Hospital participation in clinical trials for patients with acute myocardial infarction: Results from the National Cardiovascular Data Registry

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Background Little is known about the proportion of hospitals in the United States that offer clinical trial enrollment opportunities and how patient outcomes differ between hospitals that do and do not participate in clinical trials.

Methods In the nationwide Chest Pain–MI registry, we described the proportion of hospitals that enrolled patients with acute myocardial infarction (MI) in clinical trials from 2009 to 2014. Hospital-level adherence to every eligible MI performance measure was compared between hospitals that did and did not enroll patients in clinical trials. Using linked Medicare data, we also compared 1-year major adverse cardiovascular events (MACE: death, MI, heart failure, or stroke) among patients ≥65 years old treated at trial versus nontrial hospitals.

Results Among 766 hospitals, 430 (56.1%) enrolled ≥1 MI patient in a clinical trial during the study period, but the proportion of hospitals enrolling patients in clinical trials declined from 36.8% in 2009 to 26.6% in 2014. Complete adherence to performance measures was delivered to a greater proportion of patients at trial hospitals than nontrial hospitals (72.6% vs 64.9%, $P < .001$; adjusted OR 1.07, 95% CI 1.03-1.12). One-year MACE rates were also lower for trial hospitals (adjusted HR 0.96, 95% CI 0.93-0.99).

Conclusions Hospitals are becoming less likely to engage in clinical trials for patients with MI. Patients admitted to hospitals that participated in clinical trials more often received guideline-adherent care and had better long-term outcomes. (Am Heart J 2019;214:184-93.)

Clinical trials form the foundation of evidence-based recommendations following acute myocardial infarction (MI), but low and declining rates of patient participation have led to concerns about the generalizability of study results.[1-4] Among patients hospitalized with MI between 2008 and 2011 and enrolled in a nationwide registry, only 2.8% were enrolled in a clinical trial during their index hospitalization, including only 4.2% of eligible patients.[5] Enrolled patients had lower risk-adjusted in-hospital mortality than both eligible and ineligible patients that did not enroll, highlighting differences between trial participants and nonparticipants.[5] Hospitals that enroll patients with MI in clinical trials may also differ from those that do not, but these differences have not been well described.

Much of the literature related to clinical trial participation has focused on the inconveniences faced by participants, including a long and difficult informed consent process, intensive trial-related testing, and distance traveled to attend study visits.[6,7] Similarly, many of the efforts to increase patient participation in clinical research and generalizability of study results have focused on reducing inconvenience faced by patients—video informed consent, phone- or Internet-based follow-up, follow-up through administrative data rather than by patient contact, and virtual clinical trials.[7-12] However, patients cannot participate in traditional clinical research if their provider or hospital does not participate. Lack of qualified investigators is often cited as a reason for declining clinical trial enrollment rates,[13] but there are sparse contemporary data regarding participation in

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clinical research at the hospital level. Furthermore, the effect of hospital participation in clinical research on quality of care and patient outcomes, whether or not the patient was enrolled into the trial, has not been reported.

We therefore used data from the Chest Pain–MI (CPMI) Registry, a large nationwide quality improvement registry enrolling consecutive MI patients, formerly known as the Acute Coronary Treatment and Interventions Outcome Network Registry, to examine hospital rates of participation in clinical trials enrolling MI patients and assess hospital processes and patient outcomes at hospitals that participate and do not participate in clinical trials.

Methods

Study population

The National Cardiovascular Data Registry (NCDR) CPMI Registry is a quality improvement registry that captures detailed clinical and demographic data, including in-hospital processes, outcomes, and discharge medications, about consecutive patients presenting to participating hospitals with ischemic symptoms and diagnosed with MI.[14,15] It includes a broad, nationally representative, cross section of US hospitals, including academic and nonacademic hospitals, tertiary care centers, and community hospitals, although hospitals voluntarily decide to participate. Since July 2008, it has asked whether patients were enrolled in a clinical trial during their hospitalizations. To enable tracking of long-term outcomes, CPMI Registry data for patients ≥65 years old have been linked to Centers for Medicare and Medicaid Services claims data using 5 indirect identifiers (date of birth, sex, hospital identifier, date of admission, and date of discharge).[16-18]

Of 641,666 patients with MI admitted to 838 sites from July 2008 through December 2014, we excluded patients who died within 24 hours of hospital arrival (n = 7,817), patients who were transferred out of the hospital within 24 hours of arrival (n = 12,944), patients who requested comfort care or were discharged to hospice (n = 22,205), patients who left against medical advice (n = 3,908), patients who had missing clinical trial participation status (n = 726), and patients admitted to hospitals that admitted ≤35 MI patients during the study period (n = 1,322). The final study population used to describe hospital-level participation in clinical trials enrolling MI patients and to analyze the association between admission to a hospital participating in clinical trials and in-hospital processes included 592,744 patients with MI admitted to 766 US hospitals (Figure 1).

