ONLINE FIRST

Intra-aortic Balloon Counterpulsation and Infarct Size in Patients With Acute Anterior Myocardial Infarction Without Shock

The CRISP AMI Randomized Trial

Manesh R. Patel, MD
Richard W. Smalling, MD, PhD
Holger Thiele, MD
Huiman X. Barnhart, PhD
Yi Zhou, PhD
Praveen Chandra, MD
Derek Chew, MD
Marc Cohen, MD
John French, MBChB, PhD
Divaka Perera, MD
E. Magnus Ohman, MD

Context Intra-aortic balloon counterpulsation (IABC) is an adjunct to revascularization in patients with cardiogenic shock and reduces infarct size when placed prior to reperfusion in animal models.

Objective To determine if routine IABC placement prior to reperfusion in patients with anterior ST-segment elevation myocardial infarction (STEMI) without shock reduces myocardial infarct size.

Design, Setting, and Patients An open, multicenter, randomized controlled trial, the Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction (CRISP AMI) included 337 patients with acute anterior STEMI but without cardiogenic shock at 30 sites in 9 countries from June 2009 through February 2011.

Intervention Initiation of IABC before primary percutaneous coronary intervention (PCI) and continuation for at least 12 hours (IABC plus PCI) vs primary PCI alone.

Main Outcome Measures Infarct size expressed as a percentage of left ventricular (LV) mass and measured by cardiac magnetic resonance imaging performed 3 to 5 days after PCI. Secondary end points included all-cause death at 6 months and vascular complications and major bleeding at 30 days. Multiple imputations were performed for missing infarct size data.

Results The median time from first contact to first coronary device was 77 minutes (interquartile range, 53 to 114 minutes) for the IABC plus PCI group vs 68 minutes (interquartile range, 40 to 100 minutes) for the PCI alone group ($P=.04$). The mean infarct size was not significantly different between the patients in the IABC plus PCI group and in the PCI alone group (42.1% [95% CI, 38.7% to 45.6%] vs 37.5% [95% CI, 34.3% to 40.8%], respectively; difference of 4.6% [95% CI, –0.2% to 9.4%], $P=.06$; imputed difference of 4.5% [95% CI, –0.3% to 9.3%], $P=.07$) and in patients with proximal left anterior descending Thrombolysis in Myocardial Infarction flow scores of 0 or 1 (46.7% [95% CI, 42.8% to 50.6%] vs 42.3% [95% CI, 38.6% to 45.9%], respectively; difference of 4.4% [95% CI, –1.0% to 9.7%], $P=.11$; imputed difference of 4.8% [95% CI, –0.6% to 10.1%], $P=.08$). At 30 days, there were no significant differences between the IABC plus PCI group and the PCI alone group for major vascular complications (n=7 [4.3%; 95% CI, 1.8% to 8.8%] vs n=2 [1.1%; 95% CI, 0.1% to 4.0%], respectively; $P=.09$) and major bleeding or transfusions (n=5 [3.1%; 95% CI, 1.0% to 7.1%] vs n=3 [1.7%; 95% CI, 0.4% to 4.9%]; $P=.49$). By 6 months, 3 patients (1.9%; 95% CI, 0.6% to 5.7%) in the IABC plus PCI group and 9 patients (5.2%; 95% CI, 2.7% to 9.7%) in the PCI alone group had died ($P=.12$).

Conclusion Among patients with acute anterior STEMI without shock, IABC plus primary PCI compared with PCI alone did not result in reduced infarct size.

Trial Registration clinicaltrials.gov Identifier: NCT00833612

JAMA. 2011;306(12):1329-1337
Published online August 30, 2011. doi:10.1001/jama.2011.1280 www.jama.com

PRIMARY PERCUTANEOUS REPERfusion for patients with acute ST-segment elevation myocardial infarction (STEMI) has been shown to reduce mortality and is considered the standard of care when available.[1,2] The benchmarked standards for time to reperfusion have shortened over time; despite significant reductions in door-to-balloon times over the past few years in the United States, the STEMI mortality rate has not significantly improved.[3,4]

Patients with acute STEMI, representing 30% to 45% of approximately 1.5 million hospitalizations for acute coronary syndromes annually in the United States,[5] are still at substantial acute mortality risk with 1-year mortality estimated to be between 6% and 15%.[2,5] This may be related to microvascular obstruction resulting in no reflow at the time of mechanical reperfusion and infarct expansion over time.[6,7] Additionally, this increase in infarct size is associated with adverse remodeling and decreased left ventricular (LV) function leading to heart failure and long-term morbidity following STEMI.[8,9]

For editorial comment see p 1376.

Author Affiliations are listed at the end of this article.
Corresponding Author: Manesh R. Patel, MD, Duke Clinical Research Institute, Duke University Medical Center, PO Box 17969, Durham, NC 27715 (manesh.patel@duke.edu).

Intra-aortic balloon counterpulsation (IABC) mechanically augments coronary blood flow, unloads the left ventricle, and reduces myocardial oxygen demand.[10,11] These favorable hemodynamic effects have led to demonstrated improvements in outcomes, and the recommendation that patients with acute MI and cardiogenic shock be treated with IABC support and reperfusion.[2,12,13] Although an older randomized trial of IABC in patients undergoing percutaneous transluminal coronary angioplasty for high-risk STEMI showed a modest potential effect on recurrent ischemia,[14] more recent observational studies suggest a possible clinical benefit in patients with high-risk STEMI receiving IABC prior to reperfusion with percutaneous coronary intervention (PCI) and stenting,[15] with increased clinical use at an early stage in the United States.[16] Preclinical animal studies have demonstrated that unloading of the left ventricle with IABC prior to reperfusion reduces infarct size and myocardial salvage.[17-19]

Therefore, we performed a randomized controlled trial to determine if IABC inserted prior to primary PCI compared with primary PCI alone (standard of care) reduced infarct size in patients with acute anterior STEMI without cardiogenic shock. In addition, a 6-month follow-up for clinical events including all-cause mortality, repeat infarction, and new congestive heart failure was planned.

METHODS

The methods used in the Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction (CRISP AMI) trial have been previously reported.[20] In brief, CRISP AMI was a prospective, open, international, multicenter (N=30) randomized controlled trial to determine if a routine strategy of IABC insertion prior to primary PCI reduced infarct size in patients with acute anterior STEMI without cardiogenic shock. Patients in the standard of care group of the trial received primary PCI without planned IABC support.

Institutional review boards and ethics committees approved the trial, and each enrolled patient provided written informed consent. The Duke Clinical Research Institute (Durham, North Carolina) coordinated the trial and carried out the data management and analyses with oversight from the steering committee. An independent data and safety monitoring board monitored the study and oversaw the safety and efficacy of the trial. Members of the steering committee were involved in study design, provided oversight during the conduct of the study, and had full access to the data after data lock and unblinding.

