Acute Coronary Syndrome Quality Improvement in Kerala (ACS QUIK): Rationale and Design for a Cluster Randomized Stepped Wedge Trial

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Abstract

Ischemic heart disease is the leading cause of death in India, and there are likely more myocardial infarctions in India than in any other country in the world. We have previously reported heterogeneous care for patients with myocardial infarction in Kerala, a state in southern India, including both gaps in optimal care and inappropriate care. Based on that prior work, limitations from previous non-randomized quality improvement studies, and promising gains in process of care measures demonstrated from previous randomized trials, we and the Cardiological Society of India – Kerala chapter sought to develop, implement, and evaluate a quality improvement intervention to improve process of care measures and clinical outcomes for these patients. In this paper, we report the rationale and study design for the Acute Coronary Syndrome Quality Improvement in Kerala (ACS QUIK) cluster randomized stepped wedge clinical trial (NCT02256657) in which we aim to enroll 15,750 participants with acute coronary syndromes across 63 hospitals. To date, the majority of participants are men (76%) and has ST-segment

elevation myocardial infarction (63%). The primary outcome is 30-day major adverse cardiovascular events defined as death, recurrent infarction, stroke, or major bleeding. Our secondary outcomes include health-related quality of life and individual- and household-level costs. We also describe the principal features and limitations of the stepped wedge study design, which may be important for other investigators or sponsors considering cluster randomized stepped wedge trials.

Keywords

acute coronary syndrome; quality improvement; stepped wedge trial

Background

Ischemic heart disease (IHD) is the leading cause of death in India.(1) There are likely more myocardial infarctions in India than in any other country in the world, due to the combination of a large population and relatively high disease burden.(2,3) We have previously reported data on the heterogeneous presentation, management, and outcomes among 25,748 patients with acute coronary syndromes (ACS) from 2007 to 2009 across 125 hospitals that were part of the Kerala Acute Coronary Syndrome Registry.(4) Our findings demonstrated gaps in optimal medical care during hospitalization and at the time of discharge.(5) For example, while in-hospital antiplatelet use was >90%, in-hospital use of anticoagulants, beta-blockers, ACE-inhibitors, and statins was 70% or less for each medication. We also demonstrated examples of acute coronary syndrome management that was contraindicated according to clinical practice guidelines, including use of thrombolytics among 19% of patients with non-ST-segment myocardial infarction, which was associated with increased odds of in-hospital mortality (OR = 1.33 [95% CI 0.92, 1.91]) and major adverse cardiovascular events (OR = 1.63 [95% CI 1.19, 2.23]).(4)

Adherence to guideline-based therapies has been associated with improved in-hospital, 30-day and 1-year clinical outcomes in acute coronary syndrome patients in multiple studies performed in the United States and other high-income countries. For example, the CRUSADE investigators demonstrated a 2.2% absolute difference in in-hospital mortality between the highest and lowest quartiles of adherence to acute coronary syndrome guidelines.(6) However, reported associations between guideline-based adherence and outcomes may not necessarily be causal because of potential confounding at the patient, clinician, or hospital levels. To overcome this potential limitation, investigators from Brazil(7) and China(8) have performed cluster randomized trials of acute coronary syndrome quality improvement interventions. Both previously reported trials demonstrated improvements in process measures but neither has been powered for nor has demonstrated improvements in outcomes. One large, ongoing trial in China (target N=25,000), the Clinical Pathways in Acute Coronary Syndrome – 3 (CPACS 3), is powered to detect a difference in clinical outcomes.(9)

Similar large-scale cluster randomized trials have not been carried out in India, a research gap at odds with the burden of disease. One pilot investigation in Kerala showed potential

benefits from the implementation of community and clinician education coupled with a health system intervention aimed to standardize treatment(10) and another pre/post study of pre-hospital health system improvement is ongoing in Karnataka.(11) Therefore, based on results from the Kerala Acute Coronary Syndrome Registry, limitations from previous non-randomized studies, and promising gains demonstrated from previous randomized trials, we and the Cardiological Society of India – Kerala chapter sought to develop, implement, and evaluate a quality improvement intervention to improve process of care measures and clinical outcomes for patients with ACS in Kerala through our cluster randomized, stepped wedge Acute Coronary Syndrome Quality Improvement in Kerala (ACS QUIK) trial.