Definitions and outcomes

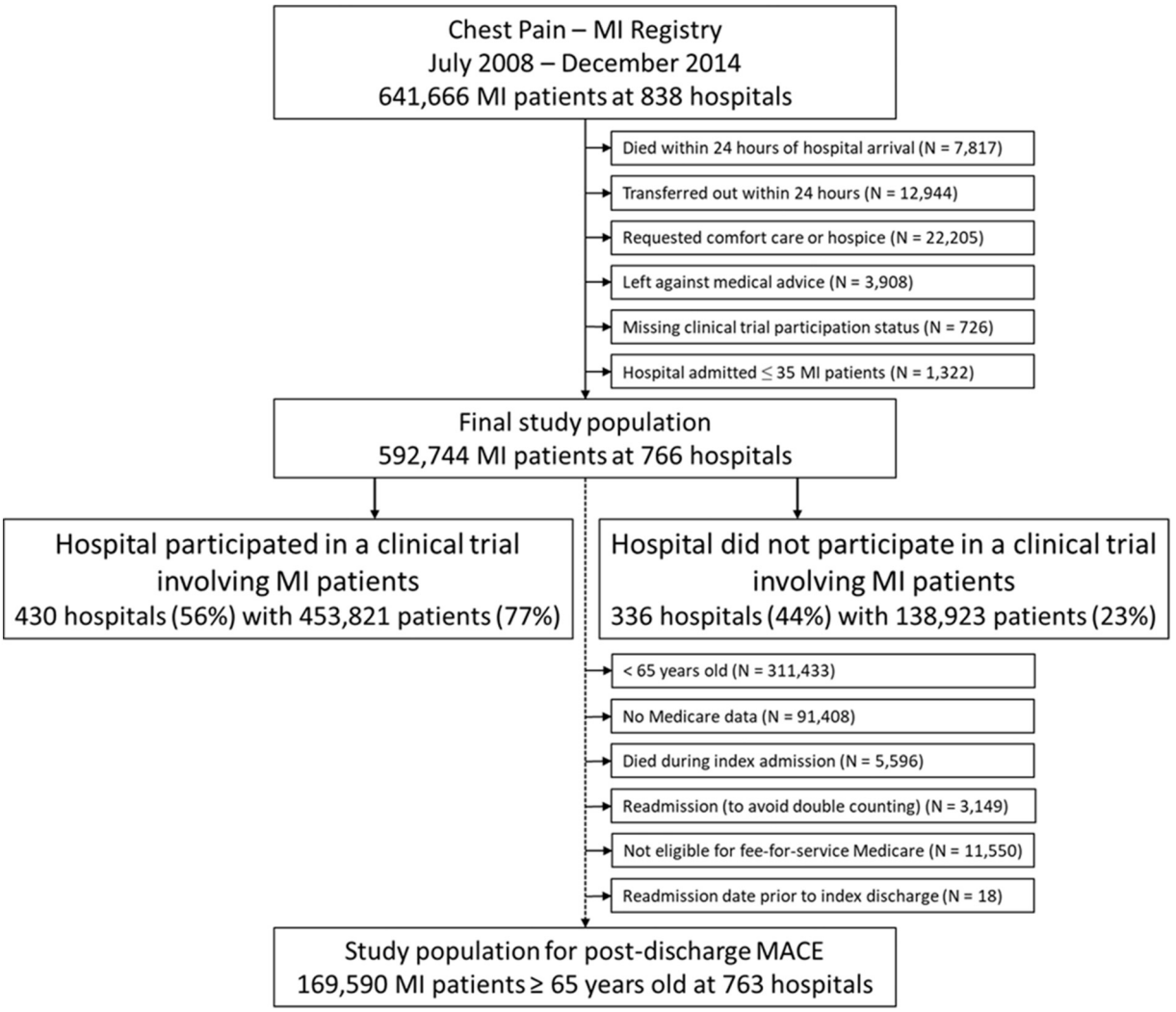
All study definitions were derived from the NCDR data dictionary. The primary exposure for this analysis was hospital participation in clinical trials involving patients with MI, which we defined as enrollment of at least 1 patient in a clinical trial during the study period (July 2008–December 2014). This definition was chosen to reflect the fact that enrolling even a single patient in a clinical trial requires establishing infrastructure supporting site-based research (regulatory approval, resources and personnel dedicated to screening and consenting patients, training of personnel in Good Clinical Practice, etc). We also calculated the percentage of patients each hospital enrolled in clinical trials over the entire study period and each year, defined as the number of patients that participated in a clinical trial divided by the total number of MI patients in the study population admitted to that hospital.