Study Population

To determine if IABC reduces infarct size, a population of adult patients within 6 hours of chest pain onset and planned primary PCI for acute anterior STEMI with significant myocardium at risk were sought for inclusion into the study. A 12-lead electrocardiogram demonstrating ST-segment elevation of 2 mm or higher in 2 contiguous anterior leads or a total elevation of 4 mm or higher in anterior leads was required for inclusion demonstrating significant at-risk myocardium. Patients with indications for planned IABC insertion such as cardiogenic shock, inability to undergo IABC implantation, fibrinolysis within 72 hours of presentation, or known contraindication for cardiac magnetic resonance imaging (MRI) for end point assessment were excluded. Because the primary end point was infarct size, patients with known prior myocardial infarction (MI) or coronary artery bypass graft surgery also were excluded.

Interventions and Procedures

Patients were randomized to prereperfusion initiation of IABC and mechanical reperfusion with PCI (IABC plus PCI) or primary PCI alone. Patients randomized to receive counterpulsation therapy were required to have the intra-aortic balloon inserted and pumping prior to PCI (defined by insertion of the guidewire into the infarct-related artery). Patients randomized to PCI alone may have had subsequent insertion of IABC if there was clinical deterioration. Criteria provided to investigators considering rescue IABC and crossover to counterpulsation included sustained hypotension or cardiogenic shock, uncontrolled arrhythmias, and acute mitral regurgitation or ventricular septal defect.

To ensure rapid reperfusion, sites with demonstrated ability to meet guideline standards were chosen (median door-to-device time <90 minutes). A 24-hour interactive voice response system was used for stratified block randomization, which was based on a computer-generated algorithm. Allocation occurred in random blocks and was stratified by region. In addition, data regarding the timing of first medical contact, randomization, IABC insertion, and first device were captured and monitored by the steering committee and the data and safety monitoring board during the conduct of the trial to ensure continued high-quality care.

For participants randomized to receive IABC plus PCI, balloon counterpulsation was recommended for at least 12 hours with a maximum of 24 hours after PCI. For patients with hemodynamic instability, counterpulsation could be continued for longer periods at the discretion of the investigators. Standard guideline-driven therapy (specifically, the use of antiplatelet and antithrombin agents) was recommended at the time of PCI at the investigator's discretion in accordance with the standard of care at the institution.[2] In addition to standard demographic information, site investigators also reported race and ethnicity on a standard predefined case report form to explore potential differences in outcomes. Sites also collected data regarding the primary PCI procedures, a 12-lead electrocardiogram, available laboratory tests and cardiac biomarkers, and concomitant pharmacotherapy and performed cardiac MRI recommended between 3 and 5 days after PCI.

Cardiac MRI

The cardiac MRI protocol to determine infarct size has been described.[21,22] In general, cardiac MRI using standard sequences was performed for microvascular obstruction, area at risk, LV dimensions, and function. Delayed enhancement infarct size imaging was performed after intravenous administration of 0.15 to 0.20 mmol of gadolinium-chelate administered per kilo-

gram of body weight.[23] A central cardiac MRI laboratory at the University of Leipzig Heart Center (Leipzig, Germany) qualified participating sites, performed quality assessment on images during the conduct of the study, and manually performed blinded assessment for LV myocardial mass, microvascular obstruction, area at risk, and infarct size.[21] Myocardial salvage index was calculated as area at risk – infarct size/area at risk × 100.

Outcome Measures

The primary efficacy end point of the trial was infarct size as a percentage of the total LV mass as measured by cardiac MRI. The primary objective was to determine if infarct size was reduced with IABC in at least 1 of the 2 primary analysis populations: (1) modified intention-to-treat (ITT) population or the (2) subset of the modified ITT population, which included patients with a nondistal left anterior descending lesion and Thrombolysis in Myocardial Infarction (TIMI) flow score of 0 or 1.

The primary safety end point included all-cause mortality and the rate of major adverse cardiac events including death, repeat MI, and heart failure at discharge, at 30 days, or at 6 months. Secondary safety end points included major bleeding events defined by the Global Use of Strategies To Open Coronary Arteries (GUSTO) trial, transfusions, and major vascular complications defined to include limb ischemia requiring intervention, distal embolization, major dissection, pseudoaneurysm or arteriovenous fistula, hematoma larger than 5 cm, and amputations. An exploratory analysis also was conducted for the composite of death, shock, and heart failure.

Statistical Analysis

Baseline characteristics, procedural characteristics, and primary and secondary outcomes were described using mean, median, standard deviation, and 25th and 75th percentiles for continuous variables; frequencies and proportions were used for categorical variables. For the primary end point of infarct size measured by cardiac MRI, the null hypothesis of equal infarct size between the IABC plus PCI group and the PCI alone group was tested using the *t* test for both of the 2 primary analysis populations. The point estimate and the *P* value based on the *t* test are reported.

For secondary end points, χ^2 tests or Fisher exact tests (for small frequencies) were used to compare the 2 groups with discrete outcomes, while *t* tests or Wilcoxon tests (for nonnormal data) were used to compare the 2 groups with continuous variables. Kaplan-Meier curves and log-rank tests were used for the survival analyses to compare the outcomes of time to death and time to composite end points. The time to events (death; death, MI, or congestive heart failure; or death, shock, or congestive heart failure) analyses included all randomized patients and censored individuals at the time of withdrawal or when lost to follow-up; the analyses for infarct size for the modified ITT population included only those individuals with available data on the outcome.

To account for missing data, sensitivity analyses were conducted to supplement the primary analyses. This included a multiple imputation approach that used baseline characteristics to build a regression model to impute missing data with 1000 imputations, as well as best and worst case scenarios (if data were not missing at random) in which the best case used minimal (or maximum) infarct size to impute missing data for the IABC plus PCI group (or the PCI alone group) and the worst case used maximum (or minimal) infarct size to impute missing data for the IABC plus PCI group (or the PCI alone group). Given the observed imbalances in baseline variables, a post hoc analysis adjusting for the degree of ST-segment elevation at baseline was conducted for infarct size.

A *P* value of less than .025 (2-sided significance testing) was considered statistically significant in the 2 primary analyses with Bonferroni adjustment. A *P* value of less than .05 was considered statistically significant in all secondary analyses. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina).

