients with non–type I myocardial infarction, and patients for whom the presumptive admission diagnosis of ACS was not confirmed.

### Baseline Survey

We conducted a baseline survey in all participating clusters using the same eligibility criteria for patient inclusion. The survey was conducted prior to randomization to avoid potential systematic errors caused by awareness of allocation to intervention and control groups. The main objective of the baseline survey was to assess if clusters were comparable with regard to baseline prescription rates of evidence-based therapies and to obtain reliable estimates for our sample size estimation. Methods and results of the baseline survey are presented in the eAppendix available at http://www.jama.com.

### Randomization and Allocation Concealment

Clusters were randomly allocated (1:1) to a multifaceted QI strategy (intervention group) or to routine practice (control group). Randomization was stratified by teaching vs nonteaching hospitals and presence or absence of percutaneous coronary intervention (PCI) capabilities. All clusters were randomized at once on December 30, 2010, by a statistician using a central web-based randomization system before enrollment of the first patient.

### QI Intervention

The multifaceted QI intervention included reminders, a checklist, case management, and educational materials and was implemented in all clusters during the time of patient enrollment in the study. Clusters randomized to the intervention received on-site training visits complemented by web-based and telephone training. Additionally, 2 health professionals from these clusters (a physician who acted as the local leader and a research nurse who acted as case manager) attended a workshop on how to implement the BRIDGE-ACS QI intervention. These training sessions used simulation-based learning techniques. The 2 key study personnel were responsible for continuous training of the health care staff at their site and for guaranteeing adequate implementation of the QI tools. At least 80% of the research medical staff from each site was trained for this study.

The reminders and the checklist were designed to be implemented sequentially during the care of patients with ACS. As soon as a patient with suspected ACS arrived in the ED, a printed reminder ("Chest Pain" label) was attached to the clinical evaluation form to serve as a rapid triage tool. The ED nurse then gave the attending physician the clinical evaluation form with the chest pain label and an attached checklist. The checklist contained an algorithm for risk stratification (based on clinical presentation, electrocardiogram analysis, and cardiac enzyme levels) and recommended evidence-based therapies for each risk category. The algorithm divided patients into 3 risk categories, each corresponding to a specific color: red for STEMI; yellow for non–ST-segment elevation ACS; and green for patients with a normal electrocardiogram tracing and cardiac enzyme levels.

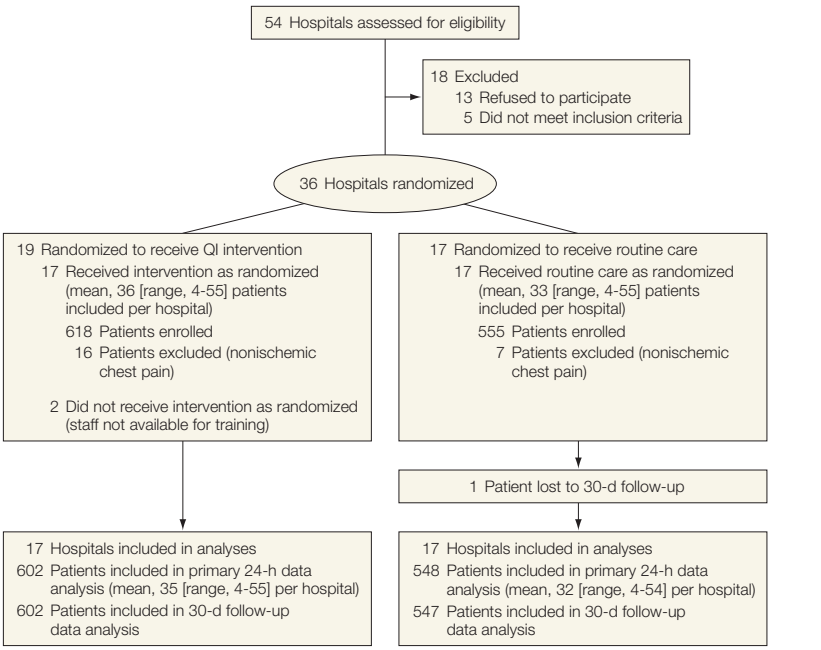
The attending physician was required to check and confirm the use (or no use in the case of contraindications) of all suggested evidence-based interventions. Once patients were classified into 1 of the 3 categories, they received a colored bracelet (red, yellow, or green) according to the risk stratification category. These bracelets helped to promptly identify patients with ACS in the ED to avoid delays in initiating recommended evidence-based therapies.

A nurse trained in the QI intervention acted as a case manager and performed follow-up of all patients during their hospital stay. The responsibilities of the case manager included interacting with physicians to avoid gaps in the use of evidence-based interventions, ensuring that all components of the QI intervention were being used for every

patient with ACS, and overseeing continuous training of health care staff involved with the care of such patients.

Educational materials were provided for all clusters randomized to the experimental group, including pocket guidelines, an interactive website containing presentations about ACS, instructional videos on how to implement the QI intervention, and posters containing evidence-based recommendations for the management of ACS to be displayed in the ED, coronary care unit, and clinical wards.

**Figure 1.** Study Flow Diagram




QI indicates quality improvement.

