The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 4, 2012 VOL. 367 NO. 14

Intraaortic Balloon Support for Myocardial Infarction with Cardiogenic Shock

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ABSTRACT

BACKGROUND

In current international guidelines, intraaortic balloon counterpulsation is considered to be a class I treatment for cardiogenic shock complicating acute myocardial infarction. However, evidence is based mainly on registry data, and there is a paucity of randomized clinical trials.

METHODS

In this randomized, prospective, open-label, multicenter trial, we randomly assigned 600 patients with cardiogenic shock complicating acute myocardial infarction to intraaortic balloon counterpulsation (IABP group, 301 patients) or no intraaortic balloon counterpulsation (control group, 299 patients). All patients were expected to undergo early revascularization (by means of percutaneous coronary intervention or bypass surgery) and to receive the best available medical therapy. The primary efficacy end point was 30-day all-cause mortality. Safety assessments included major bleeding, peripheral ischemic complications, sepsis, and stroke.

RESULTS

A total of 300 patients in the IABP group and 298 in the control group were included in the analysis of the primary end point. At 30 days, 119 patients in the IABP group (39.7%) and 123 patients in the control group (41.3%) had died (relative risk with IABP, 0.96; 95% confidence interval, 0.79 to 1.17; P=0.69). There were no significant differences in secondary end points or in process-of-care measures, including the time to hemodynamic stabilization, the length of stay in the intensive care unit, serum lactate levels, the dose and duration of catecholamine therapy, and renal function. The IABP group and the control group did not differ significantly with respect to the rates of major bleeding (3.3% and 4.4%, respectively; P=0.51), peripheral ischemic complications (4.3% and 3.4%, P=0.53), sepsis (15.7% and 20.5%, P=0.15), and stroke (0.7% and 1.7%, P=0.28).

CONCLUSIONS

The use of intraaortic balloon counterpulsation did not significantly reduce 30-day mortality in patients with cardiogenic shock complicating acute myocardial infarction for whom an early revascularization strategy was planned. (Funded by the German Research Foundation and others; IABP-SHOCK II ClinicalTrials.gov number, NCT00491036.)

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*Investigators in the Intraaortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on August 27, 2012, at NEJM.org.

N Engl J Med 2012;367:1287-96.
DOI: 10.1056/NEJMoa1208410
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The rate of death among patients with cardiogenic shock complicating acute myocardial infarction is high even when the patients undergo early revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).[1-4] Intraaortic balloon counterpulsation is the most widely used form of mechanical hemodynamic support in this clinical setting.[5] In U.S. and European guidelines, the use of an intraaortic balloon in the treatment of cardiogenic shock is given a class IB and class IC recommendation, respectively.[6-8] However, evidence is based mainly on registry data, and there is a lack of adequately powered randomized trials. A meta-analysis that included only cohort studies suggested that the use of an intraaortic balloon pump is associated with a reduction by 11% in the risk of death.[9] In the recent Intraaortic Balloon Pump in Cardiogenic Shock (IABP-SHOCK) trial, which involved only 45 patients, no significant difference was observed with respect to the Acute Physiology and Chronic Health Evaluation II (APACHE II) score for severity of illness between patients assigned to intraaortic balloon counterpulsation and those assigned to a control group that received standard care, although serial brain natriuretic peptide levels were significantly reduced in the balloon-pump group.[10] The inconclusive evidence might be one explanation for the current use of intraaortic balloons in only 25 to 40% of patients with cardiogenic shock, despite the recommendations in the guidelines.[5] The IABP-SHOCK II trial was designed to test the hypothesis that intraaortic balloon counterpulsation, as compared with the best available medical therapy alone, results in a reduction in mortality among patients with acute myocardial infarction complicated by cardiogenic shock for whom early revascularization is planned.

Methods

Study Oversight

The IABP-SHOCK II trial was a multicenter, open-label, randomized study. The design of the trial has been published previously.[11] The trial was designed by the first author and modified by the steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org); the trial design was approved by the ethics committee at each participating center. Neither Maquet Cardiopulmonary nor Teleflex Medical, both of which supported the study with unrestricted grants, had any involvement in the study. Data were maintained at the Myocardial Infarction Research Institute in Ludwigshafen, Germany, where all the statistical analyses were performed by independent personnel. The steering committee vouches for the integrity and completeness of the data, and the statistician for the accuracy of data analysis; all the authors vouch for the fidelity of the study to the trial protocol, which is available at NEJM.org.