Sample Size

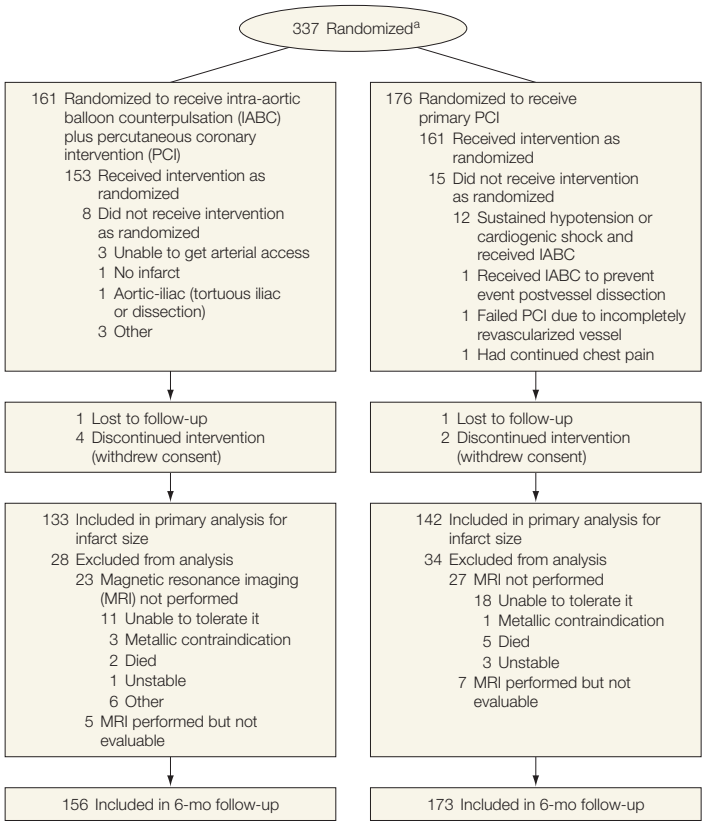
Sample size and power calculations have been reported.[20] In brief, the computations were based on 2 primary analyses with the same primary outcome of infarct size in 2 different populations: (1) the modified ITT population and (2) a subset of the modified ITT population, which includes all participants with a nondistal left anterior descending lesion and a TIMI flow score of 0 or 1. The study was designed to detect a 25% reduction in infarct size for the IABC plus PCI group relative to the PCI alone group in at least 1 of the 2 ITT populations. Based on prior trials evaluating ischemia reperfusion therapies, a 25% reduction in infarct size was believed to be both feasible and clinically meaningful.[24,25]

Assumptions such as the mean and standard deviation of infarct size as well as the missing rate and the percentage of participants in the subset of the modified ITT population were based on 2 sets of preliminary data.[16,22,26] A type I error of 0.025 was used for each of the 2 primary analyses to maintain an overall type I error rate of 0.05. Accounting for a 10% to 13% missing data rate, a total of 300 randomized participants were planned to be included to maintain at least 81% power in both primary analyses to detect the clinical significance of a 25% reduction in infarct size in at least 1 of the 2 ITT populations. The data and safety monitoring board reviewed the power recalculation using the updated assumptions based on the blinded interim data of the first 150 patients; the updated power was at least 83% or higher with a total of 300 participants.

RESULTS

A total of 337 patients with anterior STEMI without shock were randomized and enrolled at 30 sites in 9 countries from June 2009 through February 2011; 161 patients were randomized to the IABC plus PCI group and 176 patients were randomized to the PCI alone group. Fifteen patients (8.5%) in the PCI alone group crossed over and also received IABC (5 patients prior to PCI and 10 patients after PCI). Four of the 15 patients in the PCI alone group who also received IABC died by day 30. Eight patients (4.9%) in the IABC plus PCI group did not receive IABC (FIGURE 1). Two patients in the IABC plus PCI group and 5 patients in the PCI alone group

Figure 1. Flow of Patients Through Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction Randomized Controlled Trial



[a] Two patients immediately excluded due to improper consent.

died prior to receiving a cardiac MRI; however, MRI was performed and evaluable in 275 patients (82%). Complete follow-up (median of 183 days in both groups) was available in all but 8 patients (2.3%); 5 patients in the IABC plus PCI group and 3 patients in the PCI alone group withdrew consent or were lost to follow-up prior to the scheduled 6-month follow-up (Figure 1).

Baseline Characteristics

The 2 groups were well balanced with regard to baseline characteristics (TABLE 1). The median age was 56.1 years (interquartile range [IQR], 48.3-64.3 years) in the IABC plus PCI group compared with 57.7 years (IQR, 48.6-66.4 years) in the PCI alone group; 82% and 81.8%, respectively, were male. At presentation, patients were hemodynamically stable and had a median systolic blood pressure of 130 mm Hg (IQR, 113-150 mm Hg) in the IABC plus PCI group compared with 135 mm Hg (IQR, 120-151 mm Hg) in the PCI alone group; the median heart rate was 81 beats/minute (IQR, 71-93 beats/minute) and 80 beats/minute (IQR, 70-94 beats/minute), respectively. A significant amount of myocardium was at risk in both groups; there was ST-segment elevation of 6 mm or higher in 62.1% of patients in the IABC plus PCI group and in 57.4% of patients in the PCI alone group.

Procedural Characteristics and Medical Therapy

The majority of the patients received PCI (96.3% in the IABC plus PCI group and 92.6% in the PCI alone group; TABLE 2). The left anterior descending was the infarct-related artery in 99.4% of the patients in the IABC plus PCI group and in 96.0% of the patients in the PCI alone group; more than 60% of patients in both groups had total occlusion. Patients were treated in a rapid fashion with a median time from first medical contact to insertion of first device of 77 minutes (IQR, 53-114 minutes) in the IABC plus PCI group and 68 minutes (IQR, 40-100 minutes) in the PCI alone group ($P = .04$). The overall median time from symptom onset to insertion of first device was 202.5 minutes (IQR, 145.0-272.0 minutes) in the IABC plus PCI group and 193.0 minutes (IQR, 136.0-275.0 minutes) in the PCI alone group. Aspiration thrombectomy was used in 34.8% of patients in the IABC plus PCI group and in 37.4% of the patients in the PCI alone group. Bare metal stents were used in 53.4% of all patients. In 55 patients (35.9%), IABC was continued for more than 24 hours and the median duration of counterpulsation in the IABC plus PCI group was 22.1 hours (IQR, 16.8-26.1 hours).