## Blinding

Because of the nature of the intervention in the BRIDGE-ACS trial, only members of the clinical events classification committee were blinded to group assignment. At each site, independent data collectors, trained in web-based data capture systems, were not blinded to the intervention (because they measured compliance to the QI tools) but were unaware of the main study objectives and hypothesis.

## Data Collection

In all participating clusters, data were collected prospectively by independent health professionals trained in web-based data capture systems and not involved in the care of patients with ACS. Adherence to guidelines was assessed by chart review, patient files, and physician prescriptions. Additionally, the independent data collectors sent copies of charts, patient files, and physician prescriptions (with confidentiality protected) to the coordinating site, and these copies were validated by blinded outcome assessors. Study coordinators were unblinded regarding cluster assignment.

Data were entered using an electronic web-based data capture system. Data quality control was guaranteed by automated data entry checks, weekly contact with investigators, on-site monitoring, and central statistical checks.[22] Feedback was provided at investigator meetings and in monthly newsletters. The feedback and newsletters were provided to all clusters from both groups, including information on number of included patients. However, all communications sent to control group clusters did not mention the nature of the QI interventions or the identity (hospital names) of clusters randomized to the intervention group. Feedback on study end points (audit and feedback strategy), in particular adherence to therapies, was not provided to any of the groups.

## End Points

The primary end point was adherence to all eligible evidence-based therapies (aspirin; clopidogrel; anticoagulation with enoxaparin, unfractionated heparin, or fondaparinux; and statins) during the first 24 hours in patients without contraindications using the "all or none" approach. Secondary end points included individual components of the primary end point; overall adherence to all eligible evidence-based therapies at admission and within 1 week of discharge among patients without contraindications (aspirin, clopidogrel, and anticoagulation during the first 24 hours; aspirin, β-blockers, statins, and angiotensin-converting enzyme inhibitors at discharge), using the same "all or none" approach; and overall composite adherence scores (defined as the sum of use of proven therapies among the patients' total number of eligible opportunities).[23] The pharmacological interventions that comprised our primary end point were all tested previously in large-scale, high-quality randomized trials and systematic reviews and are recommended by all current guidelines.[7,8,24,25] A detailed list of the end point definitions and contraindications are shown in eTable 1.

Clinical events were also considered as secondary end points, including a combined end point of total mortality, nonfatal myocardial infarction, nonfatal stroke, and nonfatal cardiac arrest at discharge; all-cause mortality at discharge and at 30 days; and major bleeding (in-hospital). An independent events committee adjudicated all outcomes based on standardized definitions.[21]

## Sample Size

We performed a prerandomization survey (January 2010-December 2010) in participating sites and found that the rates of our primary end point were in the range of 40%. More details of the survey results are provided in the eAppendix. To detect a 20% improvement in our primary composite end point with 80% power, a 2-tailed α of 5%, and an intracluster

correlation coefficient (ICC) of 0.21 (value based on a prerandomization pilot phase), we needed to randomize 34 clusters and 1020 patients (median of 30 patients with ACS per cluster).[26,27]

### Data Analysis

All analyses followed the intention-to-treat principle.[28] Because we randomized hospitals rather than patients and measured outcomes at the patient level, the analysis was adjusted for clustering of the data. Therefore, comparisons between intervention and control groups were conducted using a generalized estimating equation extension of logistic regression procedures for cluster-randomized trials. Effects were expressed as a population average odds ratio ($OR_{PA}$) in the case of qualitative variables (such as prescription rates of evidence-based medications and clinical events) or as the mean difference in the case of quantitative variables (such as composite adherence scores), with their respective 95% CIs. The $OR_{PA}$ (obtained using generalized estimating equation models) represents how the intervention affects outcomes for the combined population of all clusters instead of 1 specific cluster (as would be the case with cluster-specific odds ratios obtained using logistic random-intercept models).

We also conducted a generalized estimating equation analysis adjusted for age, sex, hospital teaching status, use of a chest pain protocol in the ED, and presence of on-site PCI facilities, because previous evidence suggests an association between these variables and quality of care delivered to patients with ACS.[29-32] Sensitivity analyses were also performed excluding statins during the first 24 hours as part of our primary end point and also from the end point adherence to all eligible evidence-based therapies at admission and at discharge. We also compared the effects of our intervention in the following subgroups: teaching vs nonteaching hospitals, hospitals with and without PCI capabilities, hospitals with and without a surgery team available 24 hours, hospitals with and without a cardiologist in the ED, hospitals with and without a chest pain protocol in the ED, and different types of ACS presentation (STEMI, NSTEMI, or unstable angina).

Statistical analyses were performed by the Research Institute HCor, São Paulo, Brazil, and validated by the Duke Clinical Research Institute, Durham, North Carolina. $P<.05$ (2-sided) was established as the level of significance for all tests. All analyses were conducted using Stata SE version 11[33] and R version 2.13.[34]