Patients

Patients were eligible for the trial if they presented with an acute myocardial infarction (with or without ST-segment elevation) complicated by cardiogenic shock and if early revascularization (by means of PCI or CABG) was planned. A patient was considered to be in cardiogenic shock if he or she had a systolic blood pressure of less than 90 mm Hg for more than 30 minutes or needed infusion of catecholamines to maintain a systolic pressure above 90 mm Hg, had clinical signs of pulmonary congestion, and had impaired end-organ perfusion. The diagnosis of impaired end-organ perfusion required at least one of the following: altered mental status; cold, clammy skin and extremities; oliguria with urine output of less than 30 ml per hour; or serum lactate level higher than 2.0 mmol per liter.

Patients were not eligible for the study if they had undergone resuscitation for more than 30 minutes; had no intrinsic heart action; were in a coma with fixed dilatation of pupils that was not induced by drugs; had a mechanical cause of cardiogenic shock (e.g., ventricular septal defect or papillary muscle rupture); had onset of shock more than 12 hours before screening; had a massive pulmonary embolism, severe peripheral arterial disease precluding insertion of an intraaortic balloon pump, or aortic regurgitation greater than grade II in severity (on a scale of I to IV, with higher grades indicating more severe regurgitation); were older than 90 years of age; were in shock as a result of a condition other than acute myocardial infarction; or had a severe concomitant disease associated with a life expectancy of less than 6 months. Patients in cardiogenic shock who were not eligible for randomization were entered into a registry. All patients or their legally authorized representatives provided written informed consent.[11]

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Table 1. Baseline Characteristics of the Patients.*

Characteristic	IABP (N=301)	Control (N=299)
Age — yr		
Median	70	69
Interquartile range	58–78	58–76
Male sex — no. (%)	202 (67.1)	211 (70.6)
Weight — kg		
Median	80	81
Interquartile range	73–90	73–90
Height — cm		
Median	172	175
Interquartile range	165–178	168–180
Body-mass index†		
Median	27.5	26.9
Interquartile range	24.7–30.1	24.7–29.4
Cardiovascular risk factors — no./total no. (%)		
Current smoking	96/295 (32.5)	108/299 (36.1)
Hypertension	213/296 (72.0)	199/299 (66.6)
Hypercholesterolemia	122/295 (41.4)	105/299 (35.1)
Diabetes mellitus	105/297 (35.4)	90/299 (30.1)
Prior myocardial infarction — no./total no. (%)	71/300 (23.7)	61/299 (20.4)
Prior stroke — no./total no. (%)	24/300 (8.0)	20/299 (6.7)
Known peripheral arterial disease — no./total no. (%)	40/300 (13.3)	33/299 (11.0)
Prior PCI — no./total no. (%)	63/299 (21.1)	52/299 (17.4)
Prior bypass surgery — no./total no. (%)	20/300 (6.7)	12/299 (4.0)

* Patients were randomly assigned to intraaortic balloon counterpulsation (IABP) or no intraaortic balloon counterpulsation (control); all the patients were expected to undergo early revascularization and to receive the best available medical therapy. There were no significant differences between the groups in the baseline characteristics listed here. PCI denotes percutaneous coronary intervention.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

TREATMENT

Eligible patients were randomly assigned, in a 1:1 ratio, to intraaortic balloon counterpulsation (IABP group) or no intraaortic balloon counterpulsation (control group). Randomization was performed centrally with the use of an Internet-based program, with stratification according to center.

The intraaortic balloon pump was inserted either before the PCI or immediately after the PCI, with the timing of the insertion at the discretion of the investigator. Support was initiated with the use of 1:1 electrocardiographic triggering (i.e., balloon inflation and deflation triggered by the R wave) and was maintained until there was sustained hemodynamic stabilization, which was defined as a systolic blood pressure higher than 90 mm Hg for more than 30 minutes without the need for catecholamines.[11] Weaning from the pump was achieved by means of reduction of the trigger ratio.[11] Crossover of patients in the control group to intraaortic balloon counterpulsation was allowed only if mechanical complications (ventricular septal defect or papillary muscle rupture) developed after randomization.

All the patients were expected to undergo early revascularization and to receive the best available medical treatment according to guidelines.[6-8,12] The mode of revascularization (primary PCI with treatment of the target lesion only, PCI of the target lesion plus additional immediate or staged PCI of nontarget lesions, or CABG) was left to the discretion of the operator. Intensive care treat-

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ment was standardized according to the German–Austrian S3 Guideline, which was provided to all study sites.[12]

END POINTS

The primary study end point was 30-day all-cause mortality. Secondary end points included serial assessments of serum lactate levels, creatinine clearance (measured with the use of the Cockcroft–Gault formula[13]), C-reactive protein levels, and severity of disease as assessed with the use of the Simplified Acute Physiology Score (SAPS) II. The SAPS II is calculated from 17 variables; scores range from 0 to 163, with higher scores indicating more severe disease.[14] We also assessed process-of-care outcomes including blood pressure and heart rate before and after revascularization, the time to hemodynamic stabilization, the dose and duration of catecholamine therapy, the requirement for renal-replacement therapy, the length of stay in the intensive care unit, the requirement for and length of time on mechanical ventilation, and the requirement for implantation of an active (percutaneous or surgical) left ventricular assist device or for heart transplantation.