Patients in the study also were well treated with medical therapy. At discharge, aspirin was used in 99.4% of patients in the IABC plus PCI group and in 96.4% of patients in the PCI alone group; clopidogrel, 74.4% and 78.1%, respectively; prasugrel, 21.8% and 18.9%; and statin therapy, 95.5% and 96.4%. More than 70% of patients in both groups were prescribed at discharge either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Primary Outcome

The mean infarct size in all patients (42.1% [95% CI, 38.7% to 45.6%] vs 37.5% [95% CI, 34.3% to 40.8%] of LV mass; difference of 4.6% [95% CI, –0.2% to 9.4%] of LV mass, $P = .06$) and in patients with proximal left anterior descending and TIMI flow scores of 0 or 1 (46.7% [95% CI, 42.8% to 50.6%] vs 42.3% [95% CI, 38.6% to 45.9%] of LV mass; difference of 4.4% [95% CI, –1.0% to 9.7%] of LV mass, $P = .11$) was not significantly different between the IABC plus PCI group and the PCI alone group (TABLE 3). The multiple imputation approach (using baseline covariates in Table 1 as well as treatment group and region for imputing missing data) found a difference in infarct size between the 2 groups that was similar to the per-protocol analysis (Table 3). The observed treatment difference could range

from –14.7% to 21.9% based on conservative best and worst case scenarios. The post hoc analysis adjusting for baseline ST elevation resulted in a difference in infarct size between the 2 groups of 4.58% (P=.06) compared with 4.6% in the per-protocol analysis. Secondary cardiac MRI findings also were in keeping with the infarct size findings. The mean microvascular obstruction was 6.8% of LV mass for the IABC plus PCI group and 5.7% of LV mass for the PCI alone group (P=.34); the mean LV ejection fraction was 46.1% and 48.2%, respectively (P=.17); and the mean LV systolic volume was 76.9 mL and 70.3 mL (P=.10).

Clinical Events

Patients were followed up for clinical events at 30 days and at 6 months. At 30 days, major bleeding or transfusion occurred in 5 patients (3.1%; 95% CI, 1.0%-7.1%) in the IABC plus PCI group and in 3 patients (1.7%; 95% CI, 0.4%-4.9%) in the PCI alone group (P=.49). Major vascular complications occurred in 7 patients (4.3%; 95% CI, 1.8%-8.8%) in the IABC plus PCI group and in 2 patients (1.1%; 95% CI, 0.1%-4.0%) in the PCI alone group (P=.09; eTable 1 and eTable 2 at http://www.jama.com).

By 6 months, 3 patients (1.9%; 95% CI, 0.6%-5.7%) in the IABC plus PCI group and 9 patients (5.2%; 95% CI, 2.7%-5.7%) in the PCI alone group had died (log-rank test P=.12; FIGURE 2). The time to the composite end point of death, recurrent MI, or new or worsening heart failure also was not significantly different between the 2 groups (10 patients [6.3%; 95% CI, 3.4%-11.4%] in IABC plus PCI group and 19 patients [10.9%; 95% CI, 7.1%-16.5%] in PCI alone group; log-rank test P=.15). There was a significant difference between the IABC plus PCI group and the PCI alone group in the exploratory composite end point of time to death, shock, or new or worsening heart failure (8 events [5.0%; 95% CI, 2.6%-9.8%] vs 21 events [12.0%; 95% CI, 8.0%-17.8%], respectively; log-rank test P=.03). This was driven by no shock events in the IABC plus PCI group while 5 patients developed shock during index hospitalization in the PCI alone group.

COMMENT

The CRISP AMI trial was designed to test the hypothesis that IABC inserted prior to primary PCI and continued for at least 12 hours after PCI would reduce myocardial infarct size in patients with large anterior STEMI presenting without cardiogenic shock. Review of the baseline and procedural characteristics demonstrates

Table 1. Baseline Characteristics

	Total (N = 337)	IABC Plus PCI (n = 161)	PCI Alone (n = 176)
Age, median (IQR), y	56.6 (48.4-65.6)	56.1 (48.3-64.3)	57.7 (48.6-66.4)
Male sex, No. (%)	276 (81.9)	132 (82.0)	144 (81.8)
Race, No. (%)			
American Indian/Alaska Native	1 (0.3)	0	1 (0.6)
Asian	152 (45.1)	75 (46.6)	77 (43.8)
Black	16 (4.7)	3 (1.9)	13 (7.4)
White	161 (47.8)	81 (50.3)	80 (45.5)
Other[a]	7 (2.1)	2 (1.2)	5 (2.8)
Height, median (IQR), cm	169.9 (163.1-177.0)	170.2 (165.1-175.8)	168.9 (162.8-178.1)
Weight, median (IQR), kg	74.3 (64.5-85.7)	74.4 (66.3-84.3)	74.4 (64.5-88.2)
Medical history, No. (%)			
Prior PCI	5 (1.5)	3 (1.9)	2 (1.1)
Hypertension (receiving drug therapy)	99 (29.4)	39 (24.2)	60 (34.1)
Stroke	1 (0.3)	0	1 (0.6)
Transient ischemic attack	1 (0.3)	0	1 (0.6)
Current nicotine use	107 (31.8)	53 (32.9)	54 (30.7)
Dyslipidemia (receiving drug therapy)	42 (12.5)	20 (12.4)	22 (12.5)
Prior atrial fibrillation	4 (1.2)	3 (1.9)	1 (0.6)
Renal insufficiency	6 (1.8)	2 (1.2)	4 (2.3)
Diabetes mellitus	63 (18.7)	27 (16.8)	36 (20.5)
Insulin-dependent	7 (11.1)	5 (18.5)	2 (5.6)
Non–insulin-dependent	56 (88.9)	22 (81.5)	34 (94.4)
Prior peripheral arterial disease	1 (0.3)	0	1 (0.6)
At presentation			
Blood pressure, median (IQR), mm Hg			
Systolic	131.0 (118.0-150.0)	130.0 (113.0-150.0)	135.0 (120.0-151.0)
Diastolic	80.0 (70.0-92.0)	80.0 (70.0-92.0)	80.0 (71.5-92.0)
Heart rate, median (IQR), beats/min	81.0 (71.0-94.0)	81.0 (71.0-93.0)	80.0 (70.0-94.0)
Degree of ST elevation in anterior leads, mm, No. (%)			
0-<2	0	0	0
2-<4	1 (0.3)	0	1 (0.6)
4-<6	135 (40.1)	61 (37.9)	74 (42.0)
≥6	201 (59.6)	100 (62.1)	101 (57.4)

Abbreviations: IABC, intra-aortic balloon counterpulsation; IQR, interquartile range; PCI, percutaneous coronary intervention.
[a] Patients unable to identify race using the available choices.

that the patients were hemodynamically stable at enrollment, had a significant amount of myocardium at risk, and were rapidly treated with reperfusion. The principal finding from this study was that early planned IABC did not reduce myocardial infarct size as measured by cardiac MRI.

Review of all cardiac MRI parameters demonstrates consistent findings. As prespecified, in addition to all patients randomized, analysis of the subset of patients with the highest risk defined by proximal occlusions of the left anterior descending artery also did not demonstrate a reduction in infarct size or any other cardiac MRI parameter with IABC. Several possible mechanisms may explain the observed findings.

One explanation may be that the beneficial effects with IABC are offset by an increase in infarct size associated with the amount of time required to insert the intra-aortic balloon. Although plausible, this seems less likely because the IABC plus PCI group had a median time of first contact to first device that was less than 10 minutes longer than the PCI alone group.