Outcomes included hospital processes of care and patient outcomes. Processes of care were specified by the "American College of Cardiology/American Heart Association 2008 Performance Measures for Adults with ST-Elevation and Non–ST-Elevation Myocardial Infarction"+ report, which was in force during the study period.[19] The document includes up to 8 measures for patients admitted with non–ST segment elevation MI (NSTEMI) (receipt of aspirin while hospitalized, assessment of left ventricular ejection fraction [LVEF] during the hospitalization, prescription of aspirin at discharge, prescription of a β-blocker at discharge, prescription of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker at discharge for patients with LVEF ≤40%, prescription of a statin at discharge, smoking cessation advice for smokers, and a cardiac rehabilitation referral) and an additional 3 measures for patients admitted with ST segment elevation MI (STEMI) (delivery of reperfusion therapy, time from arrival to fibrinolytic therapy ≤30 minutes, and time from arrival to primary percutaneous coronary intervention ≤90 minutes). The primary hospital process measure for this analysis was the proportion of patients receiving care consistent with all performance measures for which they were eligible, or "defect-free care" as defined by the NCDR and used in similar analyses of NCDR registries.[20]

Clinical outcomes of interest included 30-day and 1-year mortality, and 30-day and 1-year *major adverse cardiac events* (MACE), defined as death, readmission for heart failure, readmission for MI, or readmission for stroke. Postdischarge outcomes were measured among all patients ≥65 years old in the CPMI Registry linked to their Centers for Medicare and Medicaid Services claims data, as described in previous NCDR studies.[16-18] Reasons for readmission were determined based on *International Classification of Diseases, Ninth Revision*, codes (heart failure: 398.91, 402.01, 402.11, 402.91, 404.*x*1, 404.*x*3, 415.0, 425.*xx* 428.*xx*; MI: 410.*x*1; stroke: 430.*xx*, 431.*xx*, 432.*xx*, 433.*x*1, 434.*x*1, 436.*xx*, 437.1, 997.02).

To ensure that a change in hospital participation in clinical trials enrolling MI patients over time was not caused by a decrease in the overall number of trials enrolling MI patients, we calculated the total number of

Figure 1



Study flow.We described hospital-level participation in clinical trials involving MI patients and in-hospital processes of care among all patients participating to Chest Pain–MI Registry hospitals with MI; long-term outcomes were compared between hospitals enrolling ≥1 MI patient and those enrolling no patients among patients ≥65 years old only.

trials enrolling each year by downloading data for trials enrolling acute MI patients at ≥1 US site from clinicaltrials.gov and extracting study start and study completion dates. A trial was considered open for enrollment in a given year if study start date occurred in that year or earlier and study completion date occurred in that year or later.

Statistical analysis

The hospital-level distribution of proportion of MI patients enrolled in clinical trials was plotted as a histogram, and descriptive statistics were calculated. We repeated this process after excluding hospitals that did not enroll any MI patients in clinical trials. We then described the proportion of MI patients enrolling in clinical trials each year from 2008 to 2014 and the proportion of hospitals enrolling at least 1 MI patient in a clinical trial each year from 2009 to 2014; 2008 was excluded because our study period only included part of this year. As a sensitivity analysis, we repeated our analyses including only hospitals that participated in the CPMI Registry for the entire study period (2009-2014) to account for the fact that a decline in the proportion of hospitals participating in clinical trials could be attributed to new hospitals participating in the CPMI Registry rather than existing registry hospitals stopping participation in

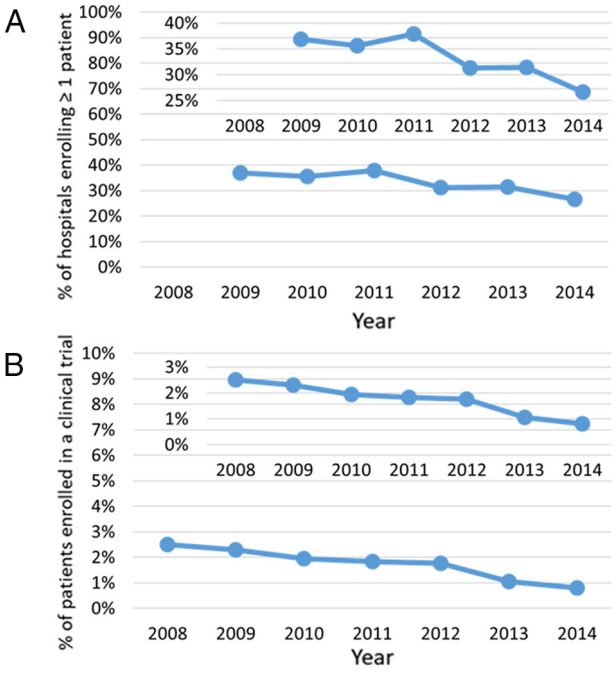
clinical trials. We used logistic generalized estimating equations regression to evaluate trends in clinical trial participation over time.

Hospital and patient characteristics, including demographics, medical history, presentation features, hospital processes of care, and in-hospital outcomes, are presented for hospitals that did and did not enroll patients in clinical trials. Categorical variables were reported as frequencies with percentages and compared using χ^2 tests, and continuous variables were reported as medians with 25th and 75th percentiles and compared using Wilcoxon rank-sum tests.

