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Effect of a Quality of Care Improvement Initiative in Patients With Acute Coronary Syndrome in Resource-Constrained Hospitals in China
A Randomized Clinical Trial

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IMPORTANCE Prior observational studies suggest that quality of care improvement (QCI) initiatives can improve the clinical outcomes of acute coronary syndrome (ACS). To our knowledge, this has never been demonstrated in a well-powered randomized clinical trial.

OBJECTIVE To determine whether a clinical pathway–based, multifaceted QCI intervention could improve clinical outcomes among patients with ACS in resource-constrained hospitals in China.

DESIGN, SETTING, PARTICIPANTS This large, stepped-wedge cluster randomized clinical trial was conducted in nonpercutaneous coronary intervention hospitals across China and included all patients older than 18 years and with a final diagnosis of ACS who were recruited consecutively between October 2011 and December 2014. We excluded patients who died before or within 10 minutes of hospital arrival. We recruited 5768 and 0 eligible patients for the control and intervention groups, respectively, in step 1, 4326 and 1365 in step 2, 3278 and 3059 in step 3, 1419 and 4468 in step 4, and 0 and 5645 in step 5.

INTERVENTIONS The intervention included establishing a QCI team, training clinical staff, implementing ACS clinical pathways, sequential site performance assessment and feedback, online technical support, and patient education. The usual care was the control that was compared.

MAIN OUTCOMES AND MEASURES The primary outcome was the incidence of in-hospital major adverse cardiovascular events (MACE), comprising all-cause mortality, reinfarction/myocardial infarction, and nonfatal stroke. Secondary outcomes included 16 key performance indicators (KPIs) and the composite score developed from these KPIs.

RESULTS Of 29 346 patients (17 639 men [61%]; mean [SD] age for control, 64.1 [11.6] years; mean [SD] age for intervention, 63.9 [11.7] years) who were recruited from 101 hospitals, 14 809 (50.5%) were in the control period and 14 537 (49.5%) were in the intervention period. There was no significant difference in the incidence of in-hospital MACE between the intervention and control periods after adjusting for cluster and time effects (3.9% vs 4.4%; odds ratio, 0.93; 95% CI, 0.75-1.15; $P = .52$). The intervention showed a significant improvement in the composite KPI score (mean [SD], 0.69 [0.22] vs 0.61 [0.23]; $P < .01$) and in 7 individual KPIs, including the early use of antiplatelet therapy and the use of appropriate secondary prevention medicines at discharge. No unexpected adverse events were reported.

CONCLUSIONS AND RELEVANCE Among resource-constrained Chinese hospitals, introducing a multifaceted QCI intervention had no significant effect on in-hospital MACE, although it improved a few of the care process indicators of evidence-based ACS management.

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Supplemental content

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Cardiovascular disease accounts for almost a third of all deaths worldwide and is the leading cause of death in China.[1,2] Compared with the previous decade, China is predicted to experience a 69% increase in the incidence of acute coronary disease between 2010 and 2019, amounting to nearly 8 million additional episodes of myocardial infarction (MI) or unstable angina pectoris.[3] Given that more than two-thirds of cardiovascular events will occur in adults younger than 65 years,[2,3] this rapidly escalating burden of acute coronary syndromes (ACS) will have profound economic and social implications for China.[4,5]

Despite the widespread promulgation and endorsement of ACS treatment guidelines[6,7] and the strong evidence base underpinning many guideline recommendations,[8-10] their translation into clinical practice remains suboptimal, globally. This is particularly true for low-income and middle-income countries[11-14] and for nontertiary hospitals where financial, technical, and staff resources are more limited.[13,14] In China, nontertiary regional hospitals account for 40% of all hospitals in the country and provide first-line care for 900 million patients annually.[15]

Many strategies have been proposed to narrow evidence practice gaps in ACS care, including clinical pathways and patient education, as well as data audits and feedback.[11,16-19] Among these, clinical pathways have been studied most extensively, with good evidence to associate pathway use with a reduction in in-hospital complications.[20] Consequently, clinical pathways have been incorporated into routine practice in many high-income countries and are also highly promoted in low-income and middle-income countries.[20,21] However, this practice is largely supported by effects on surrogate process outcomes[11,22]; these effects on clinical outcomes have been largely derived from observational studies.[10] To our knowledge, the effects of such programs on clinical events, such as cardiovascular death, reinfarction, or other diseases or complications, have not previously been studied in a randomized clinical trial and thus remain uncertain.