**Table 1.** Baseline Characteristics of Participating Patients and Clusters (Hospitals)

| Characteristics | No. (%) | |
|---|---|---|
| | Intervention | Control |
| **Patient baseline characteristics** | **n = 602** | **n = 548** |
| Men | 413 (68.6) | 376 (68.6) |
| Age, mean (SD), y | 62 (13) | 62 (13) |
| Diabetes | 175 (29.1) | 182 (33.2) |
| Hypertension | 433 (71.9) | 402 (73.4) |
| Dyslipidemia | 216 (35.9) | 162 (29.6) |
| Current smoking | 187 (31.1) | 147 (26.8) |
| Family history of CAD | 242 (40.2) | 242 (44.2) |
| Angina | 243 (40.4) | 177 (32.3) |
| Renal failure | 31 (5.1) | 24 (4.4) |
| Cerebrovascular disease | 53 (8.8) | 48 (8.8) |
| Previous myocardial infarction | 146 (24.3) | 121 (22.1) |
| Previous PCI | 91 (15.1) | 88 (16.1) |
| Previous CABG surgery | 57 (9.5) | 34 (6.2) |
| Use of aspirin in the last month | 197 (32.7) | 178 (32.5) |
| Final diagnosis | | |
| STEMI | 232 (38.5) | 236 (43.1) |
| NSTEMI | 230 (38.2) | 180 (32.8) |
| Unstable angina | 140 (23.3) | 132 (24.1) |
| **Cluster baseline characteristics** | **n = 17** | **n = 17** |
| Cardiologist available in ED | 12 (70.6) | 12 (70.6) |
| Cardiac surgery team available 24 h | 6 (35.3) | 7 (41.2) |
| PCI capabilities | 7 (41.2) | 7 (41.2) |
| Coronary care unit | 10 (58.8) | 9 (52.9) |
| Teaching hospital | 14 (82.4) | 13 (76.5) |
| Chest pain protocol at ED | 13 (76.5) | 11 (64.7) |
| Prior participation in multicenter clinical trial | 8 (47.1) | 7 (41.2) |
| Volume of patients seen in ED per mo, median (IQR) | 4537 (2698-13 485) | 4175 (1000-10 500) |
| No. of beds (coronary care unit), median (IQR) | 8 (7-10) | 9 (7-10) |
| Baseline rate of primary end point, %[a] | 48.4 | 46.3 |

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; ED, emergency department; IQR, interquartile range; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

[a] No statistically significant difference between clusters later randomized to intervention and control groups with respect to prescription rates of all eligible evidence-based therapies during the first 24 hours.

## RESULTS

From 54 potentially eligible clusters (hospitals) invited, 18 were excluded (5 did not meet inclusion criteria; 13 refused to participate). From the remaining 36 clusters that confirmed interest, 2 withdrew after randomization but prior to intervention because they were unable to send any research staff to attend training sessions. The 2 excluded clusters were nonteaching hospitals and were initially assigned to the intervention group. There were no differences in cluster characteristics between the 2 clusters that were excluded and the other 34 clusters. Details regarding the characteristics of the excluded clusters are shown in eTables 2 and 3. From the 34 randomized clusters that completed the study, a total of 1150 patients were enrolled prospectively and included in the primary analysis (FIGURE 1).

### Hospital and Patient Characteristics

Baseline cluster and patient characteristics were generally similar in each group (TABLE 1). From the included clusters, 41.2% had PCI capabilities available 24

hours, 79.5% were teaching hospitals, and the median volume of patients seen in the ED was about 4000 patients per month. Mean age of the patients enrolled was 62 (SD, 13) years, 68.6% were men, 23.4% had experienced a prior myocardial infarction, 72% had a history of hypertension, and 31% had diabetes. From the included patients, 40% presented with STEMI, 35.6% with NSTEMI, and 23.6% with unstable angina. The mean number of patients in each center was 34 (range, 4-55).

### Adherence to the QI Intervention and Cointerventions

In the intervention group, adherence to the reminders and checklists was 82.7%, and research coordinators were able to act as case managers in 86.7% of the included cases. At baseline and through study follow-up, cointerventions (such as use of a chest pain protocol for patients with ACS) were similar between groups ($P=.44$)

### Effects on Evidence-Based Therapies During the First 24 Hours and at Discharge

The effects of the QI intervention on prescription rates of evidence-based therapies are shown in TABLE 2. Among eligible patients (923/1150 [80.3%]), those in intervention cluster hospitals were more likely to receive all eligible acute therapies within the first 24 hours than those in control cluster hospitals (67.9% vs 49.5%; $OR_{PA}$, 2.64 [95% CI, 1.28-5.45]; ICC, 0.32; $P=.01$). These results remained consistent after adjusting for important baseline covariates (adjusted $OR_{PA}$, 3.97 [95% CI, 1.52-10.37]; ICC, 0.32; $P=.01$) and after excluding statins during the first 24 hours as part of our primary outcome ($OR_{PA}$, 2.63 [95% CI, 1.27-5.42]).

Similarly, use of all evidence-based therapies during the first 24 hours and at discharge among eligible patients (801/1150 [69.7%]) was higher in the intervention clusters vs controls (50.9% vs 31.9%; $OR_{PA}$, 2.49 [95% CI, 1.08-5.74]; ICC, 0.36; $P=.03$). Overall composite adherence scores were also higher in QI intervention clusters than in control group clusters (89% vs 81.4%; $P=.01$) (Table 2).