Methods

The methods described are based on the Standardized Reporting Items: Recommendations for Intervention Trials (SPIRIT) statement and checklist.(12) The cluster randomized stepped wedge design of ACS QUIK meant that the 63 participating hospitals (clusters) were randomized to one of five pre-defined steps for implementation of the intervention at study initiation in November 2014. Only the study biostatisticians knew the allocation schedule. After a four-month baseline period, the quality improvement toolkit was implemented among the hospitals randomized to step 1 (cohort 1, **Figure 1**). Through a one-way crossover design, hospitals in cohort 1 use the quality improvement toolkit through the end of the trial. Cohorts 2 through 5 implemented the quality improvement toolkit at months 8, 12, 16 and 20, respectively, and use the toolkits from that time forward to the end of the study in November 2016.

Participants

Prior to study initiation, we invited hospitals that participated in the Kerala Acute Coronary Syndrome Registry to participate in ACS QUIK. To diversify our sample, we invited government hospitals, including government medical colleges, and hospitals with and without cardiac catheterization laboratories and those with and without cardiologists to participate. To be eligible, hospitals had to identify a principal investigator and either junior physician or nurse who would serve as a quality improvement champion for the trial.

Patients were eligible for inclusion if they presented with acute myocardial infarction and met at least 2 out of 3 criteria for myocardial infarction (chest pain, ST segment elevation on electrocardiography, and cardiac biomarker elevation greater than 3 times the upper limit of normal) consistent with the 3rd universal definition of myocardial infarction.(13) We chose to exclude patients with unstable angina because of the low event rate associated with this presentation, which would reduce our statistical power to demonstrate a difference with the study intervention. Informed consent in the local language, Malayalam, was obtained from eligible patients at admission and follow-up was conducted at 30-days post discharge.

We collected data based on the American College of Cardiology/American Heart Association's Key Data Elements and Definitions for Measuring the Clinical Management and Outcomes Key of Patients With Acute Coronary Syndromes and Coronary Artery Disease.(14) Data included, but were not limited to socio-demographics, presenting signs and symptoms, medical history, laboratory studies (e.g., cardiac biomarkers, serum

creatinine, hemoglobin), diagnostic studies (e.g., electrocardiography, echocardiography, angiography), therapeutics details (e.g., medications, coronary stenting, cardiopulmonary resuscitation), in-hospital events, discharge status/diagnosis, and follow-up events.

Intervention

To develop our intervention, we followed recommendations from the Medical Research Council guidelines for complex interventions.(15) Starting in 2011, we performed in-depth interviews and focus groups among participating clinicians (cardiologists and internists) and nurses to identify facilitators, barriers, and context to optimal in-hospital acute coronary syndrome care to create a theoretical model for improving care. We supplemented these qualitative data with data from systematic reviews evaluating the effects of components of typical quality improvement interventions, including audit and feedback(16) and checklists. (17) Based on data from previous systematic reviews, audit and feedback reports, which were generated by our electronic data capture system, were electronically delivered monthly and were linked to monthly quality improvement team meetings with standardized agendas using the Plan-Do-Study-Act change cycle to guide change management. To help prepare quality improvement teams, we provided free quality improvement training through the Institute for Healthcare Improvement's Open School online training program (www.ihi.org/education/ihiopenschool).

We added tools for improving health behaviors, including: 1) tobacco cessation materials and training developed by Quit Tobacco International that have been demonstrated to be effective for tobacco cessation among patients with diabetes in India;(18) 2) pamphlets for recommendations on health diets, lifestyle, and physical activity developed for a post-myocardial infarction yoga intervention in India (CTRI/2012/02/002408); and 3) recommendations for home-based cardiac rehabilitation given the lack of facility-based cardiac rehabilitation programs in Kerala. We also provided contact information on American Heart Association emergency cardiovascular care training centers in Kerala for the development of in-hospital cardiac arrest (code) or rapid response teams for hospitals that did not have these teams in place.