Since 2009, the Chinese government has initiated a new round of health care reforms.[23] One objective is to strengthen the health care system, which regards nontertiary county hospitals as regional centers.[23,24] As an official implementation research project of the National Health Commission (former Ministry of Health), the third phase of the Clinical Pathways for Acute Coronary Syndromes in China (CPACS-3) was initiated to evaluate a clinical pathway–based, multifaceted quality of care improvement intervention aimed at improving clinical outcomes among patients with ACS in resource-constrained hospitals.

Key Points

Question What is the effect of a multifaceted quality of care improvement initiative for acute coronary syndrome (ACS) on major adverse cardiovascular events in low-resource hospitals in China?

Findings In this stepped-wedge cluster randomized clinical trial that included 101 hospitals and 29 346 patients with ACS, the in-hospital rates of major adverse cardiovascular events were 4.4% in the control phase and 3.9% in the intervention phase; the difference was not statistically significant after adjusting for cluster and temporal trends.

Meaning Among patients with ACS in low-resource hospitals in China, a multifaceted quality of care initiative did not reduce the in-hospital major adverse cardiovascular events compared with usual care.

Methods

Study Design

The study design has been previously published.[25] Briefly, CPACS-3 was a stepped-wedge cluster randomized clinical trial among resource-constrained hospitals in China (**Figure 1**). The primary objective was to determine whether routinely using a clinical pathway–based, multifaceted quality of care initiative (QCI) led to a measurable reduction in the number of in-hospital major adverse cardiovascular events (MACE) in patients with ACS presenting to resource-limited hospitals in China. The secondary objectives were to determine: (1) whether the QCI would improve the quality of care and (2) any major facilitators and barriers to the implementation and uptake of the interventions in these settings. To be eligible, hospitals had to be nontertiary centers with (1) more than 90 minutes taken to transfer a patient with ACS to the nearest large tertiary hospital with a cardiac catheterization laboratory, (2) no plans to develop the capacity for onsite percutaneous coronary intervention (PCI) within the next 4 years, (3) more than 40 patients with ACS hospitalized every 6 months, and (4) no participation in another hospital QCI. Patients with ACS in eligible hospitals that agreed to participate were consecutively enrolled in 5 6-month steps (ie, cycles). No intervention was applied in the first cycle in all participating hospitals. Study hospitals were randomly allocated to 4 wedges. Each wedge commenced the intervention in one of the 4 remaining cycles. All hospitals were on the intervention in the last cycle. The intervention was applied at the hospital level, with outcomes measured at the patient level. A stepped-wedge design was chosen mainly because it was anticipated that the study would be beneficial and receipt of the intervention was the strong preference of all participating hospitals and the government officials in charge of the project. The Peking University institutional review board reviewed and approved the study and all participating patients provided written informed consent. The trial protocol and statistical analysis plan are available in Supplement 1-3.

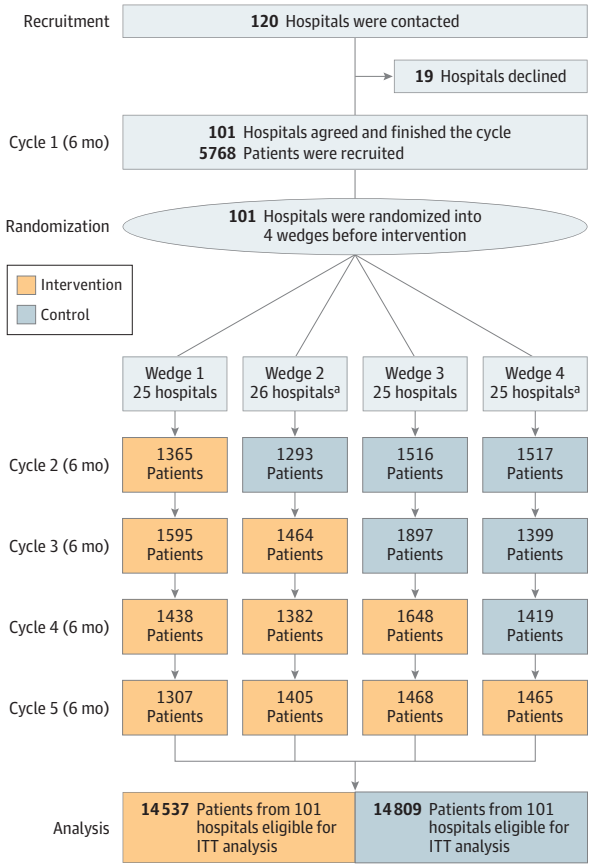
Patients

All patients older than 18 years with a final diagnosis of ACS at discharge or death were recruited consecutively in 2 batches of hospitals. The first batch included 76 hospitals and recruited study patients from October 9, 2011, to May 31, 2014, and the second batch included 25 hospitals recruiting patients between June 1, 2012, and December 29, 2014. We excluded patients who died before or within 10 minutes of hospital arrival.

