Size of Anterior Wall Acute Myocardial Infarction Treated by Primary Percutaneous Coronary Intervention in United States Versus Europe/Australia Versus India (from the CRISP-AMI Randomized Controlled Trial)

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International variability in infarct size following acute anterior ST-elevation myocardial infarction without shock treated with primary percutaneous coronary intervention (PCI) has been little studied. Patients enrolled in the Counterpulsation to Reduce Infarct Size pre−PCI for Acute Myocardial Infarction international randomized trial were analyzed according to their region of enrollment: United States (US) (n = 60), Europe/Australia (EU/AU) (n = 104), or India (n = 123). Cardiac magnetic resonance imaging was performed 3−5 days after PCI to assess infarct size, expressed as percentage of left ventricular mass, and analyzed by an imaging core laboratory. The relation between infarct size and region was modelled using multivariable linear regression adjusting for time from symptom onset to first hospital contact, myocardial infarction severity, and baseline characteristics. Infarct size was 36.4% of left ventricular mass in US patients (95% confidence interval [CI] 31.5 to 41.4), 36.5% (95% CI 32.6 to 40.4) in EU/AU patients, and 44.7% (95% CI 41.1 to 48.2) in patients from India (p = 0.01). In multiplicity-adjusted regression analysis, mean infarct size in patients from India was higher than in US patients (mean difference of 8.3%; 95% CI 0.7 to 15.8; p = 0.03), and EU/AU patients (mean difference of 8.2%; 95% CI 1.6 to 14.8; p = 0.01). There was no significance difference in infarct size between patients from the EU/AU and the US (mean difference of 0.1%; 95% CI −7.5 to 7.4; p = 0.99). In conclusion, in patients with anterior ST-elevation myocardial infarction without cardiogenic shock treated with primary PCI, infarct size was larger in India compared to the United States and EU/AU, even after adjustment for performance metrics, including time to treatment, and other potential confounders. Future studies are needed to better elucidate this discrepancy. **(Am J Cardiol 2019;123:1026−1034)**

In order to improve outcomes of primary percutaneous coronary intervention (PCI) in ST-elevation myocardial infarction (STEMI), coordinated efforts have been implemented to optimize performance measures of processes of care,[1−3] and thereby reduce infarct size, a surrogate marker of adverse clinical outcomes.[3−5] Apart from delay metrics, a number of other factors affect final infarct size or prognosis, including concomitant administration of beta blockers and statins, the degree of ST-segment elevation, and angiographic thrombus burden.[6−9] The extent to which regional factors independently affect infarct size remains unexplored, mainly because this prognostically relevant outcome is not routinely collected. If region influences infarct size following primary PCI, it would have important implications for future research focusing on its determinants. The objective of this analysis was to explore the regional variability in infarct size in patients presenting with acute anterior STEMI without shock treated with primary PCI, in the Counterpulsation to Reduce Infarct Size pre−PCI for Acute Myocardial Infarction trial conducted on four continents.

Methods

The Counterpulsation to Reduce Infarct Size pre−PCI for Acute Myocardial Infarction study was an open-label,

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international, multicenter randomized trial conducted from June 2009 to February 2011 at 30 centers in the United States, Europe, India, and Australia. Trial coordination, data management, and statistical analyses were carried out by the Duke Clinical Research Institute (Durham, North Carolina), with oversight from the steering committee. Local ethics committees and institutional review boards approved the study, and all patients provided written informed consent. The trial was registered with ClinicalTrials.gov (NCT00833612). The methods and main results have been published previously.[10,11] Briefly, adult patients with an acute anterior STEMI without cardiogenic shock presenting within 6 hours of ischemic symptoms, and for whom a primary PCI was planned, were randomized (regionally stratified) to intra-aortic balloon counterpulsation (IABC) implantation followed by PCI, versus PCI alone. Key exclusion criteria were previous myocardial infarction (MI), coronary artery bypass graft, inability to undergo IABC, or recent fibrinolysis. Only sites with a proved sustained capability of median door-to-device time <90 minutes were selected for participation in the study. The primary end point of the study was infarct size, expressed as percentage of total left ventricular (LV) mass as measured by cardiac magnetic resonance (CMR) 3−5 days following PCI. Secondary end points included microvascular obstruction (percentage of LV mass), myocardial salvage index (MSI) ([area at risk − infarct size]/area at risk), LV ejection fraction (LVEF) (%), LV end-systolic volume (LVESV) (mL), and LV end-diastolic volume (LVEDV) (mL). CMR protocols for this study have been described previously,[9−11] and a central laboratory at the University of Leipzig Heart Center (Leipzig, Germany) performed blinded assessment of LV parameters, quality assessment on images, and qualified the sites. Process of care time delay metrics including symptom onset to first hospital contact, hospital contact to vascular access, hospital to first device (door-to-balloon time), and symptom onset to device (total ischemic time) were recorded. For this analysis, exploratory clinical outcomes included 2 major adverse cardiovascular event (MACE) composites, evaluated through 6 months postbaseline. MACE-1 (ischemic clinical end point) included all-cause mortality, stroke, or recurrent MI. MACE-2 (heart failure clinical end point) included all-cause mortality, shock, or new or worsening heart failure. In 2014, a study was initiated to retrospectively collect longer term (up to 5 years) follow-up on the original trial participants for clinical events that occurred after study completion. Using the data from the extension study, all-cause mortality at 5 years was analyzed and reported.

