

Better Outcomes for Patients Treated at Hospitals That Participate in Clinical Trials

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ABSTRACT

Background Barriers to institutions participating in clinical trials include concerns about harms and costs. However, we hypothesized that patients treated at hospitals participating in trials would have better outcomes than patients treated at nonparticipating hospitals. We tested this hypothesis in 494 CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) hospitals treating 174 062 patients with non-ST-segment elevation acute coronary syndrome.

Methods Hospitals were classified into tertiles by percentage of patients concurrently enrolled in non-ST-segment elevation acute coronary syndrome trials. Outcomes were use of composite guideline-indicated care and in-hospital mortality. Multivariate regression was used to examine the association between hospital trial participation and outcomes.

Results Overall, 4590 patients (2.6%) were enrolled in trials, ranging from 0% (145 hospitals) to low-enrollment tertile (1.0%; interquartile range [IQR], 0.5%-1.4%; n = 226) to high-enrollment tertile (4.9%; IQR, 3.5%-9.7%; n = 123). The composite guideline adherence score increased with increasing tertiles of trial participation: 76.9% (IQR, 71.8%-81.3%) vs 78.3% (IQR, 73.2%-82.4%) vs 81.1% (IQR, 76.2%-84.1%) (adjusted $P = .008$). Hospitals that participated in trials had higher adjusted guideline adherence than nonparticipating hospitals (low enrollment, 0.8% greater [95% confidence interval {CI}, -0.9% to 2.6%]; and high enrollment, 2.5% greater [95% CI, 0.5%-4.5%]). In-hospital mortality decreased with increasing trial participation: 5.9% vs 4.4% vs 3.5% (adjusted $P = .003$). Patients treated at hospitals that participated in trials had significantly lower mortality than patients treated at nonparticipating hospitals (low enrollment adjusted odds, 0.9 [95% CI, 0.8-1.0]; and high enrollment adjusted odds, 0.8 [95% CI, 0.7-0.9]).

Conclusions The CRUSADE hospitals enrolled less than 3% of their patients with non-ST-segment elevation acute coronary syndrome into trials, and one-third never participated in trials. Compared with hospitals that do not participate in trials, those hospitals that do participate in trials seem to provide better care and to have lower mortality.

The quality of care for common conditions treated in hospitals, such as acute coronary syndromes, has improved over time in response to new evidence, clinical guidelines,

performance measurement and reporting, and quality improvement efforts.¹⁻³ Nevertheless, the rate of improvement has been slow and nonuniform, with marked variability between hospitals.¹⁻³ Furthermore, the link between better processes of care (eg, provision of guideline-concordant care) and better outcomes (eg, mortality) has only recently been convincingly demonstrated.^{4,5} A better understanding of the structures and characteristics of hospitals that deliver high-quality care, beyond easy-to-measure attributes such as size, caseload, or teaching status, is, thus, desirable.¹⁻⁶

Bradley et al¹ examined 1 performance measure (use of β -blockers after myocardial infarction) and determined that 4 hospital characteristics were associated with better performance: physician leadership, presence of shared goals, administrative (infrastructure) support, and credible feedback. While it is difficult to characterize hospitals according to such attributes for multiple measures or conditions, we have previously observed that 3 of these characteristics (physician leadership, shared goals, and infrastructure support) are also essential to the successful conduct of hospital-based clinical trials.

Indeed, much of the clinical trial enterprise has been developed to ensure that trial subjects receive safe, high-quality, protocol-driven care from highly trained research personnel overseen by experienced and well-informed investigators.⁷⁻¹³ We hypothesized that these same elements required for hospitals to participate in trials could induce beneficial changes in the hospital environment, thereby leading to better processes and outcomes of care for patients treated outside the trial setting. To test this hypothesis, we studied 174 062 patients treated at 494 hospitals that were part of the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) Initiative.^{4,6,10} Specifically, we hypothesized that patients with non-ST-segment acute coronary syndromes treated at hospitals that participated in trials would receive better care (ie, greater adherence to American College of Cardiology/American Heart Association treatment guidelines) and have better outcomes (ie, lower mortality) than patients treated at hospitals that did not participate.

METHODS

SETTING AND SUBJECTS

The CRUSADE Initiative has previously been described.^{4,6,10} In brief, CRUSADE is an ongoing, voluntary, observational data collection and quality improvement initiative that involves 557 hospitals in the United States. It was initiated in November 2001, with retrospective data collection starting in January 2001. The institutional review board of each hospital approved participation, and because unique identifiers were not collected, individual consent was waived.