Randomization

The randomization was done centrally among all 101 hospitals, with stratification by province, before initiating the in-

Figure 1. Study Flow Chart



ITT indicates intention to treat.

[a] One hospital from wedge 2 and 1 hospital from wedge 4 dropped out in cycle 2.

tervention in the first-wedge hospitals in the first batch. The allocation codes were concealed by the statistician separately and would be given to the project manager who was in charge of the initiation of the intervention when it began. Because the second batch of hospitals started roughly 6 months after the first batch of hospitals, the intervention in these hospitals also initiated 6 months later in each wedge.

Data Collection

A trained hospital staff member who was not involved in treating patients with ACS was responsible for collecting and entering data into a dedicated web-based data management system. Data for each patient were collected from medical records and from survivors before hospital discharge. The data included sociodemographic information; symptoms and signs relating to the presenting ACS; medical history; electrocardiographic results; biomarker findings; investigations performed; treatments administered before admission, during hospitalization, and at death or hospital discharge; final diagnosis and discharge status; major in-hospital clinical events; personal insurance status; and the total cost of hospitalization. Data quality was maintained through in-person and online study monitoring activities.

Intervention

The intervention was a multifaceted QCI comprising 6 components: the establishment of a QCI team, chaired by the hospital director and including the department chiefs for emergency, general medicine/cardiology, and the medical services administration; implementation of clinical pathways for managing different subtypes of ACS that were developed in CPACS-2 and tailored to fit the hospital when necessary[26]; regular reports provided every 6 months on key performance indicators (KPIs) that used information collected through the study data management system through which hospitals could self-assess their peer-ranked clinical performance; technical training and a compulsory test for medical staff engaged in ACS care; a web-based online technical support to get advice from senior cardiologists; and patient educational materials on ACS clinical manifestation, treatment, secondary prevention, and lifestyle modification.

The fidelity of the study intervention components was monitored at each site by the clinical associates from the study coordinating center at the George Institute for Global Health at Peking University Health Science Center in Beijing, China, at the beginning, middle, and end of the study. The participating and passing rates of the technical training for participating physicians and nurses were obtained from the background records from the online system for training.

Outcomes

The primary outcome of the study was in-hospital MACE, defined as all-cause mortality, MI, or recurrent MI and nonfatal stroke. We chose all-cause mortality rather than cardiac death because our definition of in-hospital all-cause mortality not only included patients who died in the hospital but also those who were discharged against medical advice and died within 1 week and those who transferred to upper-level hospitals but died within 24 hours. For the 2 latter cases, we were not able to collect reliable data to confirm cause of death. Recurrent MI during hospitalization was classified as an event during which a hospitalized patient with MI demonstrated a rise of the cardiac biomarker (troponin or creatine kinase myocardial band) at least once above the 99th percentile reference limit or the value increased more than 20% compared with the former measurement and with at least 1 of the following 3 criteria: new symptoms of ischemia, new significant ST-T wave changes, and imaging evidence of new regional wall motion abnormality. All primary outcome events were adjudicated by an independent committee masked to the hospital's randomization status.

Secondary outcomes were a patient-level composite score of the KPIs and each of the individual 16 KPIs of ACS care (the definitions of KPIs are provided in eTable 1 in Supplement 4). The patient-level KPI composite score was calculated by allocating a score of 1 for each of the binary KPIs achieved, adding these, and dividing by the number of KPIs relevant to that individual. Accordingly, length of hospital stay was the only KPI not used for the calculation of the composite score. Because of the changes in clinical guidelines and also in our study intervention, we added 3 new KPIs after the trial initiation: the percentage of patients receiving dual antiplatelet therapy, loading dose dual antiplatelet therapy, and intensive statin therapy. This change was made be-

fore the statistical analysis plan was finalized and the database locked but after the study protocol was published.[25]

Sample Size

Assuming a primary outcome event rate of 8% and a 2-sided 5% significance test, 96 hospitals and 40 patients per 6-month cycle from each hospital would provide 98% and 85% power to detect relative risk reductions of 20% and 15%, respectively. The control period event rate was based on that observed in the published CPACS study among nontertiary hospitals.[13] The sample size calculations also assumed that there was no delay in the effects of the intervention and that the intraclass correlation coefficient was 0.10. To account for dropout, we aimed to recruit from 104 hospitals.[25]

Data Analysis

The primary analysis was performed according to the intention-to-treat principle. All analyses on outcomes were at the individual level but accounted for the clustering of patients at the hospital level. Comparisons of baseline characteristics between intervention and control participants were conducted using the *t* test and χ^2 test.