For the purpose of this analysis, patients were categorized into 3 groups according to the regions where they were enrolled: US, Europe/Australia (EU/AU), or India (Supplemental Table 1). Patients from Australia and Europe were combined because only 4 patients were randomized in the former country and acute MI management is similar in these 2 regions. Analyses were performed on patients in the modified intention to treat cohort, which includes all the randomized patients who underwent CMR after PCI. Categorical variables were summarized with frequencies and percentages, and continuous variables were summarized with medians and interquartile ranges. Comparisons of baseline and procedural characteristics between regions were performed with Fisher's exact and Chi-square tests, and Kruskal-Wallis tests were used to compare the distribution of continuous variables across regions. Linear regression models were fit to model the association between infarct size and region in the univariable and multivariable analyses. Six variables were selected a priori based on clinical judgement to be forced into the multivariable model and additional adjustment variables were candidates for inclusion based on a significant univariable association with infarct size (see Supplemental Table 2). Mean infarct sizes by region were calculated using least-square mean estimates. A 2-way ANOVA model with flexible variance by subgroup was fit to examine regional differences in infarct size by ST-segment elevation. Univariable and multivariable generalized linear models were also fit to assess regional differences in the secondary MRI end points. The treatment effect (IABC + PCI vs PCI alone) on infarct size was estimated by region using a 2-way ANOVA model allowing for differing variance by subgroup, with the Satterthwaite method applied to estimate 95% confidence interval (CI). A p value for the Type 3 test of the interaction between treatment and region was calculated using this model. Kaplan-Meier (KM) estimates of the cumulative incidence of cardiovascular outcomes mortality through were determined by region, and regional differences were assessed with a log-rank test. A 2-sided p value ≤ 0.05 was considered statistically significant through all the analyses. No penalty for multiple analyses was implemented, given the exploratory nature of the project. Analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina).

Results

Among the 337 patients randomized in the trial, 73 (21.7%) were enrolled in the United States, 124 (36.8%) in EU/AU, and 140 (41.5%) in India. The number of patients who underwent CMR for the evaluation of the primary end point and who were included in the modified intention to treat cohort were respectively 60/73 (82.2%), 104/124 (83.9%), and 123/140 (94.3%). The CONSORT flowchart of study participants, stratified by regions, is presented in Figure 1. Baseline and procedural characteristics of the participants, stratified by regions, are shown in Tables 1 and 2, respectively. A number of factors were distributed differently across regions, including smoking and dyslipidemia, for which the lower rates were observed in India. The proximal left anterior descending (LAD) coronary artery was the culprit in >95% of patients in each group. The distributions of time delay metrics were significantly different across regions, including time from symptom onset to hospital contact ($p = 0.01$), hospital contact to vascular access ($p < 0.001$), hospital to first device ($p < 0.001$), and symptom onset to first device ($p < 0.001$; Figure 2). Regional distributions of infarct size did not differ significantly by baseline ST-segment elevation (<6 mm or ≥6 mm) ($p = 0.75$; Figure 3).

Unadjusted and adjusted means of infarct size were significantly different across regions overall (Table 3). After