### Effects on Clinical Events

TABLE 3 shows the effects of our intervention on major clinical events at discharge. The rates of major cardiovascular events were 5.5% for patients from clusters randomized to the QI intervention and 7.0% in control group clusters, without a statistically significant difference ($OR_{PA}$, 0.72 [95% CI, 0.36-1.43]; ICC, 0.15; $P=.35$). Total mortality rates at 30 days were 7.0% in patients from clusters randomized to the QI intervention and 8.4% in patients from control group clusters ($OR_{PA}$, 0.79 [95% CI, 0.46-1.34]; ICC, 0.01; $P=.38$). We observed lower rates of new myocardial infarction ($P=.09$) and higher incidence of major bleeding in the intervention group as compared with the control group ($P=.06$), but these differences did not reach statistical significance. Over the course of the study, 194 patients (32.2%) in the intervention group and 156 patients (28.5%) in the control group underwent PCI (corresponding data for CABG surgery not available).

### Subgroup Analysis

The subgroup analysis is shown in FIGURE 2. The effect of our QI intervention in 100% evidence-based acute therapies was greater in hospitals with PCI capabilities ($OR_{PA}$, 7.97 [95% CI, 3.11-20.42]; $P<.001$ [$P=.004$ for interaction]) and in patients whose final diagnosis was NSTEMI or unstable angina ($OR_{PA}$, 3.47 [95% CI, 1.56-7.71]; $P=.001$ [$P<.001$ for interaction]).

**Table 2.** Results of the Quality Improvement Intervention on Adoption of Evidence-Based Therapies in Eligible Patients

| Therapy/End Point | No./Total (%) Intervention | No./Total (%) Control | $OR_{PA}$ (95% CI) | *P* Value | ICC |
|---|---|---|---|---|---|
| Acute medications during first 24 h | | | | | |
| Aspirin | 584/599 (97.5) | 520/543 (95.8) | 1.73 (0.84-3.56) | .14 | 0.01 |
| Clopidogrel | 534/592 (90.2) | 410/539 (76.1) | 2.16 (0.77-6.01) | .14 | 0.41 |
| Aspirin + clopidogrel | 525/590 (89.0) | 403/539 (74.8) | 2.12 (0.88-5.10) | .09 | 0.33 |
| Any anticoagulation[a] | 509/587 (86.7) | 433/535 (80.9) | 1.34 (0.72-2.49) | .36 | 0.13 |
| LMWH or fondaparinux | 444/522 (85.1) | 316/418 (75.6) | 1.87 (0.97-3.59) | .06 | 0.30 |
| Unfractionated heparin | 112/190 (58.9) | 138/239 (57.7) | 0.83 (0.31-2.22) | .71 | 0.35 |
| Statins | 492/592 (83.1) | 395/542 (72.9) | 2.52 (1.15-5.56) | .02 | 0.34 |
| Discharge medications | | | | | |
| Aspirin | 556/576 (96.5) | 493/531 (92.8) | 2.08 (0.83-5.24) | .12 | 0.05 |
| Clopidogrel | 450/536 (84.0) | 365/520 (70.2) | 1.51 (0.60-3.77) | .38 | 0.39 |
| β-Blockers | 451/525 (85.9) | 425/520 (81.7) | 1.35 (0.64-2.81) | .43 | 0.16 |
| ACE inhibitors | 415/509 (81.5) | 383/503 (76.1) | 1.21 (0.58-2.51) | .61 | 0.24 |
| Statins | 508/577 (88.0) | 461/536 (86.0) | 1.87 (0.81-4.30) | .14 | 0.33 |
| Concomitant use of aspirin, β-blockers, ACE inhibitors, and statins | 309/469 (65.9) | 276/488 (56.6) | 1.55 (0.75-3.18) | .23 | 0.30 |
| End points | | | | | |
| Primary (complete adherence to all acute evidence-based therapies)[b] | 344/507 (67.9) | 206/416 (49.5) | 2.64 (1.28-5.45) | .01 | 0.32 |
| Secondary (complete adherence to all acute and discharge therapies)[c] | 205/403 (50.9) | 127/398 (31.9) | 2.49 (1.08-5.74) | .03 | 0.36 |
| Composite adherence score, mean (SD), %[d] | 89.0 (15.9)[e] | 81.4 (18.0)[f] | 8.6 (2.2-15.0)[g] | .01 | 0.38 |

Abbreviations: ACE, angiotensin-converting enzyme; ICC, intracluster correlation coefficient; LMWH, low-molecular-weight heparin; $OR_{PA}$, population average odds ratio.

[a] Low-molecular-weight heparin, fondaparinux, or unfractionated heparin.

[b] Number of patients who received all acute evidence-based medications (aspirin + anticoagulation + clopidogrel + statins during first 24 hours) divided by the total number of patients without contraindications to receiving these medications.

[c] Number of patients who received all acute and discharge evidence-based medications (aspirin + anticoagulation + clopidogrel + statins + β-blockers + ACE inhibitors) divided by the total number of patients without contraindications to receiving these medications.

[d] Composite adherence score was defined as the sum of use of proven therapies among the patients' total number of eligible opportunities.

[e] n=602.

[f] n=548.

[g] Effect estimate presented as mean difference (95% CI), obtained using generalized estimating equations with identity link function and gaussian distribution.