There were a few variables, such as education, health insurance, and smoking status, that had missing data. We disclosed number of patients with missing data in **Table 1** and **Table 2** but calculated the proportions for each classification without including patients with missing data. In the multivariable analyses, we treated these variables as categorical and the patients with missing data as a separate subgroup of patients.

To analyze intervention effects, generalized estimating equation models were used to account for the clustering within hospitals.[27] The primary model included a fixed effect for time and a binary variable for the effect of the intervention. Within-cluster correlations were modeled using generalized estimating equations with an exchangeable working correlation structure. Sensitivity analyses included a model without the effect of time

Table 1. Characteristics of CPACS-3 Study Participants by Randomized Allocation

Characteristic	No. (%)		Difference (95% CI)[a]	*P* Value
	Control (n = 14 809)	Intervention (n = 14 537)		
Age, mean (SD), y	64.1 (11.64)	63.9 (11.72)	−0.2 (−0.4 to 0.1)	.28
Male	8888 (60.0)	8751 (60.2)	0.2 (−0.9 to 1.3)	.75
Education[b]				
Illiteracy	3479 (30.6)	3132 (27.6)	−3.0 (−5.2 to −0.8)	<.001
Primary	3426 (30.1)	3760 (33.1)	3.0 (0.9 to 5.2)	
Secondary	2656 (23.3)	2842 (25.0)	1.7 (−0.6 to 4.0)	
High school and above	1815 (16.0)	1616 (14.2)	−1.7 (−4.1 to 0.7)	
Farmer[b]	9062 (64.3)	8816 (66.1)	1.9 (0.7 to 3.0)	.001
Health insurance[b]	10 892 (94.8)	9817 (95.5)	0.6 (0.1 to 1.2)	.03
Diagnosis				
STEMI	5383 (36.3)	4911 (33.8)	−2.6 (−3.7 to −1.5)	<.001
NSTEMI	2191 (14.8)	2512 (17.3)	2.5 (1.7 to 3.3)	
UAP	7235 (48.9)	7114 (48.9)	0.1 (−1.1 to 1.2)	
Smoking status[b]				
Never smoked	9440 (64.8)	9131 (64.4)	−0.4 (−1.8 to 0.9)	.63
Ex-smoker	1509 (10.4)	1467 (10.3)	−0.0 (−2.2 to 2.2)	
Smoking	3611 (24.8)	3580 (25.3)	0.5 (−1.6 to 2. 5)	
History of disease				
Myocardial infarction	1290 (8.7)	1174 (8.1)	−0.6 (−2.8 to 1.6)	.05
Angina	2995 (20.2)	3226 (22.2)	2.0 (−0.1 to 4.0)	<.001
Heart failure	601 (4.1)	560 (3.9)	−0.2 (−2.4 to 2.0)	.37
Stroke	1140 (7.7)	1165 (8.0)	0.3 (−1.9 to 2.5)	.31
Transient ischemic attack	152 (1.1)	242 (1.8)	0.7 (−1.6 to 3.0)	<.001
Diabetes	1973 (13.3)	2025 (13.9)	0.6 (−1.5 to 2.7)	.13
Hypertension[c]	10159 (68.6)	9804 (67.4)	−1.2 (−2.2 to −0.1)	.03
Dyslipidemia[d]	2024 (13.7)	1975 (13.6)	−0.1 (−0.9 to 0.7)	.84
Physical signs at presentation				
SBP <90 mm Hg	391 (2.6)	357 (2.5)	−0.2 (−0.6 to 0.2)	.32
Heart rate ≥100 beats/min	1673 (11.3)	1642 (11.3)	−0.0 (−0.7 to 0.7)	>.99
Hospital characteristics				
No. of beds				
>1000 (n = 9)	1179 (8.0)	758 (5.2)	−2.8 (−3.3 to −2.2)	<.001
501-1000 (n = 33)	8612 (58.2)	8618 (59.3)	1.1 (0.0 to 2.3)	
201-500 (n = 47)	4382 (29.6)	4664 (32.1)	2.5 (1.4 to 3.6)	
≤200 (n = 12)	636 (4.3)	497 (3.4)	−0.9 (−1.3 to −0.4)	

Abbreviations: CVD, cardiovascular disease; NSTEMI, non–ST-elevation myocardial infarction; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; UAP, unstable angina pectoris.