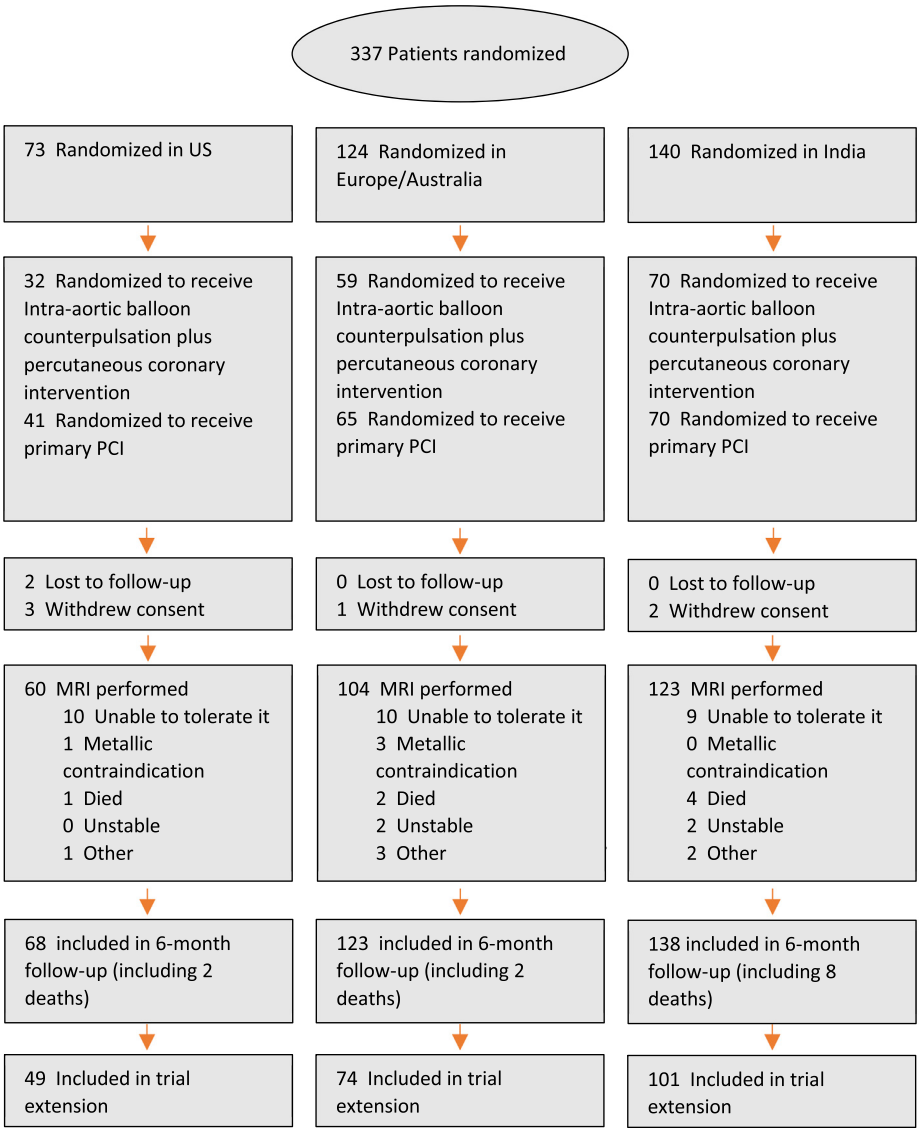


Figure 1. CONSORT flowchart of study participants.

multivariable adjustment, the differences in adjusted means infarct size was 8.3% greater in India versus the United States (95% CI 0.7 to 15.8, p = 0.03) and 8.2% greater in India versus EU/AU (95% CI 1.6 to 14.8, p = 0.01). There was no difference in infarct size between the EU/AU and the United States (0.1%; 95% CI −7.4 to 7.5; p = 0.99). Unadjusted and adjusted means of microvascular obstruction, MSI, LVEF, LVESV, and LVEDV are also shown in Table 3. After adjustment, there was a significant overall regional difference in LVEF, LVESV, and LVEDV but not in microvascular obstruction and MSI. Pairwise differences between the United States and India, and EU/AU and India, were significant in LVEF, LVESV, and LVEDV (all $p < 0.01$). There was no significant interaction between region and treatment assignment (IABC vs no IABC) for infarct size (p = 0.58). In all regions, the IABC randomization did not significantly affect infarct size compared to standard of care (US: +1.3% [95% CI −9.3, 12.0%]; EU/AU: +2.4% [95% CI −5.5, 10.2%]; India: +6.9% [95% CI −0.1, 13.9%]).

The KM estimates for the clinical end points at 6 months are provided in Figure 4. There was no statistically significant difference in 6-month clinical outcomes between the regions (p = 0.48 for ischemic end point; p = 0.90 for the heart failure end point). In the extension cohort of the trial, median follow-up postbaseline for all-cause mortality was 4.04 years (interquartile ranges 0.51 to 4.39). Over 5 years of follow-up postbaseline there was a significant difference in the rate of all-cause mortality between regions (p = 0.01) with higher mortality in patients enrolled in India (Figure 4c).

Discussion

In patients presenting with an acute anterior STEMI without cardiogenic shock, we presented a descriptive

Table 1
Baseline characteristics by region

Variables	United States (N = 73)	Europe/Australia (N = 124)	India (N = 140)	p Value
Age (years)	57 (49, 66)	61 (51, 70)	53 (46, 61)	<0.0001
Men	56 (76.7%)	100 (80.6%)	120 (85.7%)	0.24
American Indian/Alaska Native	1 (1.4%)	0 (0.0%)	0 (0.0%)	<0.0001
Asian	4 (5.5%)	8 (6.5%)	140 (100.0%)	
Black	15 (20.5%)	1 (0.8%)	0 (0.0%)	
White	48 (65.8%)	113 (91.1%)	0 (0.0%)	
Other	5 (6.8%)	2 (1.6%)	0 (0.0%)	
Height (cm)	173 (165, 180)	175 (168, 179)	167 (161, 170)	<0.0001
Weight (kg)	86 (68, 96)	83 (71, 90)	70 (62, 75)	<0.0001
Body mass index (kg/m^2)	28 (25, 32)	27 (25, 29)	25 (23, 27)	<0.0001
Prior PCI	4 (5.5%)	1 (0.8%)	0 (0.0%)	0.004
Hypertension (receiving drug therapy)	23 (31.5%)	39 (31.5%)	37 (26.4%)	0.61
Stroke	1 (1.4%)	0 (0.0%)	0 (0.0%)	0.21
Trans ischemic attack	1 (1.4%)	0 (0.0%)	0 (0.0%)	0.22
Current smoker	31 (42.5%)	49 (39.8%)	27 (19.3%)	0.0002
Dyslipidemia (receiving drug therapy)	14 (19.2%)	28 (22.8%)	0 (0.0%)	<0.0001
Prior atrial fibrillation	2 (2.7%)	2 (1.6%)	0 (0.0%)	0.120
Renal insufficiency	3 (4.1%)	3 (2.4%)	0 (0.0%)	0.047
Diabetes mellitus	13 (17.8%)	16 (12.9%)	34 (24.3%)	0.06
Insulin dependent	3 (23.1%)	2 (12.5%)	2 (5.9%)	
Noninsulin dependent	10 (76.9%)	14 (87.5%)	32 (94.1%)	
Prior peripheral arterial disease	0 (0.0%)	1 (0.8%)	0 (0.0%)	0.59
Presenting systolic blood pressure (mm Hg)	138 (123, 160)	136 (120, 155)	130 (110, 140)	0.002
Presenting diastolic blood pressure (mm Hg)	84 (76, 96)	80 (71, 95)	80 (70, 90)	0.17
Heart rate (bpm)	82 (70, 95)	77 (64, 88)	85 (75, 98)	0.0002
Degree of ST elevation in anterior leads (mm)				<0.0001
<6	40 (54.8%)	32 (25.8%)	64 (45.7%)	
≥6	33 (45.2%)	92 (74.2%)	76 (54.3%)	