## COMMENT

In this cluster-randomized trial, a multifaceted QI intervention including reminders, checklists, case management, and educational materials was effective in improving quality of ACS care in public hospitals. Our intervention increased the uptake of evidence-based therapies during the first 24 hours, mainly driven by increased prescription rates of antithrombotic therapies and statins. These results were consistent among different subgroups but with greater effect in hospitals with PCI capabilities and in patients presenting with non–ST-segment elevation ACS. Overall quality of care as assessed by composite adherence to evidence-based treatments at admission and discharge was also superior in the intervention vs the control group. However, the study was not powered for the evaluation of clinical outcomes, and the low number of events and the wide confidence intervals around point estimates make the interpretation of our clinical end point results inconclusive.

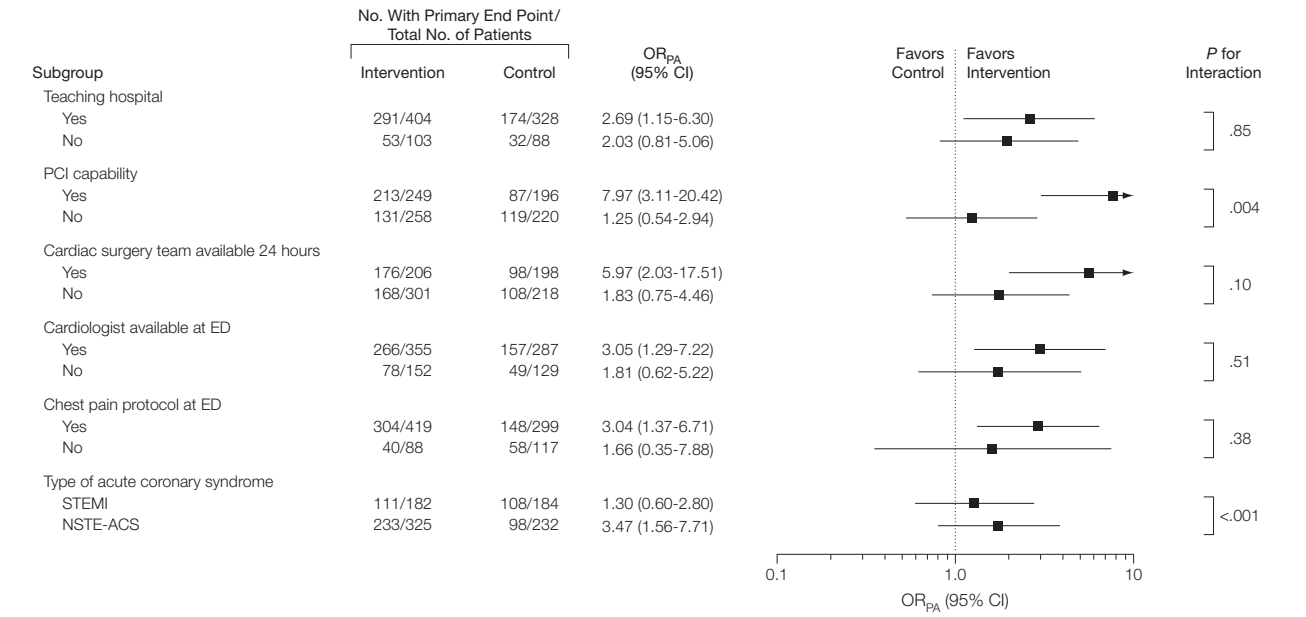
To our knowledge, this is the first cluster-randomized trial testing a QI intervention in ACS to be conducted in a middle-income country. It provides useful information because more than 80% of the global burden of cardiovascular diseases occurs in low- and middle-income countries.[19,20] Although the background rate of approximately 40% adherence is lower than what is reported in the European and North American literature (CRUSADE [Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines][23]; GRACE [Global Registry of Acute Coronary Events][9]), it is not lower than that observed for several

**Table 3.** Results of the Quality Improvement Intervention on Major Cardiovascular Events, In Hospital and at 30 Days[a]

| | No. (%) | | | | |
|---|---|---|---|---|---|
| | Intervention (n = 602) | Control (n = 548) | $OR_{PA}$ (95% CI) | *P* Value | ICC |
| Events (in hospital) | | | | | |
| New myocardial infarction | 4 (0.7) | 14 (2.6) | 0.25 (0.05-1.26) | .09 | 0.60 |
| Cardiac arrest | 26 (4.3) | 22 (4.0) | 0.96 (0.42-2.21) | .93 | 0.06 |
| Major bleeding | 7 (1.2) | 1 (0.2) | 6.88 (0.93-51.10) | .06 | <0.01 |
| Stroke | 2 (0.3) | 4 (0.7) | 0.45 (0.08-2.50) | .36 | <0.01 |
| Total mortality | 29 (4.8) | 28 (5.1) | 0.82 (0.37-1.82) | .62 | 0.05 |
| Cardiovascular mortality | 26 (4.3) | 23 (4.2) | 0.91 (0.42-1.96) | .81 | 0.05 |
| Major cardiovascular events[b] | 33 (5.5) | 38 (7.0) | 0.72 (0.36-1.43) | .35 | 0.15 |
| Events (within 30 d)[c] | | | | | |
| Total mortality | 42 (7.0) | 46 (8.4) | 0.79 (0.46-1.34) | .38 | 0.01 |
| Cardiovascular mortality | 40 (6.6) | 39 (7.1) | 0.87 (0.48-1.57) | .64 | 0.02 |
| Major cardiovascular events[b] | 49 (8.1) | 55 (10.1) | 0.76 (0.45-1.27) | .30 | 0.05 |

Abbreviations: ICC, intracluster correlation coefficient; $OR_{PA}$, population average odds ratio.
[a] Over the course of the study, 194 patients (32.2%) in the intervention group and 156 patients (28.5%) in the control group underwent percutaneous coronary intervention (corresponding data for coronary artery bypass graft surgery not available).
[b] New nonfatal myocardial infarction, nonfatal cardiac arrest, nonfatal stroke, or total mortality.
[c] n=547 for control group.