[a] Crude difference = intervention minus control.

[b] Data missing: education, 6620 cases (22.6%); farmer, 1921 cases (6.5%); insurance, 7577 cases (25.8%); smoking status, 608 cases (2.1%).

[c] Including patients with medical history of hypertension, a systolic blood pressure of 140 mm Hg higher, or a diastolic blood pressure of 90 mm Hg or higher when presenting at the hospital.

[d] Including patients with medical history of dyslipidemia, total cholesterol level of 240 mg/dL or higher, or low-density lipoprotein cholesterol level of 160 mg/dL or higher (to convert to millimoles per liter, multiply by 0.0259) when presenting at the hospital.

Table 2. Observed Rates and Means of Primary and Secondary Outcomes by Randomized Allocation and Corresponding Mean Differences and Adjusted Odds Ratios in Intervention and Control Periods

Outcomes	ICC[a]	Cases, No. (%)		Cluster-Adjusted		Primary Analysis	
		Intervention (n = 14 537)	Control (n = 14 809)	Difference (95% CI)	Odds Ratio or β Coefficient (95% CI)[b]	Difference (95% CI)	Odds Ratio or β Coefficient (95% CI)[b]
Primary outcome							
In-hospital MACE	0.01	559 (3.8)	655 (4.4)	−0.6 (−1.1 to −0.1)	0.87 (0.75 to 1.01)	−0.3 (−0.8 to 0.2)	0.93 (0.75 to 1.15)
Secondary outcome							
Composite score of KPIs to mean (SD)	0.34	0.69 (0.22)	0.61 (0.231)	0.1 (0.1 to 0.1)	0.08 (0.06 to 0.10)b	0 (0 to 0.1)	0.04 (0.02 to 0.06)[b]
Single KPIs, in-hospital therapy							
Aspirin	0.07	13 334 (91.7)	13 241 (89.4)	2.6 (1.9 to 3.3)	1.32 (1.15 to 1.50)	0.1 (−0.6 to 0.8)	1.01 (0.80 to 1.28)
Clopidogrel	0.23	10 913 (75.1)	8891 (60.0)	16.7 (15.7 to 17.8)	2.12 (1.84 to 2.45)	4.3 (3.3 to 5.4)	1.21 (1.02 to 1.44)
Statin	0.09	12 501 (86.0)	12 479 (84.3)	2.6 (1.8 to 3.5)	1.21 (1.08 to 1.35)	0.5 (−0.4 to 1.4)	1.04 (0.87 to 1.24)
Dual antiplatelet	0.22	10 725 (73.8)	8680 (58.6)	16.6 (15.5 to 17.7)	2.08 (1.81 to 2.39)	4.4 (3.3 to 5.5)	1.21 (1.03 to 1.43)
Loading dose dual antiplatelet	0.21	5768 (39.7)	3563 (24.1)	15.5 (14. to 16.5)	2.13 (1.70 to 2.66)	4.5 (3.46 to 5.5)	1.24 (0.93 to 1.66)
High-intensive statin	0.35	4954 (34.1)	5524 (37.3)	−3.6 (−4.7 to −2.6)	0.85 (0.70 to 1.03)	3.3 (2.2 to 4.4)	1.16 (0.95 to 1.42)
STEMI receiving reperfusion	0.15	1414 (48.9)	1683 (52.2)	−1.8 (−4.4 to 0.7)	0.93 (0.81 to 1.06)	−2.2 (−4.7 to 0.3)	0.92 (0.72 to 1.16)
Acceptable D2N time	0.12	539 (37.4)	516 (30.0)	5.7 (2.5 to 9.0)	1.30 (1.02 to 1.65)	2.4 (−0.9 to 5.7)	1.12 (0.77 to 1.62)
Single KPIs, discharge therapy							
Aspirin	0.20	11 975 (85.5)	11 565 (81.5)	4.7 (3.9 to 5.6)	1.40 (1.08 to 1.81)	5.5 (4.7 to 6.4)	1.48 (1.14 to 1.93)
Clopidogrel	0.26	9824 (70.1)	7718 (54.4)	17.3 (16.2 to 18.4)	2.07 (1.74 to 2.47)	7.3 (6.2 to 8.4)	1.36 (1.12 to 1.64)
β-Blocker	0.11	8358 (59.7)	7458 (52.5)	8.5 (7.3 to 9.6)	1.41 (1.21 to 1.65)	7.6 (6.5 to 8.8)	1.36 (1.17 to 1.59)
Statin	0.18	11 532 (82.3)	11 166 (78.7)	5.3 (4.4 to 6.2)	1.38 (1.13 to 1.70)	4.6 (3.7 to 5.6)	1.33 (1.06 to 1.67)
ACEI or ARB (in LVSD ones)	0.21	1382 (50.6)	1295 (47.9)	4.1 (1.4 to 6.7)	1.18 (1.00 to 1.38)	6.0 (3.3 to 8.6)	1.27 (1.05 to 1.53)
Single KPIs, other							
First ECG in time	0.18	9020 (62.0)	7768 (52.5)	10.3 (9.2 to 11.5)	1.52 (1.28 to 1.81)	2.8 (1.7 to 4.0)	1.12 (0.90 to 1.39)
Diagnosis consistent with ECG and biomarker findings	0.03	9957 (83.7)	9825 (84.3)	−0.3 (−1.2 to 0.7)	0.98 (0.87 to 1.11)	−2.3 (−3.2 to −1.3)	0.85 (0.71 to 1.01)
Length of stay to mean (SD)	0.11	8.8 (5.41)	9.6 (5.65)	−0.7 (−0.9 to −0.4)	−0.67 (−0.92 to −0.43)[c]	−0.1 (−0.4 to 0.2)	−0.12 (−0.44 to 0.20)[c]
In-hospital cost to mean (SD), $	0.19	1486.8 (1914)	1383.8 (1869.9)	134.7 (31.7 to 237.6)	134.7 (31.7 to 237.6)[c]	−88.6 (−282.2 to 104.9)	−88.6 (−282.2 to 104.9)[c]