To describe the association between enrolling MI patients in clinical trials and adherence to clinical performance measures, we reported rates at which eligible patients received treatment consistent with each key performance measure at hospitals participating in clinical trials and hospitals not participating in clinical trials. We also reported median hospital rates of complete adherence to performance measures at hospitals that participated and did not participate in clinical trials. To assess differences in complete adherence to performance measures at hospitals participating in and not participating in clinical trials, accounting for patient and hospital characteristics, we created a mixed-effects logistic regression model for composite adherence, treating each measure as an opportunity for adherence and including hospital as a random effect. Covariates for adjustment included all elements of the CPMI Registry in-hospital mortality risk model, plus hospital characteristics, patient demographic characteristics, elements of the patient's medical history, presentation features, in-hospital procedures, laboratory and imaging results, and in-hospital complications, selected by expert opinion (see Supplemental Methods for a complete list of covariates).

To determine the association between admission to a hospital participating in clinical trials enrolling MI patients and long-term outcomes, we used the Medicare-linked population. Among 185,736 patients in the linked database, we excluded patients who died during the index admission (n = 5,596) or were not enrolled in Medicare Part A & B fee-for-service plans at index discharge (n = 11,550). Therefore, postdischarge outcomes were assessed in 169,590 MI patients ≥65 years old admitted to 763 hospitals. We produced Kaplan-Meier curves for MACE and Kaplan-Meier estimates for mortality. Log-rank test was used to assess whether differences between the MACE curves were statistically significant. Furthermore, the cumulative incidence (accounting for the competing risk of death) of hospitalization for MI, stroke, and heart failure over 30-day and 1-year follow-up were reported, and the Gray test was performed to compare differences between hospitals that enrolled and did not enroll patients in clinical trials.[21] To assess the risk-adjusted association between admission to a hospital participating in clinical trials and MACE, we created Cox proportional-hazards models with robust standard errors to account for clustering of patients within hospitals. Covariates for adjustment were the same as for the multivariable model assessing complete adherence to performance measures, described above and listed in Supplemental Methods.

Figure 2



Trends in clinical trial participation over time.**A**, The proportion of hospitals enrolling at least 1 MI patient in a clinical trial in each year over this time period. **B**, The proportion of patients with MI enrolled in a clinical trial from 2008 to 2014. The proportion of MI patients enrolling in a clinical trial and the proportion of hospitals participating in clinical trials involving MI patients decreased significantly over time ($P < .001$ for patients; $P = .001$ for hospitals).

We observed low rates of missing data: less than 2% for all variables. When modeling long-term mortality, missing values in continuous covariates were imputed to presentation status (STEMI/NSTEMI) and sex-specific median of the nonmissing values. For categorical variables, missing values were imputed to the most frequent group. All statistical analyses were performed by the Duke Clinical Research Institute using SAS (Cary, NC) version 9.4. The Duke University Medical Center Institutional Review Board granted a waiver of informed consent and authorization for this study. This project was supported by a grant from the Agency for Healthcare Research and Quality (U19H2O21092) to Dr Wang. Dr Fanaroff is supported by a career development grant from the American Heart Association (17FTF33661087). The authors are solely responsible for the design and conduct

Table I. Characteristics of hospitals by clinical trial enrolling status

	Clinical trial enroller (n = 430 hospitals; 56.1%)	Clinical trial nonenroller (n = 336 hospitals; 43.9%)	*P* value
Total beds	348 (217, 525)	222 (147, 336)	<.001
Region			.004
West	52 (12.1%)	73 (21.7%)	
Northeast	61 (14.2%)	41 (12.2%)	
Midwest	119 (27.7%)	76 (22.6%)	
South	198 (46.0%)	146 (43.5%)	
Rural location	71 (16.5%)	74 (22.0%)	.05
Teaching hospital*	95 (22.1%)	31 (9.2%)	<.001
Cardiac procedural availability			<.001
None	3 (0.7%)	13 (3.9%)	
Diagnostic catheterization only	1 (0.2%)	20 (6.0%)	
PCI only	69 (16.0%)	107 (31.8%)	
PCI and cardiac surgery	357 (83.0%)	196 (58.3%)	

Categorical variables presented as number (%); continuous variables presented as median (25th, 75th percentiles). *PCI*, percutaneous coronary intervention.
*Membership in the Council of Teaching Hospitals.

of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Results

Of 766 CPMI Registry hospitals, 430 (56.1%) enrolled at least 1 MI patient in a clinical trial over the course of the entire study period and were defined as hospitals participating in clinical trials involving MI patients. The proportion of hospitals that enrolled at least 1 MI patient in a clinical trial each year trended down over time, from 36.8% of hospitals in 2009 to 26.6% in 2014 (Figure 2, *A*; *P* for trend = .001). This decrease was not explained by additional hospitals joining the CPMI Registry; when limited to the 246 hospitals that participated in the CPMI Registry for all years of the study period, we saw a similar pattern: 39.4% of these hospitals enrolled at least 1 MI patient in 2009 compared with 28.1% in 2014. The decrease was also not explained by substantially fewer available trials: In clinicaltrials.gov, 156 trials were open to enrollment for patients with MI in the United States in 2009 compared with 145 in 2014 (Supplemental Table I).