The comparator group was provided with no special instruction in the care of their patients and was considered to be "usual care" according to local standards.

Outcomes

Our primary outcome was the composite measure of major adverse cardiovascular events at 30 days post-discharge. Sites' local staff, supervised by the site principal investigator, adjudicated outcomes independently during index hospitalization or during in-person clinic or telephonic follow-up based on clinical decision-making and trial criteria and reported these outcomes centrally using electronic case report forms. When participants died during the 30-day follow-up period, then the events were reported by next of kin. While central, blinded adjudication is generally preferred, the potential bias is limited in the case of objective outcomes based on a 2008 meta-epidemiological analysis of 314 non-blinded versus 432 blinded trials (Odds Ratio = 1.01 [95% CI: 0.92 to 1.10]) for non-blinded trials being more likely to demonstrate a beneficial effect.(19) Further, central adjudication was

not feasible based on the resources available and thus we made the pragmatic decision to rely upon site staff for outcome assessment.

We defined major adverse cardiovascular event as any one of the following: death, recurrent infarction, stroke, or major bleeding defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial, which is defined by intracerebral hemorrhage or bleeding resulting in substantial hemodynamic compromise requiring treatment.(20) We chose this definition over others because it was the easiest for clinicians to use for outcome assessment.

Our secondary outcomes included: 1) in-hospital and discharge medication prescription rates, 2) discharge advice regarding healthy lifestyles (diet, physical activity, and tobacco cessation), 3) in-hospital and 30-day expanded major adverse cardiovascular events, which we defined as our primary outcome plus urgent revascularization or other reported cardiovascular events.

We also performed sub-studies of ACS QUIK by collecting data on health-related quality of life and individual- and household-level (or microeconomic) costs at 30-day follow-up using a previously published instrument(21) developed in conjunction with experts from the World Bank given the dearth of data for these patient-centered outcomes in India. For health-related quality of life, we used a version of the Seattle Angina Questionnaire that was translated into Malayalam, the local language, for self-administration. For evaluation of microeconomic costs, we used our previously published, interviewer-administered instrument developed to capture direct and indirect costs associated with cardiovascular disease hospitalization.(21) Our previous microeconomic survey had been performed prior to the implementation of a national government insurance program for families below the poverty line.

Sample size

To estimate our sample size, we used data from the Kerala Acute Coronary Syndrome Registry to extrapolate a baseline major adverse cardiovascular event rate for patients with myocardial infarction at 30 days (10.4%). We used these same data to estimate intra-class correlation coefficient for the primary outcome (in-hospital major adverse cardiovascular event, ICC = 0.05). We then used data from the CRUSADE Registry to estimate an effect size by using the differences in in-hospital mortality rate between highest and lowest performing centers (4.2% vs. 6.3%, respectively).(6)

We sought input from experts in stepped wedge trial design methodology(22) who created a menu-driven program for sample size estimation of cluster randomized stepped wedge trials in Stata (StataCorp LP, College Station, TX).(23) We further applied the stepped wedge design effect and increased our sample size to account for a 5% lost-to-follow-up rate to arrive at a total sample size of 15,750 participants, which would provide 80% power with a significance level of 0.05 to detect a 2.4% reduction of 30-day major adverse cardiovascular event rate by the intervention from the anticipated 10.4% by the local standard care.

Randomization, Allocation Concealment, and Blinding

We performed randomization centrally using a computer-generated, random number sequence that was only known by the 2 biostasticians on our team (DK, LZ). We stratified our randomization by hospital size to minimize imbalances throughout the trial. Three weeks prior to each step, we identified which hospitals were randomly selected to move from the comparator group to the intervention group for that step so that we could plan for site-level training on the quality improvement intervention. We did not announce which hospitals were selected at each step to other hospitals outside of their cohort; however, because of the nature of the study, formal blinding was not feasible.