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; D2N, door to needle; ECG, electrocardiograph; ICC, intraclass correlation coefficient; KPI, key performance indicator; LVSD, left ventricular systolic dysfunction; MACE, major adverse cardiovascular event; STEMI, ST-elevation myocardial infarction.

[a] The ICCs are obtained using generalized estimating equations models with exchangeable working correlation structure.

[b] Odds ratios and β coefficients represent the effect of intervention compared with control and are calculated as the difference of proportions or means in marginal effects (intervention group minus control group) in a generalized estimating equation model to account for within-hospital clustering with logit link function for binary outcomes or with identity link function for continuous outcomes. In the primary analysis model, time was taken into account as a fixed effect. The 95% CIs for difference in proportions are obtained through normal approximation of the adjusted proportions.

[c] β Coefficient.

and a model in which time was considered a continuous variable as well as a model with the interaction between time and intervention. The intervention effects were summarized as the resulting odds ratios and difference of proportions for binary outcomes or mean differences for continuous outcomes. We further conducted covariates-adjusted analyses, including patient-level baseline covariates and hospital-level covariates, using 3-level generalized linear-mixed models with hospital and province as the second and third levels, respectively.

The effect of the intervention on in-hospital MACE and the composite KPI score was analyzed according to the following prespecified baseline subgroups: subtypes of ACS, sex, and age. We did not execute any interim analysis. We did not adjust for the multiple testing in our analyses on secondary outcomes; therefore, these analyses should be considered exploratory.

All statistical tests were 2-tailed. The intervention effects for the primary and secondary outcomes were considered significant at $P = .05$. All analyses were conducted using SAS, version 9.4 (SAS Institute).

Results

Patient Recruitment

Of 120 eligible hospitals recommended through local health authorities, 19 declined to participate. Before the initiation of

the intervention, 2 hospitals withdrew from the study. A total of 29 346 patients with ACS were recruited. Of them, 14 809 patients (50.5%) were recruited before hospitals received the QCI interventions (control) and 14 537 (49.5%) were recruited after the intervention was initiated (Figure 1).

Patient Characteristics

The patient characteristics were generally similar in the control and intervention groups (Table 1). The study participants were age 19 to 102 years, with a mean (SD) age of 64.0 (11.6) years. Consistent with previous reports from China, ST-segment elevation MI accounted for only about one-third of events, while unstable angina pectoris accounted for about one-half.

Effects on Primary and Secondary Outcomes

The difference in in-hospital MACE between patients recruited in the intervention period and those in the control period was not significant after adjusting for the clustering effect and time trend (difference, −6; 95% CI, −1.1 to −0.1) (Table 2). The model with the time-by-treatment interaction showed no statistically significant effect of intervention, and the interaction term was also not significant. The temporal change in the unadjusted rates of in-hospital MACE is shown in **Figure 2**.