Safety end points included severe or life-threat-

Table 2. Clinical Course before Randomization.*

Variable	IABP (N=301)	Control (N=299)
Sign of impaired organ perfusion — no./total no. (%)		
Altered mental status	215/300 (71.7)	232/299 (77.6)
Cold, clammy skin and extremities	257/300 (85.7)	245/299 (81.9)
Oliguria	90/300 (30.0)	99/299 (33.1)
Serum lactate >2.0 mmol/liter	226/300 (75.3)	218/298 (73.2)
Serum lactate — mmol/liter		
Median	3.6	4.7
Interquartile range	2.1–7.2	2.3–8.2
Fibrinolysis <24 hr before randomization — no. (%)	28 (9.3)	20 (6.7)
Resuscitation before randomization — no. (%)	127 (42.2)	143 (47.8)
Myocardial infarction — no./total no. (%)		
Non–ST-segment elevation	96/300 (32.0)	81/298 (27.2)
ST-segment elevation	200/300 (66.7)	212/298 (71.1)
Anterior	136/298 (45.6)	116/296 (39.2)
Systolic blood pressure — mm Hg		
Median	89	90
Interquartile range	79–107	80–109
Diastolic blood pressure — mm Hg		
Median	55	55
Interquartile range	46–67	45–65
Mean blood pressure — mm Hg†		
Median	69	68
Interquartile range	59–80	59–80
Use of catecholamines at randomization — no./total no. (%)	270/301 (89.7)	268/298 (89.9)
Heart rate — beats/min		
Median	92	92
Interquartile range	72–110	75–110
Creatinine — mg/dl		
Median	1.30	1.26
Interquartile range	1.04–1.67	1.03–1.64

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Table 2. (Continued.)

Variable	IABP (N=301)	Control (N=299)
Creatinine clearance — ml/min‡		
Median	60.7	56.8
Interquartile range	43.4–86.6	39.7–78.1
No. of diseased vessels — no./total no. (%)		
1	61/296 (20.6)	65/293 (22.2)
2	81/296 (27.4)	74/293 (25.3)
3	154/296 (52.0)	154/293 (52.6)
Infarct-related artery — no./total no. (%)		
Left anterior descending	132/293 (45.1)	121/293 (41.3)
Left circumflex	55/293 (18.8)	57/293 (19.5)
Right coronary artery	73/293 (24.9)	79/293 (27.0)
Left main	26/293 (8.9)	28/293 (9.6)
Bypass graft	7/293 (2.4)	8/293 (2.7)
Left ventricular ejection fraction — %		
Median	35	35
Interquartile range	25–45	25–45

* There were no significant differences between the groups with respect to any of the variables listed. To convert the values for creatinine to micromoles per liter, multiply by 88.4.
† The mean blood pressure, an approximation of the time-weighted average of blood pressure values in large arteries during the cardiac cycle, is derived from the area under the curve for invasive blood pressure measurements.
‡ Creatinine clearance was calculated with the use of the Cockcroft–Gault formula.

ening bleeding and moderate bleeding during the hospital stay, as assessed according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria[15]; peripheral ischemic vascular complications requiring surgical or interventional therapy; sepsis with clinical signs of infection and elevated procalcitonin levels (2 ng per milliliter or higher); and stroke, identified by the presence of new neurologic symptoms in conjunction with signs of ischemia or bleeding on computed tomography.

STATISTICAL ANALYSIS

The study was powered to detect a difference of 12 percentage points in 30-day survival rates, assuming a rate of 56% in the control group. An independent data and safety monitoring board conducted interim analyses after enrollment of 33% and 66% of the patients, using a group sequential design with an O'Brien–Fleming boundary.[11] The global type I error level was set at 0.05. The trial could be discontinued if the null hypothesis of equal survival rates was rejected at a significance level of 0.0005 at the first interim analysis or 0.014 at the second interim analysis. The final analysis was undertaken at an alpha level of 0.044. Therefore, 282 patients per group were needed to test the null hypothesis with the desired power. The estimate of the sample size took into consideration a putative center effect, which was assumed to be within a range of ±5% for almost all centers (95%). The intraclass correlation coefficient was then 0.0013, yielding a total of 588 patients to be evaluated. To allow for a 2% dropout rate, we recruited 600 patients.