Table 2. Procedural Characteristics

	No. (%) of Patients[a]		
	Total (N = 337)	IABC Plus PCI (n = 161)	PCI Alone (n = 176)
PCI			
Performed	317 (94.3)	154 (96.3)	163 (92.6)
Not performed	19 (5.6)	6 (3.7)	13 (7.4)
Coronary artery bypass graft surgery instead	6 (1.8)	2 (1.3)	4 (2.3)
No infarct artery identified	7 (2.1)	1 (0.6)	6 (3.4)
Technical limitations	6 (1.8)	3 (1.9)	3 (1.7)
Infarct-related artery			
Left main	0	0	0
Left anterior descending	328 (97.6)	159 (99.4)	169 (96.0)
Left circumflex	0	0	0
Right coronary	1 (0.3)	0	1 (0.6)
No infarct-related artery identified	7 (2.1)	1 (0.6)	6 (3.4)
Infarct-related artery stenosis location			
Proximal	207 (62.9)	103 (64.8)	104 (61.2)
Mid	132 (40.1)	56 (35.2)	76 (44.7)
Distal	19 (5.8)	11 (6.9)	8 (4.7)
Infarct-related artery TIMI flow			
Preintervention grade			
0	215 (65.3)	105 (66.0)	110 (64.7)
1	34 (10.3)	18 (11.3)	16 (9.4)
2	50 (15.2)	26 (16.4)	24 (14.1)
3	30 (9.1)	10 (6.3)	20 (11.8)
Postintervention grade			
0	5 (1.5)	1 (0.6)	4 (2.4)
1	6 (1.8)	5 (3.2)	1 (0.6)
2	8 (2.5)	5 (3.2)	3 (1.8)
3	306 (94.2)	145 (92.9)	161 (95.3)
Interventions performed on non–infarct-related arteries	6 (1.9)	5 (3.2)	1 (0.6)
Left main	2 (<1)	1 (<1)	1 (<1)
Left circumflex	1 (<1)	1 (<1)	0
Right coronary	3 (<1)	3 (<1)	0
Time to treatment, median (IQR), min			
From symptom onset to first hospital contact	113.0 (65.0-175.0)	112.0 (78.0-180.0)	115.0 (62.0-175.0)
From first medical contact to first device (infarct-related artery)[b]	71.0 (47.0-105.0)	77.0 (53.0-114.0)	68.0 (40.0-100.0)
From symptom onset to first device (infarct-related artery)	196.0 (140.0-272.0)	202.5 (145.0-272.0)	193.0 (136.0-275.0)
First device used on infarct-related artery			
Aspiration thrombectomy	115 (36.2)	54 (34.8)	61 (37.4)
Balloon	152 (47.8)	78 (50.3)	74 (45.4)
Stent	51 (16.0)	23 (14.8)	28 (17.2)
Type of stent	309 (96.9)	147 (94.2)	162 (99.4)
Drug-eluting	149 (48.2)	69 (46.9)	80 (49.4)
Bare metal	165 (53.4)	79 (53.7)	86 (53.1)
Anticoagulant use			
Unfractionated heparin	261 (77.7)	127 (79.4)	134 (76.1)
Bivalirudin	57 (17.0)	24 (15.0)	33 (18.8)
Glycoprotein IIb/IIIa	154 (45.8)	79 (49.4)	75 (42.6)

Abbreviations: IABC, intra-aortic balloon counterpulsation; IQR, interquartile range; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.
[a] Values expressed as number (percentage) unless otherwise indicated. The percentages are based on the total of nonmissing data. Data are missing for up to 34 patients.
[b] The comparison between groups yielded a *P* value of .04.

Table 3. Cardiac Magnetic Resonance Imaging (MRI) Findings

	Total (N = 337)	IABC Plus PCI (n = 161)	PCI Alone (n = 176)	*P* Value
Time from symptom onset to MRI, median (IQR), d	4.0 (3.0-5.0)	4.0 (3.0-5.0)	4.0 (3.0-4.0)	.20
Primary End Point				
Infarct size, % of left ventricular mass				
Per-protocol analysis, No. (%)	275 (81.6)	133 (82.6)	142 (80.7)	
Mean (95% CI)	39.8 (37.4-42.1)	42.1 (38.7-45.6)	37.5 (34.3-40.8)	.06
Median (IQR)	38.8 (26.0-52.2)	42.8 (27.2-54.7)	36.2 (25.9-49.4)	
Multiple imputation analysis				
Mean (95% CI)	39.7 (37.3-42.1)	42.1 (38.6-45.6)	37.6 (34.3-40.9)	.07
Median (IQR)	39.0 (26.0-52.3)	42.5 (27.1-55.9)	36.4 (24.9-49.9)	
Proximal left anterior descending and TIMI flow score of 0 or 1				
Per-protocol analysis, No. (%)	192 (57.0)	93 (57.8)	99 (56.3)	
Mean (95% CI)	44.4 (41.7-47.1)	46.7 (42.8-50.6)	42.3 (38.6-45.9)	.11
Median (IQR)	42.1 (30.3-54.7)	45.1 (32.7-60.8)	38.6 (29.6-51.6)	
Multiple imputation analysis				
Mean (95% CI)	44.4 (41.7-47.1)	46.8 (42.9-50.8)	42.1 (38.4-45.7)	.08
Median (IQR)	42.5 (30.3-55.9)	45.3 (32.3-61.6)	39.2 (29.5-51.9)	
Secondary End Point				
MRI findings for ITT population				
Microvascular obstruction, No. (%)	274 (81.3)	131 (81.4)	143 (81.3)	.34
Mean (95% CI), %	6.2 (5.2-7.3)	6.8 (5.2-8.3)	5.7 (4.3-7.2)	
Median (IQR), %	2.6 (0.0-9.1)	2.8 (0.0-9.7)	2.0 (0.0-7.8)	
Left ventricular ejection fraction, No. (%)	284 (84.3)	136 (84.5)	148 (84.1)	.17
Mean (95% CI), %	47.2 (45.7-48.7)	46.1 (43.9-48.3)	48.2 (46.2-50.3)	
Median (IQR), %	46.9 (38.6-56.5)	46.2 (37.4-56.1)	47.6 (39.6-56.8)	
Left ventricular end-systolic volume, No. (%)	284 (84.3)	136 (84.5)	148 (84.1)	.10
Mean (95% CI), mL	73.5 (69.6-77.3)	76.9 (70.6-83.2)	70.3 (65.8-74.9)	
Median (IQR), mL	68.8 (51.0-86.0)	69.5 (51.7-86.5)	67.9 (49.2-86.0)	
Left ventricular end-diastolic volume, No. (%)	284 (84.3)	136 (84.5)	148 (84.1)	.32
Mean (95% CI), mL	137.5 (132.2-142.8)	140.3 (132.5-148.1)	134.9 (127.8-142.1)	
Median (IQR), mL	131.6 (107.4-166.6)	135.4 (112.0-166.8)	130.5 (103.9-166.5)	
Salvage index, No. (%)	263 (78.0)	126 (78.3)	137 (77.8)	.13
Mean (95% CI)	0.35 (0.32-0.38)	0.32 (0.27-0.37)	0.37 (0.33-0.41)	
Median (IQR)	0.30 (0.10-0.50)	0.30 (0.10-0.50)	0.30 (0.20-0.50)	