Summary statistics: median, (Q1,Q3) for continuous variables, n (%) for categorical.
PCI = percutaneous coronary intervention.
+ Stenosis may occur in more than 1 location in infarct-related artery.

analysis of the interplay between region of enrollment and infarct size, a prognostically relevant metric associated with mortality and heart failure hospitalizations.[5] In this study, regional units were not used to assess ethnic differences, but rather as an integrative composite of the systems, cultural, biological, and behavioral components encompassed by different jurisdictions. The main finding is that infarct size is significantly higher in India compared to the United States and EU/AU, even after adjusting for baseline differences in factors known to affect infarct size, including time from symptom onset to hospital contact, markers of myocardial infarction severity, and periprocedural beta blockers and statins.[12,13] The second observation is that the neutral treatment effect of IABC in addition to the standard-of-care in this trial is consistent across the regions of enrollment, as evidenced by the absence of a significant. Since this metric is a strong independent marker of adverse prognosis, and has been advocated as a surrogate marker of clinical end points,[5] understanding the regional variability in the percentage of infarcted LV mass following primary PCI is important to understand for the design of international STEMI trials. Our data suggest that other factors may contribute to discrepancies in average infarct sizes across regions. Since only sites with a demonstrated track record of median door-to-device time <90 minutes were included in the study, the exclusive involvement of these high-quality sites gives credence to factors other than time delay metrics play a role in the observed regional differences in infarct size. Our findings highlight future investigators designing multinational STEMI trials will need to account for the distribution of end point measures such as infarct size can differ according to the proportion of patients enrolled in participating regions. Accounting for such regional heterogeneity in the sample size estimation, and stratifying randomization by regions, may be necessary to control for biases due to regional differences, in order to estimate the region-specific magnitude of the treatment effects.

The younger age, in addition to the lower baseline comorbidity burden observed in participants enrolled in India (with the exclusion of diabetes), mirrors the previously described disparities in characteristics of STEMI patients in this country compared to the Western regions.[3] In this context, the findings that infarct size is larger in participants enrolled in India, both before and after multivariable adjustment, is of interest as the PCI procedural success was similar to the United States and EU/AU. Discrepancies between regions regarding the early periprocedural care unaccounted for in the model might explain some of these differences in infarct size, but most of the interventions known to improve short-term (3 to 5 days) outcomes were accounted for in the adjusted model.[6,14] Our analysis thus

Table 2
Procedural characteristics by region

	Unites States (N = 73)	Europe/Australia (N = 124)	India (N = 140)	p Value
Randomized reatment, n (%)				0.69
IABC	32 (43.8%)	59 (47.6%)	70 (50.0%)	
Non-IABC	41 (56.2%)	65 (52.4%)	70 (50.0%)	
PCI performed	68 (94.4%)	117 (94.4%)	132 (94.3%)	0.99
PCI not performed	4 (5.6%)	7 (5.6%)	8 (5.7%)	
CABG instead	1 (1.4%)	0 (0.0%)	5 (3.6%)	
No infarct artery identified	2 (2.8%)	5 (4.0%)	0 (0.0%)	
Technical limitations	1 (1.4%)	2 (1.6%)	3 (2.1%)	
Infarct-related artery				0.02
Left main	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Left anterior descending	69 (95.8%)	119 (96.0%)	140 (100.0%)	
Left circumflex	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Right	1 (1.4%)	0 (0.0%)	0 (0.0%)	
None identified	2 (2.8%)	5 (4.0%)	0 (0.0%)	
Infarct-related artery stenosis locations[+]				
Proximal	39 (55.7%)	68 (57.1%)	100 (71.4%)	0.02
Mid	37 (52.9%)	59 (49.6%)	36 (25.7%)	<0.0001
Distal	5 (7.1%)	7 (5.9%)	7 (5.0%)	0.82
Infarct-related artery TIMI flow, n (%)				
Preintervention grade, n (%)				0.02
0	40 (57.1%)	75 (63.0%)	100 (71.4%)	
1	6 (8.6%)	11 (9.2%)	17 (12.1%)	
2	15 (21.4%)	16 (13.4%)	19 (13.6%)	
3	9 (12.9%)	17 (14.3%)	4 (2.9%)	
Postintervention grade, n (%)				0.57
0	1 (1.4%)	3 (2.5%)	1 (0.7%)	
1	2 (2.9%)	3 (2.5%)	1 (0.7%)	
2	2 (2.9%)	4 (3.4%)	2 (1.5%)	
3	65 (92.9%)	108 (91.5%)	133 (97.1%)	
First device used on infarct-related artery				<0.0001
Atherectomy/thrombectomy	32 (47.1%)	49 (41.9%)	34 (25.6%)	
Balloon	35 (51.5%)	53 (45.3%)	64 (48.1%)	
Direct stent	1 (1.5%)	15 (12.8%)	35 (26.3%)	
stent	65 (95.6%)	115 (98.3%)	129 (96.3%)	0.49
Drug-eluting stent	33 (48.5%)	70 (59.8%)	46 (34.3%)	0.0003
Bare-metal stent	33 (48.5%)	48 (41.0%)	84 (62.7%)	0.002
Anticoagulant use				
Unfractionated heparin	44 (61.1%)	83 (66.9%)	134 (95.7%)	<0.0001
Bivalirudin	25 (34.7%)	32 (25.8%)	0 (0.0%)	<0.0001
Glycoprotein IIb/IIIa inhibitor	26 (36.1%)	60 (48.4%)	68 (48.6%)	0.18

Summary statistics: median, (Q1,Q3) for continuous variables, n (%) for categorical.
CABG = coronary artery bypass graft; IABC = intra-aortic balloon counterpulsation; PCI = percutaneous coronary intervention.

suggests that even although participants from India were younger and had in general a lower co-morbidity burden, their estimated infarct size was larger for equivalent time from symptom onset to hospital contact, clinical severity of MI, as well as the use of procedural pharmacotherapy known to improve prognosis (beta blockers and statins).[6,7] Region-specific unaccounted for confounding factors might be responsible for the observed differences in infarct size.