Of 592,744 MI patients, 9,015 (1.5%) were enrolled in a clinical trial during their hospitalization. The annual number of MI patients enrolled increased from 606 in 2008 to 1,854 in 2012 before declining to 1,234 and 1,021 in 2013 and 2014, respectively. The proportion of MI patients enrolled in a clinical trials declined over the entire study period, from 2.5% in 2008 to 0.8% in 2014 (Figure 2, *B*; *P* for trend < .001). Among hospitals participating in clinical trials (n = 430), the median hospital enrolled 0.6% of its MI patients in a clinical trial (25th, 75th percentiles: 0.3%, 1.9%) (Supplemental Figure 1). Only 17 hospitals (4.0%) enrolled ≥10% of their MI patients into a clinical trial; >90% of hospitals enrolled <5% of MI patients in clinical trials.

Compared with hospitals that did not enroll MI patients in clinical trials, hospitals that enrolled MI patients in clinical trials were larger, more often teaching hospitals, and more often had cardiac surgery capability (Table I). By contrast, differences in patient characteristics between hospitals that did and did not enroll MI patients in clinical trials were smaller, although nominally significant because of the large number of patients included in the sample (Table II). In-hospital mortality was lower at hospitals that participated in clinical trials involving MI patients (1.8% vs 2.1%, $P < .001$).

Adherence to performance measures by clinical trial enrolling status

Patients admitted to hospitals that participated in clinical trials enrolling MI patients more often received care consistent with each of the 11 key performance measures for STEMI and 8 key performance measures for NSTEMI than those admitted to hospitals that did not participate in clinical trials enrolling MI patients. Among hospitals that participated in clinical trials involving MI patients, the median rate of complete adherence to performance measures was 72.6% (25th, 75th percentiles: 57.2%, 83.3%) compared with 64.9% (25th, 75th percentiles: 42.1%, 79.1%) among hospitals that did not participate in clinical trials involving MI patients ($P < .001$). After adjustment for hospital characteristics, baseline characteristics, and in-hospital complications, hospitals that participated in clinical trials still had significantly greater odds of achieving complete adherence to performance measures (odds ratio [OR] 1.07, 95% CI 1.03-1.12). Among individual performance measures, significant differences between groups were observed in door to needle time ≤30 minutes among STEMI patients treated with thrombolytic therapy; evaluation of LVEF prior to discharge; referral for cardiac rehabilitation; and prescription of aspirin, β-blocker, statin, and angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker at discharge (Supplemental Table II). All

Table II. Characteristics of patients admitted at hospitals that did and did not enroll patients in clinical trials