For secondary outcomes, the composite score of KPIs was significantly higher in the intervention group and the difference remained significant after adjusting for the clustering effect and time trend. Among the 16 single KPIs, all those on discharge therapy were significantly improved by the intervention. With respect to in-hospital care, significant intervention effects were only observed for the early use of clopidogrel and dual antiplatelet therapy in the primary analysis (Table 2). The in-hospital cost did not increase in the intervention period in the primary analysis. We repeated all the previously described analyses with further adjusting for multiple variables at patient, hospital, and province levels and the results remained unchanged (eTable 2 in Supplement 4).

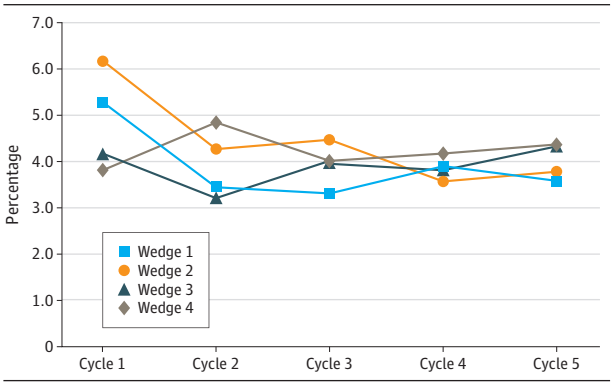
Subgroup Analysis

The prespecified subgroup analyses of the primary outcome are shown in **Figure 3**. There was no evidence of a differential effect of intervention on in-hospital MACE by age, sex, or subtype of ACS. The site monitoring data and the records from the online system for training showed that more than 90% hospitals implemented intervention components, but the fidelity to individual components was variable (eTable 3 in Supplement 4).

Discussion

In this stepped-wedge cluster randomized clinical trial, we found that implementing the QCI improved many process indicators significantly. However, these improvements were generally moderate and did not translate into a significant change in the rate of in-hospital MACE. The results align with findings from the recent systematic review that analyzed 670 reports from 337 studies of 118 strategies to improve health care clinician practices in low-income and middle-income countries.[28] The review concluded that the effect size of these strategies varied substantially

Figure 2. Unadjusted Rates of Major Adverse Cardiovascular Events by Wedge and Cycle



but was typically moderate, most strategies had low-quality evidence, and the results emphasized the need for better methods to study the effectiveness of interventions.[28]

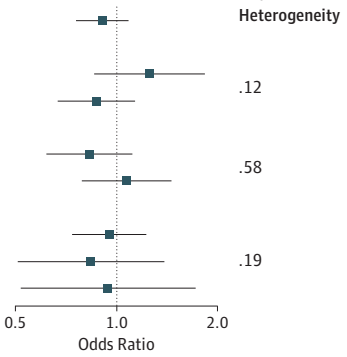
Looking at the changes by types of KPIs may help to understand why our study did not achieve a significant reduction in the clinical outcome. Most KPIs that improved significantly were discharge medical therapies, which cannot influence in-hospital clinical outcomes. For the in-hospital management KPIs, the early use of clopidogrel, dual antiplatelet therapy, and loading dose dual antiplatelet therapy all increased by 15% in the intervention group compared with the control, but these changes were primarily driven by the change in the use of clopidogrel alone. However, reperfusion therapy (those receiving the reperfusion therapy and those with an acceptable door-to-needle time), statin use (early use and high dose), and aspirin use (early use and loading dose) showed no significant differences between intervention and control. A significant reduction in in-hospital MACE is unlikely to be achieved solely by a modest increase in clopidogrel use.

The failure to change the clinical outcome might also be due to the intervention itself being incapable to generate clinically meaningful changes. The fidelity of intervention implementation in our study was generally adequate but demonstrated some variability between hospitals regarding individual components. The recently published ACS Quality Improvement in Kerala randomized clinical trial that used a similar design as our study also found that the locally adapted quality improvement kit did not improve clinical outcomes.[29]

Why should the intervention be effective at improving some KPIs but not others? First, some of the KPIs had an already high rate of use before the intervention was initiated, so there was limited scope for improvement. For example, 13 241 (89.4%) and 12 479 patients (84.3%) in this study, respectively, had been administered aspirin and statins early before the intervention initiated. By contrast, only 8891 patients (60%) received clopidogrel early, leaving much room for the intervention to improve matters. The proportion of use at discharge for 4 evidence-based secondary prevention treatments was generally between 50% and 80% at baseline and all showed significant increase in intervention. The systematic review by Rowe et al[28] also found that baseline outcome level was inversely associated with effect size. Second, with the advances in interventional therapy, thrombolytic therapy

Figure 3. Subgroup Analysis for the Effect of Intervention on Major Adverse Cardiovascular Events (MACE), Cluster, and Time Adjusted (Primary Model)