Data collection and management

Data collection occurred at each participating site through a customized electronic data capture system with in-built limits to minimize data entry errors (Data Template, Bangalore, India). The data capture system was specifically built to provide audit and feedback reports as part of the quality improvement intervention. Data cleaning was a systematic, semi-automated process led by 1 research coordinator, 1 data manager, 1 biostatistician, and 3 zonal project coordinators in conjunction with the site investigators, and staff. Data queries were performed biweekly and sent to sites for data verification or correction.

Statistical analyses

All participants who were screened and invited to participate in this trial will be accounted for, in accordance with the CONSORT statement for reporting trials of non-pharmacologic interventions.(24) Reasons for early withdrawal will be listed for all clusters that prematurely discontinued the study. Baseline demographic variables, such as age, sex, and relevant clinical variables will be summarized for each group. Summaries of continuous baseline variables will be presented as means and standard deviations together with medians and minimum and maximum values. Categorical variables will be described as frequencies and percentage.

The analysis will be performed using the intention to treat principle (i.e., all patients recorded in the data base during the 24 month period will be included and considered exposed to the intervention or unexposed according to the randomization schedule regardless of when the intervention was actually implemented). For the primary outcome analysis, 30-day major adverse cardiovascular event rates will be modeled using mixed effects logistic regression with random cluster (hospital) effects as well as a fixed time effect every 4 months. Baseline data collected from the first time period will be tabulated by order of implementation, 12 to 13 clusters in 5 groups. The adequacy of randomization will be examined and we will include any hospital level variable unbalanced at baseline in the model as a sensitivity analysis. The patient level covariates included will be derived from the previously validated Global Registry of Acute Coronary Events (GRACE) risk score.(25) In the unlikely event that patient-level GRACE risk score covariates are not balanced between two groups, we will perform a sensitivity analysis by adjusting for those factors.

Subgroup analyses—The following a priori sub-group analyses will be carried out to evaluate potential heterogeneity of effect.

Site level characteristics

- Hospital size

- Use of quality improvement toolkit components

Participant level characteristics

- Age (<65 years and 65 years)

- Sex

- ST-segment elevation myocardial infarction vs. non-ST-segment elevation myocardial infarction

The results of these subgroup analyses will be treated with caution because this study was not powered for these analyses.

Interim analysis—To adjust for one interim analysis at 12 months, the O'Brien Fleming stopping boundary for the interim analysis was set to $z = 2.797$, p-value 0.005 and for the final analysis to $z = 1.977$, p-value 0.048.

Missing data—If the data are "not obtained" on the 30-day follow-up assessment form following the outpatient department follow-up visit, three telephone call attempts, response from mailed postcard, or home visits in limited circumstances by the site coordinator, then data will be considered as missing. We will perform sensitivity analyses using multiple imputation to evaluate the potential effect of missing outcomes.

Monitoring

We performed risk-based central statistical monitoring to evaluate sites' performance and to direct risk-based, in-person, site monitoring visits. Our central statistical monitoring was largely based on freely available statistical tools developed by Kirkwood and colleagues[26] to evaluate the presence of outliers, inliers, and correlation among covariates associated with the outcome (major adverse cardiovascular events), particularly covariates part of the GRACE risk score,[25] namely age, systolic blood pressure, heart rate, and creatinine.[5] We also included covariates related to hospital size and previous trial participation.

Process evaluation

We applied methods of process evaluation as outlined by guidance documents from the Medical Research Council for process evaluation of complex interventions.[27] We asked site investigators about their use of the quality improvement intervention components approximately 4 to 8 months after crossover to the intervention group through online surveys. We supplemented these surveys with in-depth interviews to evaluate context, implementation fidelity, dose, reach, mechanisms of effect, and sustainability.

Ethics

Informed consent was obtained per guidelines for ethical research in human subjects. Ethical oversight was provided by the Institutional Ethics Committee (IEC) of participating hospitals. In instances where hospitals did not have an IEC, then hospitals deferred to the

Cardiological Society of India – Kerala chapter ethics committee, which evaluated and approved the protocol. The Northwestern University Institutional Review Board and Centre for Chronic Disease Control (ACS QUIK national coordinating center) IEC also evaluated and approved the protocol for this trial. The trial also received approval from the Indian Council for Medical Research's Health Ministry Screening Committee.