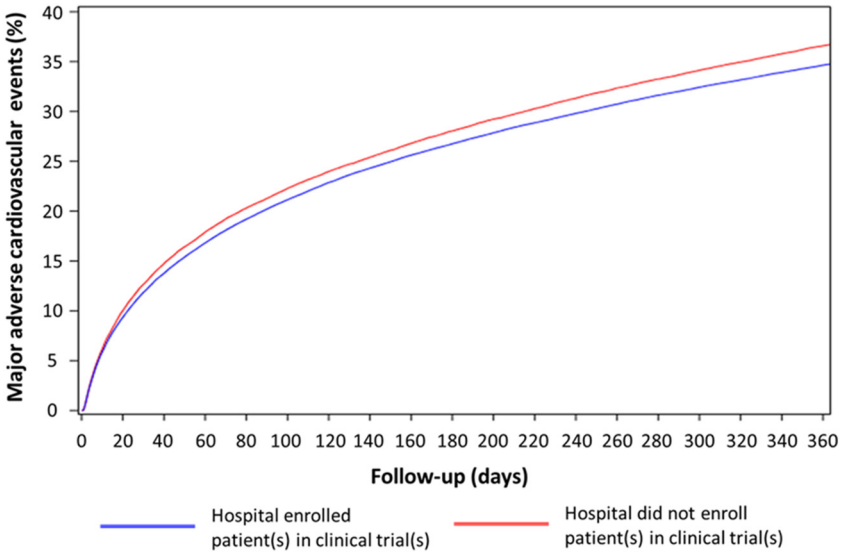
	Clinical trial enroller (n = 453,821 patients; 430 hospitals)	Clinical trial nonenroller (n = 138,923 patients; 336 hospitals)	*P* value
Demographics			
Age	64 (54, 74)	64 (54, 74)	<.001
Male sex	299,077 (65.9%)	90,804 (65.4%)	<.001
Race			<.001
White	369,055 (81.3%)	109,497 (78.8%)	
Black	50,859 (11.2%)	14,466 (10.4%)	
Asian	7070 (1.6%)	2977 (2.1%)	
Hispanic	21,268 (4.7%)	10,449 (7.5%)	
Other	3224 (0.7%)	864 (0.6%)	
Medical history			
Hypertension	330,811 (72.9%)	101,296 (72.9%)	.94
Dyslipidemia	274,750 (60.5%)	82,187 (59.2%)	<.001
Diabetes mellitus	144,721 (31.9%)	45,651 (32.9%)	<.001
Prior MI	102,625 (22.6%)	30,072 (21.6%)	<.001
Prior PCI	104,382 (23.0%)	30,920 (22.3%)	<.001
Prior CABG	58,226 (12.8%)	17,618 (12.7%)	.15
Prior revascularization	134,958 (29.7%)	40,560 (29.2%)	<.001
Prior heart failure	49,876 (11.0%)	15,679 (11.3%)	.002
Atrial fibrillation	31,501 (6.9%)	9721 (7.0%)	.49
Prior stroke	33,295 (7.3%)	9886 (7.1%)	.006
Peripheral arterial disease	41,687 (9.2%)	11,561 (8.3%)	<.001
Current/recent smoker	159,367 (35.1%)	47,766 (34.4%)	<.001
Chronic lung disease	61,939 (13.6%)	19,444 (14.0%)	.001
Currently on dialysis	9787 (2.2%)	3290 (2.4%)	<.001
Presentation details			
STEMI (vs NSTEMI)	177,460 (39.1%)	54,310 (39.1%)	.95
Symptom onset to hospital arrival (h)	2.0 (1.1, 4.7)	1.9 (1.0, 4.6)	<.001
Off-hours presentation*	286,212 (63.1%)	88,102 (63.4%)	.018
Heart failure on presentation	57,157 (12.6%)	17,194 (12.4%)	.03
Shock on presentation	14,412 (3.2%)	4207 (3.0%)	.006
Cardiac arrest on presentation	10,005 (3.2%)	3486 (3.3%)	.28
Heart rate on presentation	81 (69, 96)	82 (69, 97)	<.001
Systolic BP on presentation	146 (126, 167)	146 (125, 168)	.43
Laboratory/imaging results			
BMI (kg/m^2)	29 (25, 33)	29 (25, 33)	<.001
Initial eGFR (mL/min)†	84 (58, 113)	82 (56, 111)	<.001
Initial hemoglobin (g/dL)	14.1 (12.7, 15.3)	14.1 (12.6, 15.4)	.042
Initial troponin (× ULN)	2.0 (0.4, 13.6)	1.8 (0.4, 11.0)	<.001
Peak troponin (× ULN)	58.8 (12.0, 279.1)	49.2 (9.7, 240.7)	<.001
Left ventricular ejection fraction			<.001
Normal	250,420 (57.8%)	78,057 (59.6%)	
Mildly reduced	92,562 (21.4%)	26,975 (20.6%)	
Moderately reduced	69,422 (16.0%)	19,918 (15.2%)	
Severely reduced	19,220 (4.4%)	5579 (4.3%)	
In-hospital procedures			
Diagnostic catheterization	411,060 (90.6%)	121,899 (87.7%)	<.001
PCI	298,677 (65.8%)	88,795 (63.9%)	<.001
CABG	42,088 (9.3%)	10,754 (7.7%)	<.001
Thrombolytic therapy (among STEMI)	12,815 (19.0%)	2658 (16.2%)	<.001
Primary PCI (among STEMI)	141,891 (92.1%)	45,253 (94.1%)	<.001
Revascularization (among NSTEMI)	171,370 (62.0%)	47,491 (56.1%)	<.001
In-hospital outcomes			
Death	8202 (1.8%)	2753 (2.1%)	<.001
Reinfarction	3358 (0.8%)	978 (0.7%)	.45
Cardiogenic shock	14,826 (3.3%)	4264 (3.2%)	.019
Heart failure	22,590 (5.1%)	6026 (4.5%)	<.001
Stroke	2713 (0.6%)	745 (0.6%)	.036
Cardiac arrest	8392 (2.7%)	2956 (2.9%)	.014
Major bleeding	33,412 (7.5%)	10,218 (7.7%)	.044

Categorical variables presented as number (%); continuous variables presented as median (25th, 75th percentiles). *CABG*, coronary artery bypass graft surgery; *BP*, blood pressure; *BMI*, body mass index; *eGFR*, estimated glomerular filtration rate; *ULN*, upper limit of normal.

*Off-hours presentation defined as anytime outside 7:00 AM to 5:00 PM, Monday through Friday, and any time Saturdays, Sundays, and US holidays;

†GFR calculated using the Cockcroft-Gault formula.

Figure 3



MACE at trial hospitals and nontrial hospitals.Shown are unadjusted Kaplan-Meier curves of MACE among patients ≥65 years old discharged from hospitals participating in clinical trials enrolling MI patients versus those not participating in clinical trials enrolling MI patients. Patients discharged from hospitals that enrolled patients in clinical trials had a lower MACE rate at 1 year ($P < .001$).

differences were in favor of hospitals participating in clinical trials but were generally small (<3% difference in the proportion of patients receiving each performance measure at enrolling and nonenrolling hospitals).