Our findings also suggest that LVEF is worse in India compared to the United States and EU/AU after multivariable adjustment, mirroring the infarct size, with an absolute difference of LVEF of >5% between India and the 2 other regions. As a marker of adverse long-term prognosis following STEMI,[15] this observation is of particular interest from a population health perspective, and is aligned with the higher long-term mortality in India in the extension cohort. However, our study does not permit to decipher the underlying causes of this regional variability. Our study does not allow to associate directly the higher long-term mortality observed in India to the larger infarct size in this population, since many longitudinal confounders, such as medication adherence and different atherosclerotic burden. As a post hoc exploratory end point, the 5-year survival analysis can only be viewed as hypothesis generating.

This analysis has several limitations. First, as a post hoc analysis of a randomized trial, all findings are considered exploratory. Second, although randomization was stratified by region, the study was not powered to detect significant differences in treatment effects of IABC on clinical end points between regions. Third, in each region, the sites were chosen on the basis of evidence of high-quality rapid reperfusion and required a median door-to-balloon <90 minutes. As a consequence, the reported results might not reflect the "real-world" performance of all the primary PCI

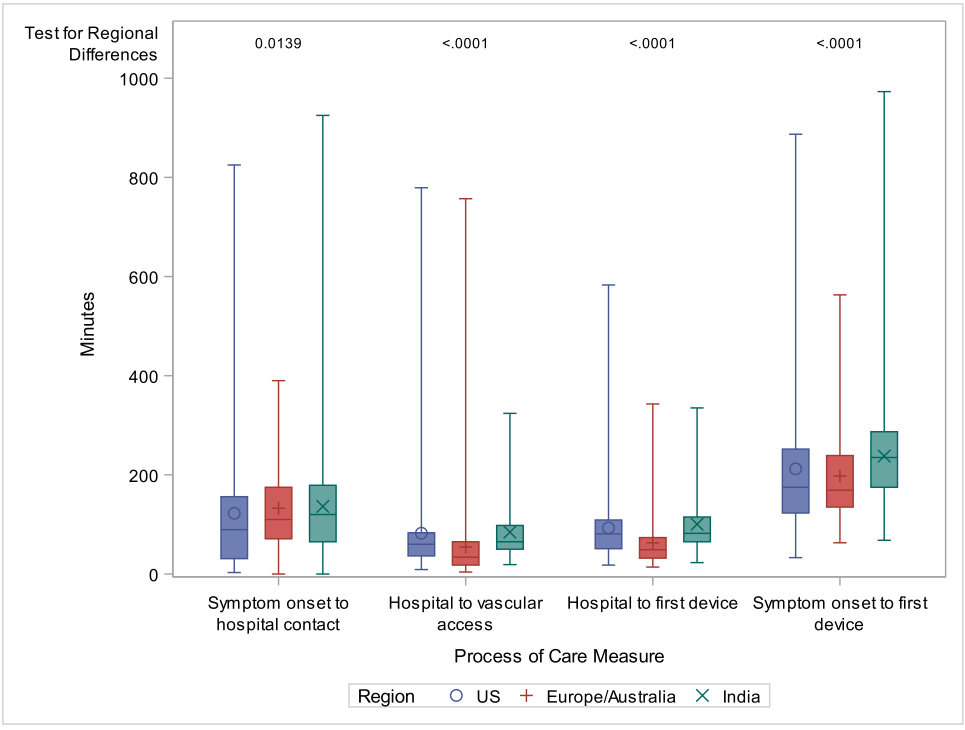


Figure 2. Process of care measures by regions.

facilities in each respective region. Fourth, we chose the covariates to include in the model based on their availability and their potential to confound the association between region and outcomes, but unknown intangible region- or race-specific confounders might exist, such as genetic variations, epigenetics, environmental and cultural factors, or disparities in periprocedural managements across regions.[16] Finally the sample size in each region in this study is small