**Figure 2.** Primary End Point According to Prespecified Subgroups




The primary end point comprised adherence to all eveidence-based therapies during the first 24 hours in patients without contraindications. ACS indicates acute coronary syndrome; ED, emergency department; NSTE-ACS, non–ST-segment elevation ACS; $OR_{PA}$, population average odds ratio; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

low- and middle-income countries.[13] Moreover, prescription rates for individual medications are consistent with rates observed from the lowest quartile in North American hospitals.[23] Thus, if patient care can be improved when adoption rates are more in the "middle range," then our results are relevant to rest of world and to the United States for diseases other than ACS, for which evidence-based medicine uptake is much less common.

We focused on improving the quality of care for patients admitted to public hospitals rather than cardiology institutes and private hospitals. In Brazil, as is the case in several low- and middle-income countries, public hospitals admit the majority of patients with ACS and have fewer resources for implementing QI initiatives.[14] Furthermore, public hospitals face additional barriers to implementing evidence-based care, such as overcrowding, heavier individual clinical workloads, and fewer personnel devoted to continuing education activities. Our results suggest that QI interventions may be feasible and effective in these settings, especially using interventions such as the one used in our study, which is simple and does not rely on expensive information technology or on complex human interventions.[35]

Our findings are in accordance with before-and-after studies, in which centers serve as both the control (before) and treated (after) groups. These studies have evaluated the effects of QI in the setting of ACS in the United States and changes on the order of 15%, which is consistent with our findings. These reports may be prone to limitations such as secular trends or sudden changes in recommended therapies, making it difficult to attribute observed changes to the intervention.[13] Furthermore, in such studies, the intervention may be confounded by the Hawthorne effect, which could lead to an overestimate of the effectiveness of an intervention. A cluster-randomized trial design diminishes the likelihood of such systematic errors.[39,40]

Previous cluster-randomized studies in the setting of ACS using different QI tools have had mixed results. The AFFECT (Administrative Data Feedback for Effective Cardiac Treatment) trial[41] randomized clusters to receive rapid or delayed feedback on quality performance and did not show changes in the prescription rates of evidence-based medications. The difference in results between AFFECT and BRIDGE-ACS may in part be explained by the fact our trial used an intervention composed of multiple QI tools rather than a single tool, as in the AFFECT trial. Systematic reviews have suggested that multifaceted QI interventions are superior to single interventions in changing behavior.[42] The PROMIS-UK (Prospective Registry of Outcomes and Management in Ischaemic Syndromes–UK) trial[43] randomized 38 clusters in the United Kingdom to receive an education program based on European Society of Cardiology guidelines or control. The primary end point was the use of aspirin, clopidogrel, β-blockers, and statins at discharge and heparin in-hospital. There was a 3.6% to 8.0% absolute increase in all of the evidence-based treatments.

In the recently published EQUIP-ACS (European Quality Improvement Programme for Acute Coronary Syndrome) trial,[44,45] 38 clusters from 5 European countries were randomly allocated to receive standard care or a QI program involving not only guideline-driven objectives but also a review of procedures used by centers to manage patient care. Similar to the results observed in the BRIDGE-ACS trial, the QI intervention in EQUIP-ACS improved a composite outcome of quality indicators. BRIDGE-ACS adds complementary information to EQUIP-ACS, because we included patients with STEMI (who were excluded from the earlier trial), measured the effect of our QI intervention on various clinical end points (which were not reported in the earlier trial), and evaluated the intervention in hospitals with a broad range of characteristics and resources levels (contrary to the EQUIP-ACS trial, which was restricted to cardiology sites).

Our trial had several strengths. We used hospitals as the unit of randomization, which reduced the possibility of contamination. We prevented bias by using concealed allocation, blinding adjudication of outcomes, and avoiding different consent refusal rates between clusters.[40] We analyzed data according to the intention-to-treat principle and took the cluster trial design into account. Our data were collected by trained independent research coordinators at each site, minimizing the risk of selective reporting of outcomes. Independent data collection was complemented by central adjudication of eligibility criteria and outcomes. We tested a multifaceted intervention targeted at identified barriers, because this approach is more likely to be effective for implementing guidelines than a single intervention. Adherence to most of our tools was more than 80%, and cointerventions were similar between groups. Our results were consistent in a broad range of public hospitals with different characteristics.

Our trial had several limitations that merit consideration. First, our results may not be applicable to private hospitals, cardiology centers, and institutions that already have very high levels of adherence to evidence-based therapies. Whether our findings are generalizable to higher-resource settings remains to be tested and cannot be inferred directly from our data. Nevertheless, our intervention was designed to be simple, making it theoretically feasible in settings with different levels of resources. Second, our intervention was delivered over 8 months, and this may be too short to detect changes in practice and in clinical end points.