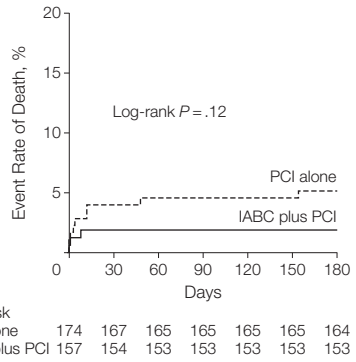
Abbreviations: IABC, intra-aortic balloon counterpulsation; IQR, interquartile range; ITT, intention-to-treat; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

In fact, the overall ischemic time as measured by the time from reported symptom onset to first device was just longer than 3 hours for all patients and there was only a 10-minute difference between the 2 groups.

Another explanation may be related to the timing of cardiac MRI that was performed between 3 and 5 days after PCI and differential end point assessment. Evaluation of the trial enrollment shows that more than 80% of patients in both groups were able to get evaluable MRIs for infarct size, yielding a sufficient number of patients for the prespecified study power. The infarct size observed was larger than expected, more than 10% of LV mass larger than in prior studies.[26] However, based on prior studies predicting infarct size,[24] the CRISP AMI trial enrolled the highest risk patients in an effort to identify a treatment difference. The observed point estimate for infarct size in both groups makes a significant treatment effect with infarct size reduction with routine IABC unlikely.

A third possibility is that the potential protective effect of LV unloading occurred too late in the course of the MI to salvage significant myocardium in this study. Francone et al[27] and Eitel et al[28] found that little myocardial salvage occurs with ischemic times beyond 120 minutes. Similarly, Bonnefoy et al[29] found that the reduction in mortality that occurred with prehospital fibrinolysis was limited to STEMI patients treated within 120 minutes of symptom onset. In the animal experiments demonstrating significant infarct salvage, unloading occurred immediately prior to reperfusion after 60 minutes of myocardial ischemia.[18] The patients in our study had ischemic times of longer than 3 hours (on average), which may have been outside the window for significant infarct salvage as assessed by cardiac MRI.

Figure 2. Event Rate of Death From 0 to 180 Days



IABC indicates intra-aortic balloon counterpulsation; PCI, percutaneous coronary intervention.

In contrast to the infarct size findings, the clinical findings demonstrate a potential for an early risk with routine primary PCI in these high-risk anterior STEMI patients without shock. Fifteen of the patients in the PCI alone group crossed over and received IABC based on the investigator's decision, often for sustained hypotension or the development of cardiogenic shock. This led to a small, nonsignificant increase in the number of patients in the PCI alone group who died during the initial hospitalization, notably patients who were not eligible for infarct size imaging. These findings continued to 6 months at which time 9 of the patients in the PCI alone group had died compared with 3 patients in the IABC plus PCI group. The composite of death, shock, or heart failure at 6 months also seems to favor the IABC plus PCI group, highlighting the potential effect of the early risk with the PCI alone group. Review of vascular complications and major bleeding and/or transfusions found similar rates between the 2 groups. These clinical findings are in keeping with data from prior randomized trials with IABC for routine high-risk PCI[30] and for high-risk STEMI patients undergoing angioplasty alone prior to the stent era.[14]

Two clinical issues related to these findings deserve comment. The first is that high-quality care currently is being provided to patients with high-risk STEMI and is characterized by systems optimized for rapid reperfusion and optimal adjunctive medical therapy; this should be taken into consideration in future trials. In the CRISP AMI trial, the 6-month mortality rate was less than 5%; even with the exclusion of patients with shock on presentation, this finding is consistent with other recent studies.

The second clinical issue revolves around the use of adjunctive ventricular support devices. Unlike patients with cardiogenic shock[12,13] for whom the guidelines recommend intra-aortic counterpulsation, patients with high-risk anterior STEMI without shock do not seem to garner a reduction in infarct size from early routine use of IABC. Clinicians should continue to be vigilant about identifying patients who are at risk for rapid deterioration and who may benefit from counterpulsation (as seen with the crossover in this trial). Future studies should be aimed at identifying the patient features associated with early deterioration.

This study has several limitations. The CRISP AMI trial used infarct size on MRI as the primary end point, and this is a validated physiological measure of myocardial damage. However, there may not be a direct correlation with long-term clinical outcome due to other physiological mechanisms affecting ventricular remodeling and function. A screening log was not kept at sites and site selection bias cannot be excluded. Additionally, clinical events occurring early prior to the MRI measurement of infarct size may also limit correlations with long-term clinical outcomes. Our study was powered to detect a 25% reduction in infarct size, and we cannot exclude a smaller treatment difference. However, this is one of the largest randomized trials with device therapy in this high-risk population in the literature, and the observed infarct sizes make a missed treatment effect less likely.

CONCLUSION

In conclusion, the CRISP AMI trial randomized patients with high-risk anterior STEMI without shock to a routine strategy of IABC prior to PCI lasting at least 12 hours after PCI compared with PCI alone. This strategy did not lead to a reduction in myocardial infarct size. Clinical outcomes at 6 months were not significantly different between the 2 groups. However, 8.5% of patients in the PCI alone group crossed over to rescue IABC therapy. These findings support a standby strategy (rather than routine use) of IABC during primary PCI in high-risk anterior STEMI patients.

Published Online: August 30, 2011. doi:10.1001/jama.2011.1280

Author Affiliations: Division of Cardiology, Departments of Medicine (Drs Patel and Ohman) and Biostatistics and Bioinformatics (Dr Barnhart), Clinical Trials Statistics Group (Dr Zhou), Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina; Division of Cardiology, Memorial Hermann Heart and Vascular Institute, University of Texas, Houston (Dr Smalling); Departments of Internal Medicine and Cardiology, University of Leipzig Heart Center, Leipzig, Germany (Dr Thiele); Division of Cardiology, Medanta-The Medicity, Haryana, India (Dr Chandra); Department of Cardiovascular Medicine, Flinders Medical Center, Bedford Park, Australia (Dr Chew); Division of Cardiology, Newark Beth Israel Medical Center, Newark, New Jersey (Dr Cohen); Department of Cardiology, Liverpool Hospital, Liverpool, Australia (Dr French); and Cardiovascular Division, King's College, London, England (Dr Perera).