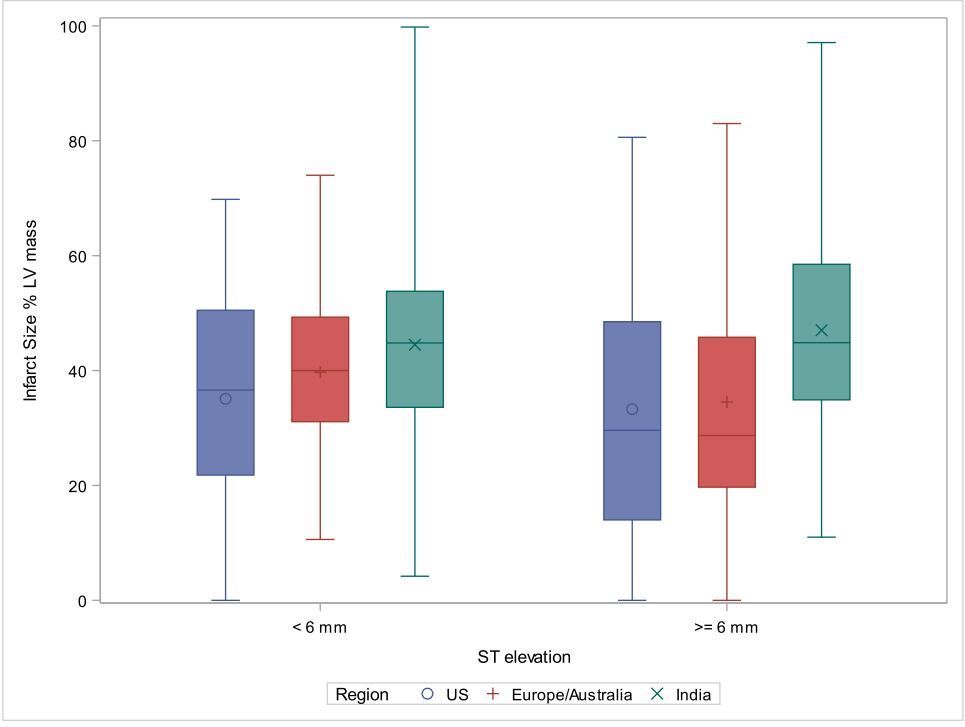


Figure 3. Regional distribution of infarct size by degree of ST-elevation.

Table 3
Unadjusted and adjusted cardiac magnetic resonance findings stratified by region

CMR finding	Analysis	Mean (95% CI) by region			p Value
		United States	Europe/Australia	India	
Infarct size, %	Unadjusted	34.24 (29.20, 39.29)	35.83 (31.99, 39.68)	45.84 (42.28, 49.39)	<0.0001
	Adjusted*	36.42 (31.47, 41.37)	36.49 (32.62, 40.36)	44.69 (41.14, 48.23)	0.006
MVO, %	Unadjusted	3.14 (2.11, 4.67)	4.49 (3.41, 5.91)	6.31 (5.00, 7.95)	0.008
	Adjusted*	2.27 (1.45, 3.56)	2.63 (1.81, 3.82)	3.39 (2.38, 4.82)	0.18
LVEF, %	Unadjusted	51.19 (48.02, 54.36)	50.19 (47.81, 52.58)	42.69 (40.47, 44.90)	<0.0001
	Adjusted*	52.23 (48.71, 55.75)	51.44 (48.61, 54.27)	45.82 (42.93, 48.72)	0.001
LVESV, mL	Unadjusted	74.28 (66.72, 82.70)	86.46 (80.66, 92.68)	61.89 (56.57, 67.72)	<0.0001
	Adjusted*	70.85 (62.82, 79.91)	80.53 (73.59, 88.12)	55.11 (49.09, 61.87)	<0.0001
LVEDV, mL	Unadjusted	148.79 (139.43, 158.15)	166.74 (159.69, 173.79)	106.88 (100.35, 113.41)	<0.0001
	Adjusted*	148.27 (137.60, 158.94)	162.96 (154.38, 171.55)	101.63 (92.86, 110.40)	<0.0001
Salvage index	Unadjusted	0.40 (0.34, 0.48)	0.37 (0.33, 0.43)	0.29 (0.25, 0.34)	0.01
	Adjusted*	0.43 (0.36, 0.51)	0.41 (0.35, 0.47)	0.35 (0.29, 0.41)	0.15

CI = confidence interval; CMR = cardiac magnetic resonance; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left-ventricular end-systolic volume; MVO = microvascular obstruction.

* The model was adjusted for time from symptom onset to first hospital contact, ST-elevation preprocedure (<6 mm vs ≥6 mm), TIMI flow preprocedure, periprocedure statins, periprocedure beta blockers, and proximal left anterior descending as the infarct-related artery.

and may be subject to variation, so the findings should be regarded as hypothesis generating and should be confirmed by larger studies.

In conclusion, in patients with anterior STEMI without cardiogenic shock treated with primary PCI, infarct size is larger in India compared with the United States and EU/AU, even after controlling for time from symptom onset to first hospital contact, severity of MI, and peri-MI administration of beta blockers and statins. In addition, despite this regional variation in the magnitude of infarct size, there is no interaction between the effect of IABC and the region of enrollment. Future studies will be required to understand the factors underlying the regional variability in infarct size. Our analysis could however be helpful to inform the design and analysis of future STEMI trials planning to enroll patients on a multinational scale.