Source	MACE, No. of Participants (%)		Adjusted Difference, % (95% CI)	Adjusted OR (95% CI)	*P* for Heterogeneity
	Intervention (%)	Control (%)			
Overall	559 (3.8)	655 (4.4)	-0.3 (-0.8 to 0.2)	0.93 (0.75-1.15)	
Age, y					
<65	153 (2.0)	144 (1.9)	0.1 (-0.3 to 0.6)	1.25 (0.86-1.82)	.12
≥65	406 (5.8)	511 (6.9)	-1.2 (-2.0 to -0.4)	0.87 (0.67-1.13)	
Sex					
Male	298 (3.4)	357 (4.0)	-0.6 (-1.2 to -0.1)	0.83 (0.62-1.11)	.58
Female	261 (4.5)	298 (5.0)	-0.5 (-1.3 to 0.3)	1.07 (0.79-1.45)	
Subgroup					
STEMI	406 (8.3)	476 (8.8)	-0.6 (-1.7 to 0.5)	0.95 (0.74-1.22)	
NSTEMI	108 (4.3)	132 (6.0)	-1.7 (-3.0 to -0.5)	0.84 (0.51-1.38)	.19
UAP	45 (0.6)	47 (0.6)	-0.0 (-0.3 to 0.2)	0.94 (0.52-1.71)	



NSTEMI indicates non–ST-elevation myocardial infarction; OR, odds ratio; STEMI, ST-elevation myocardial infarction; UAP, unstable angina pectoris.

has been declining worldwide.[12,30] In fact, thrombolytic therapy is now seldom seen in tertiary hospitals.[30] Current guidelines tend to encourage patients with MI in primary care to be transferred to medical centers with catheter laboratories for primary PCI.[7] This "new" trend may discourage physicians at primary care or non-PCI hospitals to use thrombolytic therapy, although it is highly recommended and encouraged in the hospitals in this study. Third, given the poor physician-patient relationship in China,[31] the risk of an unsuccessful opening of the culprit vessels by thrombolytic therapy, as well as the higher risk of bleeding, prevents physicians from suggesting thrombolytic therapy. Finally, the fact that only about half of the participating hospitals were very active in implementing the study interventions suggested that quality of care has not become a real goal of hospital management in many Chinese hospitals. If the performance review in hospital management would have still been linked to hospital income, but not the quality of care measurement,[32] it would be hard to expect any significant improvement in quality of care among patients. Our findings call for a better health care system that provides the foundation for the QCI to take a real effect.

Strengths and Limitations

This study has many strengths. To our knowledge, it is the first well-powered randomized clinical trial to evaluate the effectiveness of the QCIs in reducing clinical outcomes.[25] The study design, conduct, and data analyses were overseen by an experienced steering committee composed of international experts in cardiology, epidemiology, and biostatistics. All study end points were adjudicated by an independent committee and the study process was closely monitored by a quality control team. The Ministry of Health provided support to ensure that participating hospitals cooperated well, and only 2 of them withdrew during the study.

The study also has several limitations. First, the event rate for the primary end point was lower than that estimated from the previous CPACS-1 study, which led to this study being underpowered. It may be because of the advantages in clinical management of ACS, as well as the fact that the events in CPACS-1 were not adjudicated. However, the post hoc power analysis indicates that the study was still powered to detect a relative reduction of the primary outcome of at least 19%. Second, the proportion of unstable angina pectoris in the patients in this study was high (14 349 [49%]) compared with that reported in other countries,[10,29,33] which could contribute to the overall low event rates. However, the high proportion of unstable angina pectoris in this study was comparable with the CPACS-1 study (46%) as well as other previous reports among Chinese patients with ACS.[12,13] It is unclear why the proportion in Chinese patients was higher than that in other countries. Third, because of the technical constraints in hospitals at this level, many patients are often transferred to larger medical centers for better medical services. That would limit the ability for the intervention to take effect (there is not enough time for the intervention) and also prevent us from understanding the effect (eg, the causes of death, for which no data were available). In fact, 4108 patients (14%) in this study were transferred to higher-level hospitals.

By focusing on in-hospital MACE as the primary outcome, the effectiveness of the study intervention may have been underestimated, as the most significant improvements were observed on discharge therapies. We anticipate that ongoing follow-up of the patients will determine whether the intervention may have longer-term effects on clinical outcomes.

Conclusions

Among resource-constrained Chinese hospitals, introducing a multifaceted QCI did not affect in-hospital MACE, although it improved a few of the care process indicators of evidence-based ACS management, especially at the time of hospital discharge.

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