Long-term outcomes by clinical trial enrolling status

Among 169,590 patients with linked long-term outcomes data, 20,250 (11.9%) had a MACE within 30 days. Patients admitted to hospitals enrolling in clinical trials involving MI patients had a 30-day MACE rate of 11.8% (95% CI 11.7%-12.0%) compared with 12.7% (95% CI 12.3%-13.0%) for patients admitted to hospitals that did not enroll MI patients in clinical trials ($P = .01$) (Figure 3). The difference in 30-day MACE persisted after adjustment for baseline characteristics, in-hospital processes, and in-hospital complications (hazard ratio [HR] 0.94, 95% CI 0.90-0.98). At 1 year, 35.3% of patients had a MACE event: 34.8% (95% CI 34.5%-35.1%) of those admitted a hospital enrolling patients in clinical trials compared with 36.8% (95% CI 36.3%-37.3%) of those admitted to a hospital that did not enroll patients in clinical trials ($P = .009$). This difference persisted after risk adjustment (HR 0.96, 95% CI 0.93-0.99).

When components of MACE were examined separately, patients admitted to hospitals that enrolled MI patients in clinical trials had lower 1-year rates of all-cause death (15.2% vs 16.4%, $P < .001$), readmission for MI (9.1% v. 9.8%, $P < .001$), and readmission for heart failure (25.1% vs 26.4%, $P < .001$). The cumulative incidence of stroke was similar between patients discharged from the 2 groups of hospitals (2.6% vs 2.7%, $P = .45$).

Discussion

Over the duration of our study, both the proportion of hospitals and the proportion of patients participating in clinical trials for patients with MI declined such that, by 2014, only 1 in 4 CPMI Registry hospitals enrolled MI patients into clinical trials. Hospitals that enrolled MI patients in clinical trials were larger, more often teaching hospitals, and more often had cardiac surgery capability than those that did not enroll patients in clinical trials, but there were no clinically significant differences in case mix at hospitals that did and did not enroll patients. Among hospitals that did participate in clinical trials, very few MI patients were enrolled in a clinical trial. Hospitals that enrolled MI patients in clinical trials more often achieved complete adherence to performance measures and had lower rates of MACE compared with nonenrolling hospitals, which persisted after adjusting for hospital and patient characteristics.

Earlier data from the CPMI Registry (from 2008 to 2011) showed that only 2.8% of MI patients were enrolled in a clinical trial.[5] Our study, including more contemporary data, now shows the proportion decreasing each year, with <1% of MI patients enrolled in a clinical trial in 2014 and 10% fewer hospitals enrolling at least 1 MI patient in a clinical trial than in 2009. This trend is disheartening, especially given recent efforts to increase the representation of "real-world" patients in clinical trials by simplifying and innovating trial designs to enhance enrollment appeal.[22-25] A key reason for the decline in trial enrollment for patients with MI may be the decline in

hospitals engaged in clinical trials enrolling these patients. The proportion of hospitals enrolling MI patients in clinical trials declined from 36.8% in 2009 to 26.6% in 2014, even among a group of hospitals that obtain regulatory approval and employ dedicated staff to enter data into a quality improvement registry. This continues a trend of declining hospital participation in clinical trials: In the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines registry, a national quality improvement registry that enrolled MI patients from 2001 to 2006, more than 70% of hospitals participated in clinical trials enrolling MI patients.[26]

During the study period, the CPMI Registry grew significantly in size and made efforts to include both large and smaller-sized hospitals to adequately reflect the diversity of hospitals treating MI patients in the United States. The downtrend in clinical trial participation was observed even when restricting analyses to hospitals participating in the CPMI Registry during the entire study period, suggesting that this downtrend was not simply a dilution of MI clinical trial participation by the addition of new hospitals to the registry. Furthermore, the downtrend in participation in clinical trials involving MI patients is unlikely to be explained by fewer opportunities to participate in clinical trials; the number of open trials in clincaltrials.gov remained relatively stable over the course of the study period, although it is possible that, with the maturity of MI research, new studies may have been less well funded or perceived by patients or investigators to be less impactful. Importantly, even at hospitals that do enroll MI patients in clinical trials, the vast majority enroll very few of their MI patients into trials.

These findings strengthen calls to make research trials more enticing to health care institutions and clinicians. More than half of principal investigators participating in an FDA-regulated drug trial never participate in another one, with the majority of these "one-and-done" investigators noting a complex contracting process and balancing trial responsibilities with clinical responsibilities as major challenges to clinical trial participation.[27] Principal investigators are often asked to assist with the patient screening process, explain trial participation to patients and their families, conduct trial-specific office visits, and participate in trial monitoring and regulatory visits, all of which disrupt workflow and take time away from increasingly busy clinical practices.[28,29] Potential investigators also report inadequate training in research methods, lack of support staff, a complex institutional review board process, and concern for disrupting their relationship with their patients as barriers to research participation.[30] At some academic medical centers, physician participation in clinical trials as a site investigator may not be adequately rewarded in the promotions and tenure process.[28,31] Although investigators perceive a number of reasons to participate in clinical research—including altruism, enhancement of reputation, ability to use (and advertise) new technologies and devices, and financial rewards in certain practice structures[32]—the falling number of hospitals participating in clinical trials involving MI patients observed in our study indicates that the perceived benefits fail to outweigh the challenges for many investigators, and suggests that innovative changes in the structure of the clinical research enterprise are needed.