Third, we focused on evidence-based medications; however, QI in the setting of ACS involves other indicators such as adequate risk stratification, evaluation of ventricular function, smoking cessation counseling, referral for cardiac rehabilitation, and adequacy of dose of antithrombotic therapies. Fourth, 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. On the other hand, because patient baseline characteristics were similar between groups, important selection bias is unlikely.

Fifth, our study is underpowered to detect meaningful differences in clinical outcomes. Yet because most patients with ACS receive a multitude of treatments, composite end points of evidence-based therapies are relevant,[46] and previous studies have demonstrated an independent association between improvement in the combined uptake of proven therapies and beneficial effects on clinical end points, supporting the use of broad, guideline-based performance metrics as a means of assessing hospital quality.[23,47] However, despite the observed numerically lower (but nonsignificant) rates of myocardial infarction in the intervention group, one potential downside was an increase in rates of in-hospital major bleeding. Sixth, cluster randomized trials are prone to additional limitations, such as lesser statistical power and the variation within or between clusters, when compared with trials with randomization at the individual level. Nevertheless, clustering was taken into account in all reported analyses using appropriate methods.

In conclusion, among patients with ACS, a simple multifaceted educational intervention resulted in significant improvement in the use of evidence-based medications, particularly in hospitals with PCI capabilities and among patients with non–ST-segment elevation ACS. Because this intervention is relatively simple and feasible, the approaches tested in the BRIDGE-ACS trial can become the basis for developing QI programs to maximize the use of evidence-based interventions for the management of ACS, especially in limited-resource settings. Large-scale international cluster-randomized trials with adequate power are warranted to assess the effect of QI interventions on clinical outcomes as well as on cost-effectiveness.

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**Online-Only Material:** The eAppendix and eTables 1-3 are available at http://www.jama.com.

## REFERENCES


**1.** Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases, I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation*. 2001;104 (22):2746-2753.

**2.** Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases, II: variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. *Circulation*. 2001;104(23):2855-2864.

**3.** Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. *Lancet*. 1994;343(8893):311-322.

**4.** Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet*. 2003;361(9351):13-20.

**5.** Freemantle N, Cleland J, Young P, Mason J, Harrison J. beta Blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ*. 1999; 318(7200):1730-1737.

**6.** Chen ZM, Jiang LX, Chen YP, et al; COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366(9497):1607-1621.

**7.** Wenger NK. 2011 ACCF/AHA focused update of the guidelines for the management of patients with Unstable Angina/Non–ST-Elevation Myocardial Infarction (updating the 2007 Guideline): highlights for the clinician. *Clin Cardiol*. 2012;35(1):3-8.

**8.** Kushner FG, Hand M, Smith SC Jr, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines [published correction appears in *J Am Coll Cardiol*. 2010;55(6):612]. *J Am Coll Cardiol*. 2009;54(23): 2205-2241.

**9.** Fox KA, Goodman SG, Klein W, et al. Management of acute coronary syndromes: variations in practice and outcome: findings from the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J*. 2002; 23(15):1177-1189.

**10.** Hoekstra JW, Pollack CV Jr, Roe MT, et al. Improving the care of patients with non–ST-elevation acute coronary syndromes in the emergency department: the CRUSADE initiative. *Acad Emerg Med*. 2002; 9(11):1146-1155.

**11.** Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? a framework for improvement. *JAMA*. 1999;282(15):1458-1465.

**12.** Budaj A, Brieger D, Steg PG, et al; GRACE Investigators. Global patterns of use of antithrombotic and antiplatelet therapies in patients with acute coronary syndromes: insights from the Global Registry of Acute Coronary Events (GRACE). *Am Heart J*. 2003;146(6):999-1006.

**13.** 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.

**14.** Mattos LA. Rationality and methods of ACCEPT registry—Brazilian registry of clinical practice in acute coronary syndromes of the Brazilian Society of Cardiology. *Arq Bras Cardiol*. 2011;97(2):94-99.

**15.** How we classify countries. World Bank website. http://data.worldbank.org/about/country-classifications. Accessed February 25, 2012.

**16.** Bonetti D, Eccles M, Johnston M, et al. Guiding the design and selection of interventions to influence the implementation of evidence-based practice: an experimental simulation of a complex intervention trial. *Soc Sci Med*. 2005;60(9):2135-2147.

**17.** 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.

**18.** 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.

**19.** Strong K, Mathers C, Leeder S, Beaglehole R. Preventing chronic diseases: how many lives can we save? *Lancet*. 2005;366(9496):1578-1582.

**20.** Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet*. 1997;349(9063): 1436-1442.

**21.** Berwanger O, Guimarães HP, Laranjeira LN, et al. A multifaceted intervention to narrow the evidence-based gap in the treatment of acute coronary syndromes: rationale and design of the BRIDGE-ACS cluster-randomized trial. *Am Heart J*. 2012;163(3): 323-329.

**22.** Buyse M, George SL, Evans S, et al. The role of biostatistics in the prevention, detection and treatment of fraud in clinical trials. *Stat Med*. 1999; 18(24):3435-3451.

**23.** Peterson ED, Roe MT, Mulgund J, et al. Association between hospital process performance and outcomes among patients with acute coronary syndromes. *JAMA*. 2006;295(16):1912-1920.