CRUSADE included only patients with high-risk non-ST-segment elevation acute coronary syndrome with unstable angina and non-ST-segment elevation myocardial infarction. All CRUSADE patients presented with acute ischemic symptoms (lasting for at least 10 minutes at rest) within 24 hours of hospital arrival and had at least 1 of the following diagnostic features to distinguish those with an increased risk of adverse outcomes: ST-segment depression of 0.5 mm

or greater, transient ST-segment elevation of 0.5 to 1.0 mm (lasting for <10 minutes), and/or a positive result for cardiac biomarkers.

We analyzed patients included in CRUSADE from January 1, 2001, through June 30, 2006. Of 180 842 patients with non-ST-segment elevation acute coronary syndromes treated at 557 hospitals, we excluded patients with missing data regarding trial enrollment (5510 [3.0%]) and low-volume centers (1270 patients cared for at 63 hospitals). This left a final study sample of 174 062 patients with non-ST-segment elevation acute coronary syndrome treated at 494 hospitals.

DATA COLLECTION AND VALIDATION

Participating hospitals collected detailed process-of-care and in-hospital outcome data through medical record reviews of consecutive eligible patients. Data collected include use of medications within 24 hours of presentation, use of invasive cardiac procedures, laboratory results, and discharge therapies. In 2002, CRUSADE assessed reliability of data abstraction with randomly selected sites and records.⁴ The overall accuracy of audited records was 95%, and the degree of missing data was 5% across all collected data elements.⁴

EXPLANATORY VARIABLE OF INTEREST

We abstracted the dichotomous variable “clinical trial enrollment during the index hospitalization” for every patient.¹⁰ Clinical trial referred to any trial for the management of acute coronary syndrome. Beyond this, we did not gather information on whether patients were enrolled in a drug or device trial and we did not collect any information with respect to trial participation outside the field of cardiology. We conceptualized “trial participation” as a hospital-level characteristic and defined it by the proportion of CRUSADE patients who were concomitantly enrolled in a clinical trial during hospitalization. For analysis, we initially aggregated hospitals into quartiles of trial participation; for ease of presentation and because the second and third quartiles were virtually indistinguishable, we decided to aggregate hospitals into tertiles of trial participation (no trial participation vs low participation vs high participation).

OUTCOMES

To determine whether hospitals that participated in trials delivered better quality care, we examined a previously validated “composite guideline adherence score.”⁴ This was derived by determining adherence to 9 individual class 1 guideline-recommended therapies among patients eligible to receive these therapies.⁴ *Eligible* was defined, for denominator purposes, as being alive, not being transferred to another hospital, and having no contraindications to the treatment. Therapies included 4 short-term measures (aspirin, β -blockers, heparin, and glycoprotein IIb/IIIa inhibitors) and 5 discharge measures (aspirin, β -blockers, clopidogrel, angiotensin-converting enzyme inhibitors, and statins).⁴ Definitions, indications, and contraindications according to established guidelines have been previously published,^{4,6,10} and further details are available from the authors on request. For each patient, a composite adherence score was calculated as the sum of correct care according to each patient's total number of eligible opportunities for care. Thus, each patient could have received up to 9 therapies (4 within the first 24 hours and 5 by the time of discharge) and would have been eligible to receive anywhere from 1 to 9 therapies. The ratio

of the number of treatments received to the number of treatments the patient was eligible for, multiplied by 100, represents that patient's composite adherence score. The individual results were then summated to derive a hospital-level composite guideline adherence score. In the original development and validation of these composite scores, hospital-level guideline adherence ranged from 35% to 90%.⁴

To determine whether hospitals that participated in trials had better outcomes, we examined all-cause (in-hospital) mortality. A priori, we chose all-cause mortality because it would not be susceptible to bias with respect to determining the cause of death, it provided an integrated outcome that captured all serious adverse events, and it provided the most events.

ANALYSIS

We stratified hospital and patient characteristics, patterns of care, and outcomes by tertiles of hospital-level trial participation. Continuous variables are described as medians with 25th and 75th percentiles (ie, the interquartile range [IQR]), while categorical variables are described as frequencies. We used Spearman rank correlation coefficients to describe the relationship between hospital-level trial participation (as a continuous measure) and the composite guideline adherence scores and percentage of mortality.