Harmonizing the research oversight process can help lower the activation barrier for institutions and investigators and streamline the study initiation process.[33] Investigators and regulators have proposed the use of a single institutional review board to minimize the redundancy of multisite local reviews.[34] In similar fashion, other trial innovation efforts have experimented with standardized or simplified contracts, and research platforms linked to the electronic health record to better integrate research into clinical practice or directly approach patients.[12,13] Financial and academic rewards for institutions and investigators participating in research could include authorship opportunities on primary or secondary trial manuscripts for investigators with exemplary performance, letters of accomplishment for hospital leadership to consider in the promotion and tenure process, credit for maintenance of certification or continuing medical education, or greater disbursement of financial rewards for trial participation to individual investigators.

Our finding that hospital-level participation in clinical trials for patients with MI was associated with higher compliance with care recommendations and better long-term outcomes strengthens the argument to increase clinician participation in research. With so few patients participating in clinical trials among enrolling hospitals, improved outcomes for patients actually enrolled in trials (Hawthorne effect)[35] cannot realistically explain differences in care processes or patient outcomes between hospitals that enroll and do not enroll patients in clinical trials. By contrast, differences in quality of care, which we observed between hospitals participating and not participating in clinical trials for MI patients, have been more readily linked to differences in outcomes.[36] Although some of the observed gap in quality of care between hospitals that do and do not enroll patients in clinical trials may be explained by differences in baseline hospital and/or patient characteristics, the gap persisted after adjusting for these potential confounders. Hospital-level participation in clinical trials may be emblematic of a culture that embraces novel therapeutics, engages both clinicians and patients, and incentivizes continuous improvement in care. Clinician-investigators seeking to deliver cutting-edge care through participation in clinical

trials may be more likely to keep up to date on the latest literature and guidelines and to help their hospitals develop innovative care pathways. Learning health care systems, in which clinical trials are embedded into practice and supported by integrated information technology systems, well-organized electronic health record warehouses, and visionary leaders who recognize the value of clinical trial participation, may also have spillover benefits on quality patient care.[37] Fostering a culture of clinical research participation—for trainees by integrating site-based research skills into the training process, and established physicians through financial and/or academic incentives for research participation—may not only help answer critical questions related to patient care, it may even help foster a culture of quality care delivery.

Limitations

The CPMI Registry is a voluntary quality improvement registry, and hospitals participating may not be representative of US hospitals. Indeed, because these hospitals are more frequently teaching hospitals and employ staff dedicated to data entry, they may be more likely to have clinical research capability than nonparticipating hospitals (as they require institutional review board approval or waiver of review before contributing data to the registry).[38] They may also be hospitals that are more focused on quality of care, with higher levels of complete adherence to performance measures achieved compared with hospitals that choose not to participate in this quality improvement registry. As a result, our study may overestimate the proportion of patients and hospitals that participate in clinical trials involving MI patients at non–CPMI Registry hospitals. Alternatively, it is possible that CPMI hospitals devoted research resources to registry participation rather than clinical trial participation, which would cause this study to underestimate the proportion of patients participating in clinical trials at non–CPMI Registry hospitals. There was no independent assessment of each hospital's clinical trial participation; we derived trial participation as enrollment of at least 1 MI patient into a trial, and the registry captured consecutive patients treated at each hospital. Hospitals that never enrolled a patient included those that did not participate in any trials at all and those that participated in noncardiovascular clinical trials. We did not assess inclusion or exclusion criteria of the individual trials enrolling MI patients during the study period, and we cannot distinguish between patients eligible or ineligible for clinical trial enrollment or determine the proportion of patients enrolled among eligible patients at each hospital. We report long-term outcomes only among patients ≥65 years old; however, this cohort makes up a large and growing proportion of MI patients, and it is unlikely that the association between hospital-level clinical trial participation and outcomes would differ by age. Finally, although we attempted to address the association between guideline-adherent care and long-term outcomes and hospital participation in clinical trials enrolling MI patients by adjusting for a broad range of patient-level clinical factors, the possibility of confounding by unmeasured covariates remains.

Conclusions

Fewer US hospitals are participating in clinical trials for patients with MI over time. Most participating hospitals enrolled <1% of their MI patients into trials. Patients admitted to hospitals that participated in clinical trials involving MI patients more often received guideline-adherent care and had modestly better long-term outcomes than patients treated at nonenrolling hospitals. Innovations in trial design and conduct that enhance the appeal and ease of research participation are critically needed.

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Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.05.011.

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