**24.** Patti G, Cannon CP, Murphy SA, et al. Clinical benefit of statin pretreatment in patients undergoing percutaneous coronary intervention: a collaborative patient-level meta-analysis of 13 randomized studies. *Circulation*. 2011;123(15):1622-1632.

**25.** Cannon CP, Braunwald E, McCabe CH, et al; Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350(15):1495-1504.

**26.** Hayes RL, Moulton LH. *Cluster Randomised Trials*. Boca Raton, FL: Chapman & Hall/CRC; 2009.

**27.** Kerry SM, Bland JM. Sample size in cluster randomisation. *BMJ*. 1998;316(7130):549.

**28.** Campbell MJ, Donner A, Klar N. Developments in cluster randomized trials and *Statistics in Medicine*. *Stat Med*. 2007;26(1):2-19.

**29.** Patel MR, Chen AY, Roe MT, et al. A comparison of acute coronary syndrome care at academic and nonacademic hospitals. *Am J Med*. 2007;120(1): 40-46.

**30.** Halabi AR, Eisenberg MJ, Richard H, et al. Impact of on-site cardiac catheterization on cardiac procedure use and quality of life after acute myocardial infarction. *Can J Cardiol*. 2001;17(suppl C):152C.

**31.** Ayanian JZ, Hauptman PJ, Guadagnoli E, Antman EM, Pashos CL, McNeil BJ. Knowledge and practices of generalist and specialist physicians regarding drug therapy for acute myocardial infarction. *N Engl J Med*. 1994;331(17):1136-1142.

**32.** Allison JJ, Kiefe CI, Weissman NW, et al. Relationship of hospital teaching status with quality of care and mortality for Medicare patients with acute MI. *JAMA*. 2000;284(10):1256-1262.

**33.** Kreuter F, Valliant R. A survey on survey statistics: what is done and can be done in Stata. *Stata J*. 2011;7(suppl 1):1-21.

**34.** R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2008.

**35.** Schmidt MI, Duncan BB, Azevedo e Silva G, et al. Chronic non-communicable diseases in Brazil: burden and current challenges. *Lancet*. 2011;377(9781): 1949-1961.

**36.** Mehta RH, Montoye CK, Gallogly M, et al; GAP Steering Committee of the American College of Cardiology. Improving quality of care for acute myocardial infarction: the Guidelines Applied in Practice (GAP) Initiative. *JAMA*. 2002;287(10):1269-1276.

**37.** Fonarow GC, Gawlinski A, Moughrabi S, Tillisch JH. Improved treatment of coronary heart disease by implementation of a Cardiac Hospitalization Atherosclerosis Management Program (CHAMP). *Am J Cardiol*. 2001;87(7):819-822.

**38.** Carlhed R, Bojestig M, Wallentin L, et al; QUICC Study Group. Improved adherence to Swedish national guidelines for acute myocardial infarction: the Quality Improvement in Coronary Care (QUICC) study. *Am Heart J*. 2006;152(6):1175-1181.

**39.** Grimshaw J, Campbell M, Eccles M, Steen N. Experimental and quasi-experimental designs for evaluating guideline implementation strategies. *Fam Pract*. 2000;17(suppl 1):S11-S16.

**40.** Puffer S, Torgerson D, Watson J. Evidence for risk of bias in cluster randomised trials: review of recent trials published in three general medical journals. *BMJ*. 2003;327(7418):785-789.

**41.** Beck CA, Richard H, Tu JV, Pilote L. Administrative Data Feedback for Effective Cardiac Treatment: AFFECT, a cluster randomized trial. *JAMA*. 2005; 294(3):309-317.

**42.** Grimshaw J, Eccles M, Campbell M, Elbourne D. Cluster randomized trials of professional and organizational behavior change interventions in health care settings. *Ann Am Acad Pol Soc Sci*. 2005;599(1): 71-93.

**43.** Flather M, Booth J. Prospective registry of outcomes and management in ischaemic syndromes. Presented at: World Congress of Cardiology; September 2-6, 2006; Barcelona, Spain.

**44.** Flather MD, Booth J, Babalis D, et al. Improving the management of non–ST elevation acute coronary syndromes: systematic evaluation of a quality improvement programme European QUality Improvement Programme for Acute Coronary Syndrome: the EQUIP-ACS project protocol and design. *Trials*. 2010; 11:5.

**45.** Flather MD, Babalis D, Booth J, et al. Cluster-randomized trial to evaluate the effects of a quality improvement program on management of non–ST-elevation acute coronary syndromes: the European Quality Improvement Programme for Acute Coronary Syndromes (EQUIP-ACS). *Am Heart J*. 2011; 162(4):700-707, e1.

**46.** Eapen ZJ, Fonarow GC, Dai D, et al; Get With The Guidelines Steering Committee and Hospitals. Comparison of composite measure methodologies for rewarding quality of care: an analysis from the American Heart Association's Get With The Guidelines program. *Circ Cardiovasc Qual Outcomes*. 2011; 4(6):610-618.

**47.** Polanczyk CA, Biolo A, Imhof BV, et al. Improvement in clinical outcomes in acute coronary syndromes after the implementation of a critical pathway. *Crit Pathw Cardiol*. 2003;2(4):222-230.