Results

Of the hospitals participating, 84% are private or non-profit, and 16% are public, government hospitals. Participant recruitment through September 2016 is 33% above target recruitment, and 30-day follow-up has reached 96.5%. In absolute numbers, we have recruited 19,524 participants, of whom 76% are men and 63% have ST-segment elevation myocardial infarction.

Discussion

ACS QUIK aims to evaluate the effect of a quality improvement intervention on process of care measures and clinical outcomes among >15,000 patients with ACS across 63 hospitals in Kerala, India using a cluster randomized stepped wedge trial design. To our knowledge, this study is only the second cluster randomized stepped wedge myocardial infarction quality improvement program (Clinical Pathways in Acute Coronary Syndrome – 3(9) being the other such trial) and the first of its kind in India. The stepped wedge trial design was employed because of several important features.(22) First, this design has stronger causal inference in evaluating the potential effects of an intervention compared with a pre/post or even interrupted time series study design, which can be influenced by secular trends. This point is particularly relevant in Kerala where the cardiovascular health care system is changing rapidly. Second, the design allows for sequential implementation of the intervention across all (63 by the end of the trial in this case) sites. The mean period of time that hospitals spend in the intervention period is 12 months (range 4 to 20 months). Third, the stepped wedge design allows all hospitals to eventually receive the intervention, which is important when the intervention is deemed likely to be beneficial. This design helps avoid potential ethical concerns about sites being randomized to the control arm of a trial throughout the entire study period.

However, the stepped wedge design also includes important limitations. First, because all hospitals need to begin the trial at the same time, trial initiation can only begin when all sites are ready. This can lead to unexpected delays. Second, if the trial is below target recruitment, then the trial cannot be extended without causing imbalance between the intervention and control groups because the period of extension occurs only after all groups have crossed over to the intervention period. Third, if the trial is ahead of target recruitment, then the trial cannot be stopped early for similar reasons of imbalance between the intervention and control groups. Therefore, investigators will need to raise additional funds to cover these additional recruitment costs. Sponsors and expert groups should be aware of these limitations when calling for similar stepped wedge trials.(28)

ACS QUIK aims to use a cluster randomized stepped wedge clinical trial design to implement and evaluate a locally developed quality improvement intervention to improve myocardial infarction process of care and clinical outcomes in Kerala. If successful in achieving its primary outcome, then this trial will provide high quality evidence for implementation of this intervention more broadly throughout India and potentially other low- and middle-income countries. Quality improvement is more likely to succeed in the context of longitudinal stakeholder buy-in at multiple levels, including individual, institutional, and organizational;(29,30) we have found the Cardiological Society of India – Kerala chapter to be a vital partner in this research. Whether or not this intervention would be suitable for other acute cardiovascular conditions (e.g., stroke, acute heart failure) remains uncertain but is of interest to our team. Data from our ongoing process evaluation will be important to understand what site- and personnel-level factors are necessary for successful implementation of this intervention. Our team is also exploring funding models (e.g., subscription-based model, partnership model) and automation of data management, cleaning, and monitoring not only to maintain financial support for these activities but also to minimize costs to achieve long-term sustainability.

Acknowledgements

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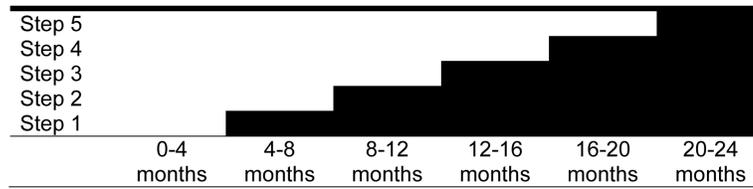
Figure 1.
Stepped wedge trial design schema. The white boxes represent periods of usual care, and the black boxes represent periods of intervention where by hospitals receive and implement the quality improvement intervention. By design, all hospitals start in the usual care, or control, arm and all end up in the intervention arm but the timing, or step, when hospitals move from control to intervention is random.