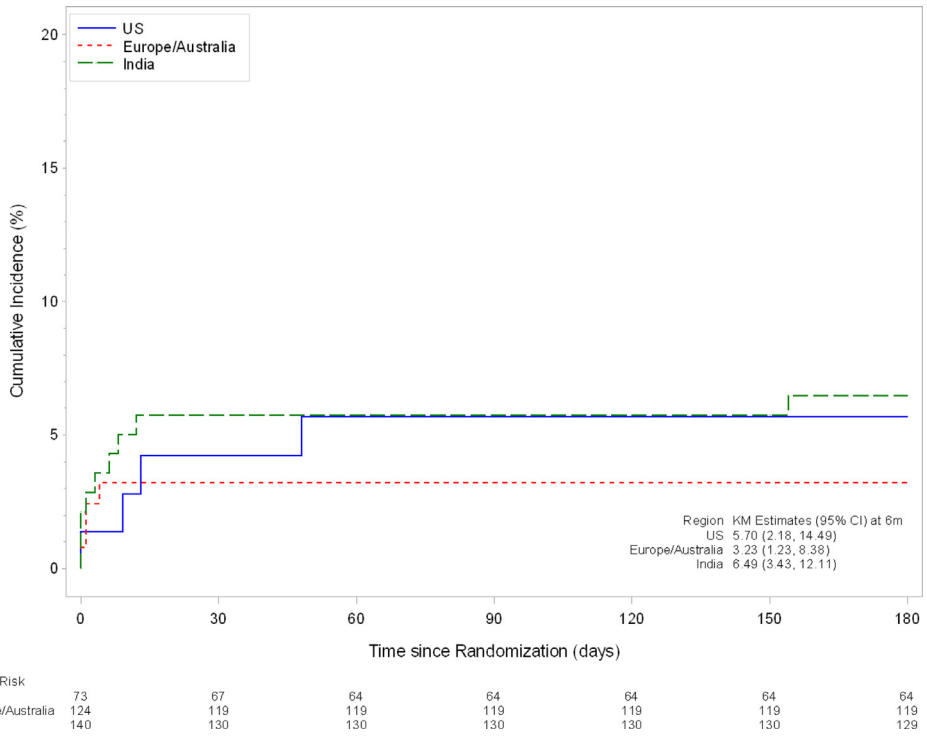
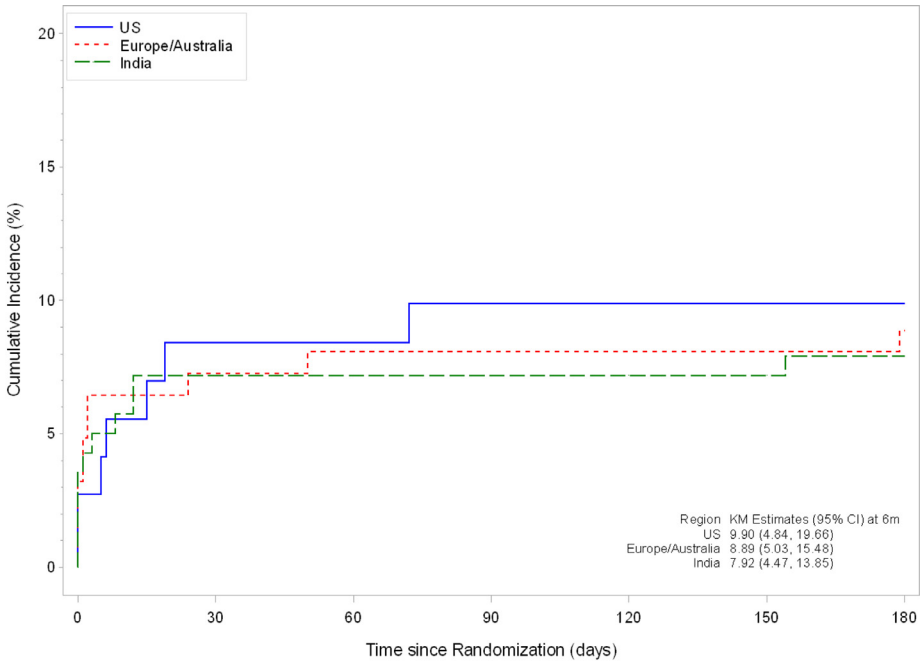


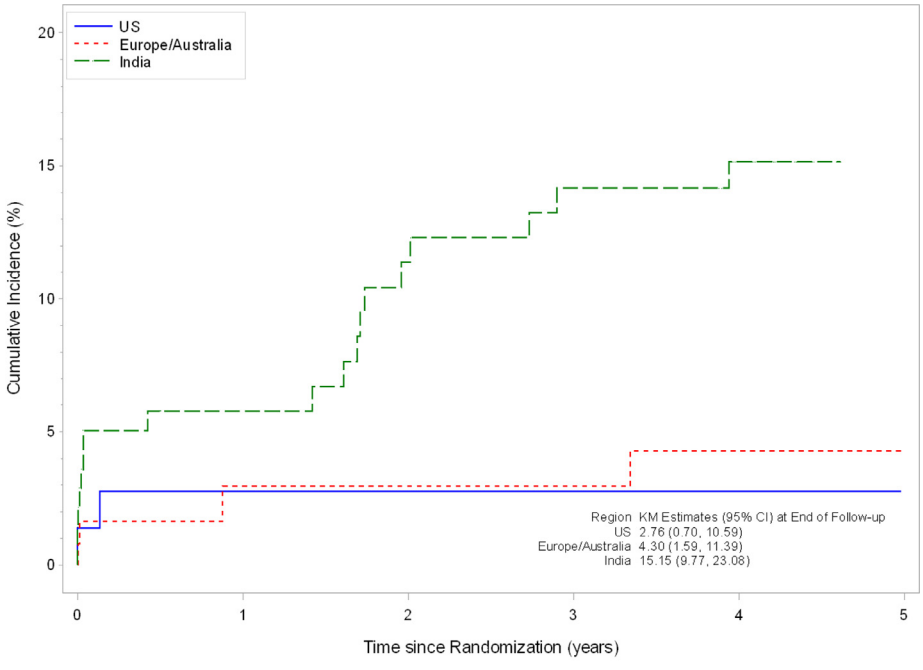
Figure 4a. Kaplan-Meier estimates for composite of death, stroke, or recurrent myocardial infarction through 6 months.



No. At Risk

US	73	64	62	61	61	61	61
Europe/Australia	124	114	113	113	113	113	112
India	140	128	128	128	128	128	127

Figure 4b. Kaplan-Meier estimates for composite of death, new congestive heart failure, or shock through 6 months.