To examine the association between hospital-level trial participation and hospital-level composite guideline adherence scores, we performed hospital-level analyses using linear regression models that accounted for the number of patients per hospital. These multivariate linear regression models adjusted for all available hospital characteristics, including total number of hospital beds, geographic region (West, Northeast, Midwest, or South), revascularization capabilities (no services, diagnostic catheterization only, and percutaneous coronary intervention without on-site cardiac surgery vs percutaneous coronary intervention with on-site cardiac surgery), and teaching status (academic vs nonacademic).

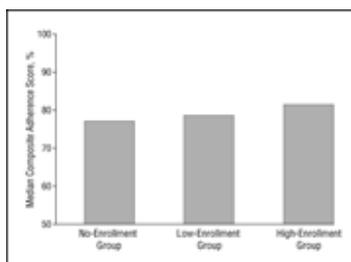
To examine the association between hospital-level trial participation and in-hospital mortality, we conducted patient-level analyses. For these analyses, to reduce bias, as has been recommended by others,⁸ we excluded patients who were transferred to another hospital (20 835 patients [12.0%]). We accounted for within-hospital clustering, whereby patients at the same hospital were more likely to have similar responses to each other relative to patients treated at other hospitals (eg, within-center correlation), by using logistic generalized estimating equation models to estimate marginal effects of percentage of hospital-level trial participation.^{14,15} This method produces estimates similar to those from ordinary logistic regression, but the variances of the estimates are adjusted for within-hospital clustering of responses. Variables entered into our model included sociodemographic factors (age [continuous], sex, race [white vs nonwhite], and insurance status), family history of coronary disease, medical history (hypertension, diabetes mellitus, smoking, hyperlipidemia, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, heart failure, stroke, and renal insufficiency), features of the initial clinical presentation (ST-segment depression, transient ST-segment elevation, signs of heart failure, heart rate [continuous], systolic blood pressure [continuous], body mass index, and specialty of attending physician [cardiology vs noncardiology]), and all hospital-level characteristics. All analyses were performed using SAS statistical software, version 9.1.3 (SAS Institute Inc, Cary, North Carolina).

ADHERENCE TO EVIDENCE-BASED GUIDELINES

In general, the hospitals that participated in clinical trials had better adherence to each of the 9 individual recommendations that constituted our guideline adherence score and other indexes of the quality of care that we measured ([Table 3](#)). The overall median composite guideline adherence score was 78.4% (IQR, 73.5%-82.6%). There was a modest direct correlation between the proportion of patients enrolled in a trial by a hospital and composite guideline adherence score (Spearman rank correlation coefficient, 0.2; $P < .001$). Median guideline adherence scores increased across tertiles of trial participation: 76.9% (IQR, 71.8%-81.3%) for no-enrollment hospitals vs 78.3% (IQR, 73.2%-82.4%) for low-tertile hospitals vs 81.1% (IQR, 76.2%-84.1%) for high-tertile hospitals (adjusted P value for trend = .008) ([Figure 1](#)). In weighted multivariate analyses adjusted for hospital-level characteristics, low-tertile trial participation hospitals achieved 0.8% higher (95% confidence interval [CI], -0.9% to 2.6%; $P = .36$) adherence scores and high-tertile hospitals achieved 2.5% higher (95% CI, 0.5%-4.5%; $P = .01$) adherence scores than did no-enrollment hospitals. The 1.7% adjusted difference in adherence scores between the high- and low-tertile hospitals was also significant (95% CI, 0.7%-3.3%; $P = .03$).

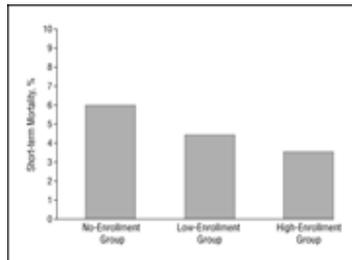
Figure 1.

Adherence to evidence-based guideline recommendations at 494 CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) hospitals, according to tertiles of hospital-level clinical trial participation. Tertiles of hospital-level trial participation include no participation tertile (0% of patients enrolled in trials) vs low trial participation tertile (1.0% enrolled [interquartile range, 0.5%-1.4%]) vs high trial participation tertile (4.9% enrolled [interquartile range, 3.5%-9.7%]). $P = .36$ for the difference between the no- and low-enrollment groups, $P = .01$ for the difference between the no- and high-enrollment groups, and $P = .03$ for the difference between the low- and high-enrollment groups. P values are weighted by the number of patients at each site and adjusted for all hospital-level variables presented in [Table 1](#) (see the “Analysis” subsection of the “Methods” section).