Author Contributions: Dr Patel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Patel, Smalling, Thiele, Barnhart, Cohen, French, Ohman.
Acquisition of data: Patel, Smalling, Thiele, Chew, Cohen, Perera.
Analysis and interpretation of data: Patel, Smalling, Thiele, Zhou, Barnhart, Chandra, Chew, Cohen, French, Perera, Ohman.
Drafting of the manuscript: Patel, Smalling, Zhou, Barnhart.
Critical revision of the manuscript for important intellectual content: Smalling, Thiele, Zhou, Barnhart, Chandra, Chew, Cohen, French, Perera, Ohman.
Statistical analysis: Zhou, Barnhart, Perera.
Obtained funding: Thiele, Ohman.
Administrative, technical, or material support: Thiele, French, Ohman.
Study supervision: Patel, Smalling, Thiele, Barnhart, Cohen,
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Patel reported that his institution has received grant funding and reimbursement for travel expenses from Maquet (formerly Datascope); that he has grants pending with the National Heart, Lung, and Blood Institute; that he is a board member for Genzyme; that he is a consultant for Bayer Healthcare and Ortho McNeil Jansen; and that he has received payment for lectures from theheart.org and the Duke Clinical Medicine Series. Dr Smalling reported that his institution has received grant funding and reimbursement for travel expenses from Maquet; and that he has received honoraria from Maquet. Dr Thiele reported that he has received honoraria and been reimbursed for travel expenses from Maquet. Dr Barnhart reported that her institution has received grant funding from Maquet. Dr Chew reported that his institution has received consulting fees from AstraZeneca Australia, Eli Lilly, and Abbott Vascular; and that he has received payment for lectures from AstraZeneca Australia. Dr Cohen reported that he has received fees for participating in review activities from Merck, Johnson & Johnson, and sanofi-aventis; that he is a board member for Johnson & Johnson, AstraZeneca, and sanofi-aventis; that he has provided expert testimony for Princeton Insurance; and that he has received payment for lectures from Merck, sanofi-aventis, and Bristol-Myers Squibb. Dr Perera reported that he has received payment for lectures and reimbursement for travel expenses from Maquet. Dr Ohman reported that his institution has received grant funding and reimbursement for travel expenses from Maquet; that he has grants pending with Daiichi Sankyo, Maquet, and Eli Lilly & Company; and that he is a consultant for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Liposcience, Merck, Pozen Inc, Roche, sanofi-aventis, The Medicines Company, and WebMD. No other disclosures were reported.
Funding/Support: Funding for this trial was provided by Maquet (formerly Datascope).
Role of the Sponsor: The sponsor had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.
Independent Statistical Analysis: All statistical analyses were performed by Drs Barnhart and Zhou at the Duke Clinical Research Institute.

CRISP AMI Steering Committee Members: Manesh R. Patel, Holger Thiele, Richard W. Smalling, Praveen Chandra, Marc Cohen, Divaka Perera, Derek Chew, John French, E. Magnus Ohman.

Data and Safety Monitoring Board Members: Eric Bates, MD, University of Michigan, Ann Arbor; David Holmes, MD, Mayo Clinic, Rochester, Minnesota; Richard Trout, PhD, Rutgers University, New Brunswick, New Jersey.

CRISP AMI Trial Investigators: *Australia:* A. Sinhal, Flinders Medical Centre, Bedford Park (n=4 patients enrolled). *Belgium:* P. Vranckx, Virga Jesse Hospital, Hasselt (n=8). *England:* J. Blaxill, Leeds General Infirmary, Leeds (n=32); M. Thomas, Saint Thomas Hospital, London (n=18). *Germany:* H. Thiele, Universitatsklinikum Leipzig, Leipzig (n=6); T. Schwab, University of Freiburg, Freiburg (n=4); R. Strasser, Klinik III Fur Innere Medizin der Universitat zu Koln, Dresden (n=1). *India:* S. Kumar, CARE Hospital, Hyderabad (n=58); P. Singh, Baroda Heart Institute and Research Centre, Vadodara (n=54); R. Passey, Sir Ganga Ram Hospital, New Delhi (n=11); G. Reddy, Gurunanak CARE Hospital, Hyderabad (n=5); P. Chandra, Medanta-The Medicity, Gurgaon (n=4); N. Garg, Tagore Hospital and Heart Care Centre Pvt. Ltd, Jalandhar (n=3); N. Khanna, Indraprastha Apollo Hospital, New Delhi (n=2); S. Banerjee, Apollo Gleneagles Hospital, Kolkata (n=2); K. Varghese, Saint John's Medical College and Hospital, Bangalore (n=1). *Ireland:* H. Mc Cann, Mater Misercordiae Dublin, Dublin (n=9). *The Netherlands:* N. Pijls, Catherina Hospital, Eindhoven (n=28). *Scotland:* P. Henriksen, Royal Infirmary of Edinburgh, Edinburgh (n=14). *United States:* J. Mills, Duke University Medical Center, Durham, North Carolina (n=23); R. Smalling, University of Texas Health Science Center, Houston (n=12); R. Bashir, Temple University Hospital, Philadelphia, Pennsylvania (n=11); A. Weintraub, Tufts Medical Center, Boston, Massachusetts (n=9); M. Cohen, Newark Beth Israel Medical Center, Newark, New Jersey (n=8); F. Ling, University of Rochester Medical Center-Strong Memorial Hospital, Rochester, New York (n=4); P. Casale, Lancaster General Hospital, Lancaster, Pennsylvania (n=3); B. Brott, University of Alabama Medical Center, Birmingham (n=2); L. Satler, Washington Hospital Center, Washington, DC (n=1); R. Biederman, Allegheny General Hospital, Pittsburgh, Pennsylvania (n=1); D. Shavelle, University of Southern California University Hospital, Los Angeles (n=1).

Online-Only Material: eTable 1 and eTable 2 are available at http://www.jama.com.

Additional Contributions: We acknowledge Pamela L. Monds, AAS, and Karen W. Ramsey, BSN, MBA, MHA (both with Duke Clinical Research Institute, Durham, North Carolina) for operational excellence in helping conduct the study. We also acknowledge Elizabeth E. S. Cook, BA (Duke Clinical Research Institute) for her editorial support with the preparation of the manuscript. They did not receive compensation for their contributions.

REFERENCES

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet*. 2003;361(9351):13-20.

2. Antman EM, Anbe DT, Armstrong PW, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *Circulation*. 2004;110(5):588-636.

3. Flynn A, Moscucci M, Share D, et al. Trends in door-to-balloon time and mortality in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Arch Intern Med*. 2010;170(20):1842-1849.