No. At Risk

US	73	49	49	49	43	6
Europe/Australia	124	73	73	72	67	6
India	140	101	95	92	77	0

Figure 4c. Kaplan-Meier estimates for death through 5 years in the extension cohort.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.12.027.

1. Jollis JG, Al-Khalidi HR, Roettig ML, Berger PB, Corbett CC, Doerfler SM, Fordyce CB, Henry TD, Hollowell L, Magdon-Ismail Z, Kochar A, McCarthy JJ, Monk L, O'Brien P, Rea TD, Shavadia J, Tamis-Holland J, Wilson BH, Ziada KM, Granger CB. Impact of regionalization of ST-segment-elevation myocardial infarction care on treatment times and outcomes for emergency medical services-transported patients presenting to hospitals with percutaneous coronary intervention: mission: lifeline accelerator-2. *Circulation* 2018;137:376–387.
2. Bagai A, Jollis JG, Dauerman HL, Peng SA, Rokos IC, Bates ER, French WJ, Granger CB, Roe MT. Emergency department bypass for ST-Segment-elevation myocardial infarction patients identified with a prehospital electrocardiogram: a report from the American Heart Association Mission: lifeline program. *Circulation* 2013;128:352–359.
3. Rossello X, Huo Y, Pocock S, Van de Werf F, Chin CT, Danchin N, Lee SW, Medina J, Vega A, Bueno H. Global geographical variations in ST-segment elevation myocardial infarction management and post-discharge mortality. *Int J Cardiol* 2017;245(27-34).
4. Alexander T, Mullasari AS, Joseph G, Kannan K, Veerasekar G, Victor SM, Ayers C, Thomson VS, Subban V, Gnanaraj JP, Narula J, Kumbhani DJ, Nallamothu BK. A system of care for patients with ST-segment elevation myocardial infarction in India: The Tamil Nadu-ST-segment elevation myocardial infarction program. *JAMA Cardiol* 2017;2:498–505.
5. Stone GW, Selker HP, Thiele H, Patel MR, Udelson JE, Ohman EM, Maehara A, Eitel I, Granger CB, Jenkins PL, Nichols M, Ben-Yehuda O. Relationship between infarct size and outcomes following primary PCI: patient-level analysis from 10 randomized trials. *J Am Coll Cardiol* 2016;67:1674–1683.
6. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr., Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;61:e78–e140.
7. Patti G, Cannon CP, Murphy SA, Mega S, Pasceri V, Briguori C, Colombo A, Yun KH, Jeong MH, Kim JS, Choi D, Bozbas H, Kinoshita M, Fukuda K, Jia XW, Hara H, Cay S, Di Sciascio G. Clinical benefit of statin pretreatment in patients undergoing percutaneous coronary intervention: a collaborative patient-level meta-analysis of 13 randomized studies. *Circulation* 2011;123:1622–1632.
8. Birnbaum Y, Drew BJ. The electrocardiogram in ST elevation acute myocardial infarction: correlation with coronary anatomy and prognosis. *Postgrad Med J* 2003;79:490–504.
9. Vemulapalli S, Zhou Y, Gutberlet M, Kumar AS, Mills JS, Blaxill J, Smalling R, Ohman EM, Patel MR. Importance of total ischemic time and preprocedural infarct-related artery blood flow in predicting infarct size in patients with anterior wall myocardial infarction (from the CRISP-AMI Trial). *Am J Cardiol* 2013;112:911–917.
10. Patel MR, Smalling RW, Thiele H, Barnhart HX, Zhou Y, Chandra P, Chew D, Cohen M, French J, Perera D, Ohman EM. Intra-aortic balloon counterpulsation and infarct size in patients with acute anterior myocardial infarction without shock: the CRISP AMI randomized trial. *JAMA* 2011;306:1329–1337.
11. Patel MR, Thiele H, Smalling RW, Chandra P, Zhou Y, Cohen M, Perera D, Ohman EM. A multicenter, randomized, controlled study of mechanical left ventricular unloading with counterpulsation to reduce infarct size prepercutaneous coronary intervention for acute myocardial infarction: rationale and design of the Counterpulsation Reduces Infarct Size Acute Myocardial Infarction trial. *Am Heart J* 2011;162:47–55.
12. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation* 2004;109:1223–1225.
13. McNamara RL, Wang Y, Herrin J, Curtis JP, Bradley EH, Magid DJ, Peterson ED, Blaney M, Frederick PD, Krumholz HM. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2006;47:2180–2186.
14. Nallamothu BK, Normand SL, Wang Y, Hofer TP, Brush JE Jr., Messenger JC, Bradley EH, Rumsfeld JS, Krumholz HM. Relation between door-to-balloon times and mortality after primary percutaneous coronary intervention over time: a retrospective study. *Lancet* 2015;385:1114–1122.
15. Meta-analysis Global Group in Chronic Heart Failure. The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J* 2012;33:1750–1757.
16. Al Rifaia M, Cainzos-Achiricaa M, Kanayae AM, Kandulaf NR, Dardardia Z, Joshia PH, Patela J, Budoffj M, Yeboahk J, Guallarl E, Blumenthala RS, Blaha MJ. Discordance between 10-year cardiovascular risk estimates using the ACC/ AHA 2013 estimator and coronary artery calcium in individuals from 5 racial/ethnic groups: comparing MASALA and MESA. *Atherosclerosis* 2018. https://doi.org/10.1016/j.atherosclerosis.2018.09.015. Epub ahead of print.