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Table 3. Measures of Processes of Care According to Tertiles of Clinical Trial Participation



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COMMENT

In a large cohort of US hospitals treating acute coronary syndromes, we found that only 2.6% of patients were ever enrolled in a clinical trial for that condition and that over more than 4 years of observation, almost one-third of hospitals never included a patient in a clinical trial. We also found that hospitals that participated in trials seemed to deliver better quality of care and have significantly lower rates of early mortality when compared with hospitals that did not enroll patients in trials.

Our findings confirm and extend the only previous study that has looked carefully for evidence of a trial participation effect. In that study, Du Bois and colleagues¹¹ examined the treatments and outcomes of 476 patients with ovarian cancer treated at 165 German hospitals. Compared with hospitals that did not participate in trials, they reported that participating hospitals had a 77% increase ($P = .04$) in guideline-concordant chemotherapy and a 28% reduction ($P = .001$) in long-term mortality.¹¹

Although rarely studied empirically, a hospital trial participation effect has been invoked in the past as one of the reasons that patients treated at certain types of hospitals (ie, high-volume, research-intensive, academic centers with residency and fellowship training programs) seem to have better outcomes.^{7,8,11-13} It has been speculated that trial investigators are prominent opinion leaders and physician advocates who gain early clinical experience with new drugs and devices and have many opportunities to interact with colleagues and exchange ideas regularly,¹⁵ that research personnel who are well trained and highly educated might develop additional capacity for training their colleagues outside the trial,^{7,8} and that the trial protocols for standard treatment might be so useful and effective that they are integrated into the delivery of usual care after the trial finishes.¹¹⁻¹³

Alternately, it is plausible that our findings could be a result of confounding by difficult to capture or unmeasured institutional characteristics that are tightly linked with a hospital's proclivity or ability to participate in trials. It could be that hospitals that foster and reward a culture of high-quality cardiac care (ie, large, high-volume, financially stable academic centers with cardiology training programs and capacity for revascularization) also attract and recruit the physicians who are most inclined to adopt new evidence; who are predisposed to implementing treatment protocols, decision support systems, and other interventions known to improve quality of care; who insist on thorough documentation of eligibility and contraindications data for each patient; and who willingly respond to credible audit and feedback. To the extent that we could, we adjusted for institutional characteristics that might capture some of these attributes (eg, size,

caseload, location, revascularization capacity, teaching status, and cardiologist supervised care), controlled for a host of patient-level sociodemographic and clinical variables, accounted for the potential lack of statistical independence of individual patients treated within the same hospital, and still demonstrated an independent association between hospital trial participation and outcomes. Nevertheless, the potential for confounding does exist, and we acknowledge that we did not survey all 494 hospitals to ascertain the level of penetration of various quality improvement interventions nor did we use qualitative methods to describe institutional culture.¹ This is certainly a worthwhile line of inquiry for future research, as would be determining if the trial participation effect is present for other conditions.

Some additional limitations need to be considered when interpreting our results. First, we did not have detailed hospital-level information regarding other possible mediators of a trial participation effect. For example, we do not have data regarding the amount of trial funding or additional research personnel brought in by investigators. Second, although we know that patients were enrolled in trials related to acute coronary syndromes, we do not know the specific trials in which they were involved. Third, we examined only hospitals that were volunteers in a quality improvement initiative, in and of itself a form of trial participation. CRUSADE sites were likely more highly motivated and interested in conducting research and improving quality of care than the average US hospital and might not be considered representative. This form of bias should lead to an underestimate in the magnitude of any trial participation effect (ie, hospitals that neither participate in trials nor quality improvement efforts might have even lower rates of guideline adherence and higher mortality).

In conclusion, patients treated at hospitals that participate in clinical trials seem to receive better quality of care and seem to have significantly better outcomes than patients treated at hospitals that do not participate in trials—at least in the setting of acute coronary syndrome. From the patient's perspective, even if our results are somewhat confounded, it still seems sensible to seek care at hospitals that participate in clinical trials. For policy makers and physicians, our findings should assuage some of the concerns related to the possible opportunity costs and potential downsides of participating in the clinical research enterprise.

ARTICLE INFORMATION

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