4. Wang TY, Fonarow GC, Hernandez AF, et al. The dissociation between door-to-balloon time improvement and improvements in other acute myocardial infarction care processes and patient outcomes. *Arch Intern Med*. 2009;169(15):1411-1419.

5. Lloyd-Jones D, Adams R, Carnethon M, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2009;119(3):480-486.

6. Rezkalla SH, Kloner RA. No-reflow phenomenon. *Circulation*. 2002;105(5):656-662.

7. Ito H, Maruyama A, Iwakura K, et al. Clinical implications of the 'no reflow' phenomenon: a predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. *Circulation*. 1996;93(2):223-228.

8. Wu E, Ortiz JT, Tejedor P, et al. Infarct size by contrast enhanced cardiac magnetic resonance is a stronger predictor of outcomes than left ventricular ejection fraction or end-systolic volume index: prospective cohort study. *Heart*. 2008;94(6):730-736.

9. Ezekowitz JA, Armstrong PW, Granger CB, et al. Predicting chronic left ventricular dysfunction 90 days after ST-segment elevation myocardial infarction: An Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) substudy. *Am Heart J*. 2010;160(2):272-278.

10. Kern MJ, Aguirre F, Bach R, Donohue T, Siegel R, Segal J. Augmentation of coronary blood flow by intra-aortic balloon pumping in patients after coronary angioplasty. *Circulation*. 1993;87(2):500-511.

11. Williams DO, Korr KS, Gewirtz H, Most AS. The effect of intraaortic balloon counterpulsation on regional myocardial blood flow and oxygen consumption in the presence of coronary artery stenosis in patients with unstable angina. *Circulation*. 1982;66(3):593-597.

12. Sanborn TA, Sleeper LA, Bates ER, et al. Impact of thrombolysis, intra-aortic balloon pump counterpulsation, and their combination in cardiogenic shock complicating acute myocardial infarction: a report from the SHOCK Trial Registry: Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock? *J Am Coll Cardiol*. 2000;36(3)(suppl A):1123-1129.

13. Hochman JS, Sleeper LA, White HD, et al; SHOCK Investigators (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock). One-year survival following early revascularization for cardiogenic shock. *JAMA*. 2001;285(2):190-192.

14. Stone GW, Marsalese D, Brodie BR, et al; Second Primary Angioplasty in Myocardial Infarction (PAMI-II) Trial Investigators. A prospective, randomized evaluation of prophylactic intraaortic balloon counterpulsation in high risk patients with acute myocardial infarction treated with primary angioplasty. *J Am Coll Cardiol*. 1997;29(7):1459-1467.

15. Brodie BR, Stuckey TD, Hansen C, Muncy D. Intraaortic balloon counterpulsation before primary percutaneous transluminal coronary angioplasty reduces catheterization laboratory events in high-risk patients with acute myocardial infarction. *Am J Cardiol*. 1999;84(1):18-23.

16. Cohen M, Urban P, Christenson JT, et al; Benchmark Registry Collaborators. Intra-aortic balloon counterpulsation in US and non-US centres: results of the Benchmark Registry. *Eur Heart J*. 2003;24(19):1763-1770.

17. Achour H, Boccalandro F, Felli P, et al. Mechanical left ventricular unloading prior to reperfusion reduces infarct size in a canine infarction model. *Catheter Cardiovasc Interv*. 2005;64(2):182-192.

18. LeDoux JF, Tamareille S, Felli PR, Amirian J, Smalling RW. Left ventricular unloading with intra-aortic counter pulsation prior to reperfusion reduces myocardial release of endothelin-1 and decreases infarction size in a porcine ischemia-reperfusion model. *Catheter Cardiovasc Interv*. 2008;72(4):513-521.

19. Azevedo CF, Amado LC, Kraitchman DL, et al. The effect of intra-aortic balloon counterpulsation on left ventricular functional recovery early after acute myocardial infarction: a randomized experimental magnetic resonance imaging study. *Eur Heart J*. 2005;26(12):1235-1241.

20. Patel MR, Thiele H, Smalling RW, et al. 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(1):47-55, e1.

21. Thiele H, Kappl MJE, Conradi S, Niebauer J, Hambrecht R, Schuler G. Reproducibility of chronic and acute infarct size measurement by delayed enhancement-magnetic resonance imaging. *J Am Coll Cardiol*. 2006;47(8):1641-1645.

22. Patel MR, Worthley SG, Stebbins A, et al. Pexelizumab and infarct size in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: a delayed enhancement cardiac magnetic resonance substudy from the APEX-AMI trial. *JACC Cardiovasc Imaging*. 2010;3(1):52-60.

23. Kim RJ, Albert TS, Wible JH, et al; Gadoversetamide Myocardial Infarction Imaging Investigators. Performance of delayed-enhancement magnetic resonance imaging with gadoversetamide contrast for the detection and assessment of myocardial infarction: an international, multicenter, double-blinded, randomized trial. *Circulation*. 2008;117(5):629-637.

24. Stone GW, Dixon SR, Grines CL, et al. Predictors of infarct size after primary coronary angioplasty in acute myocardial infarction from pooled analysis from four contemporary trials. *Am J Cardiol*. 2007;100(9):1370-1375.

25. O'Neill WW, Martin JL, Dixon SR, et al; AMIHOT Investigators. Acute Myocardial Infarction with Hyperoxemic Therapy (AMIHOT): a prospective, randomized trial of intracoronary hyperoxemic reperfusion after percutaneous coronary intervention. *J Am Coll Cardiol*. 2007;50(5):397-405.

26. Thiele H, Schindler K, Friedenberger J, et al. Intracoronary compared with intravenous bolus abciximab application in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: the randomized Leipzig Immediate Percutaneous Coronary Intervention Abciximab IV Versus IC in ST-Elevation Myocardial Infarction trial. *Circulation*. 2008;118(1):49-57.

27. Francone M, Bucciarelli-Ducci C, Carbone I, et al. Impact of primary coronary angioplasty delay on myocardial salvage, infarct size, and microvascular damage in patients with ST-segment elevation myocardial infarction: insight from cardiovascular magnetic resonance. *J Am Coll Cardiol*. 2009;54(23):2145-2153.

28. Eitel I, Desch S, Fuernau G, et al. Prognostic significance and determinants of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. *J Am Coll Cardiol*. 2010;55(22):2470-2479.

29. Bonnefoy E, Steg PG, Boutitie F, et al; CAPTIM Investigators. Comparison of Primary Angioplasty and Pre-Hospital Fibrinolysis in Acute Myocardial Infarction (CAPTIM) trial: a 5-year follow-up. *Eur Heart J*. 2009;30(13):1598-1606.

30. Perera D, Stables R, Thomas M, et al; BCIS-1 Investigators. Elective intra-aortic balloon counterpulsation during high-risk percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2010;304(8):867-874.