All the data were analyzed according to the intention-to-treat principle. In addition, a per-protocol analysis of the primary end point, which included data from all patients who had confirmed acute myocardial infarction with the exclusion of those who crossed over, was performed to evaluate the robustness of the data. For the primary end point, the chi-square test was used to compare mortality between the two groups. Cumulative mortality throughout the first 30 days after randomization was characterized with the use of Kaplan–Meier plots, with the log-rank test used for the comparison between the two groups. Secondary end points were assessed with the use of Fisher's exact test or the chi-square test for binary

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Table 3. Clinical Outcomes.

Outcome	IABP (N=300)	Control (N=298)	P Value	Relative Risk with IABP (95% CI)
	number (percent)			
Primary end point: all-cause mortality at 30 days	119 (39.7)	123 (41.3)	0.69	0.96 (0.79–1.17)
Reinfarction in hospital	9 (3.0)	4 (1.3)	0.16	2.24 (0.70–7.18)
Stent thrombosis in hospital	4 (1.3)	3 (1.0)	0.71	1.32 (0.30–5.87)
Stroke in hospital	2 (0.7)	5 (1.7)	0.28	0.40 (0.08–2.03)
Ischemic	2 (0.7)	4 (1.3)	0.45	0.49 (0.09–2.71)
Hemorrhagic	0	1 (0.3)	0.50	—
Peripheral ischemic complications requiring intervention in hospital	13 (4.3)	10 (3.4)	0.53	1.29 (0.58–2.90)
Bleeding in hospital*				
Life-threatening or severe	10 (3.3)	13 (4.4)	0.51	0.76 (0.34–1.72)
Moderate	52 (17.3)	49 (16.4)	0.77	1.05 (0.74–1.50)
Sepsis in hospital	47 (15.7)	61 (20.5)	0.15	0.77 (0.54–1.08)

* Bleeding during the hospital stay was assessed according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria.

end points and a Mann–Whitney U test for quantitative end points.

Prespecified subgroup analyses were performed in subgroups defined according to sex, age (<50 years, 50 to 75 years, or >75 years), presence or absence of diabetes, presence or absence of arterial hypertension, myocardial infarction with ST-segment elevation versus myocardial infarction without ST-segment elevation, anterior versus non-anterior myocardial infarction, and previous or no previous myocardial infarction. Post hoc subgroup analyses were performed in subgroups defined according to the presence or absence of induced mild hypothermia and systolic blood pressure of less than 80 mm Hg versus 80 or more mm Hg at the time of randomization.

RESULTS

PATIENTS

Between June 16, 2009, and March 3, 2012, we screened 790 patients with cardiogenic shock at 37 centers in Germany (Fig. S1 in the Supplementary Appendix). A total of 600 of these patients (75.9%) were enrolled and were randomly assigned to intraaortic balloon counterpulsation (IABP group, 301 patients) or no intraaortic balloon counterpulsation (control group, 299 patients). Among the patients in the control group, 30 patients (10.0%) subsequently underwent insertion of an intraaortic balloon pump, most within the first 24 hours after randomization; in the case of 26 of these patients the crossovers were considered to be protocol violations. In addition, 13 patients randomly assigned to the IABP group (4.3%) did not undergo insertion of an intraaortic balloon pump, most often because the patient died before the planned insertion. The baseline characteristics were well balanced between the two groups (Tables 1 and 2).

TREATMENT

The procedure used most often for early revascularization was primary PCI (in 95.8% of the patients) (Table S1 in the Supplementary Appendix). Only 3.5% of patients underwent immediate bypass surgery or initial PCI with subsequent bypass surgery. No revascularization was performed in 3.2% of the patients (Fig. S1 in the Supplementary Appendix). Concomitant medications and treatments are shown in Table S1 in the Supplementary Appendix. The median duration of intraaortic balloon pump support was 3.0 days (interquartile range, 2.0 to 4.0; range, 1 to 16).

PRIMARY AND SECONDARY END POINTS

One patient in the IABP group was lost to follow-up before 30 days, and 1 patient in the control group withdrew consent; therefore, 300 patients in the IABP group and 298 in the control group were

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included in the analysis of the primary end point. At 30 days, mortality was similar among patients in the IABP group and those in the control group (39.7% and 41.3%, respectively; relative risk with IABP, 0.96; 95% confidence interval [CI], 0.79 to 1.17; P=0.69) (Table 3 and Fig. 1). Only minor differences in the relative risk estimates were observed in an analysis restricted to the per-protocol population (mortality, 37.5% in the IABP group and 41.4% in the control group; relative risk, 0.91; 95% CI, 0.74 to 1.11; P=0.35) or in multivariate modeling with adjustment for variables including non–ST-segment elevation myocardial infarction, anterior myocardial infarction, resuscitation before randomization, and clinical site (relative risk, 0.95; 95% CI, 0.68 to 1.32; P=0.75).

Results with respect to the primary end points were consistent in all prespecified and post hoc subgroups (Fig. 2). Among the 277 patients in whom an intraaortic balloon pump was inserted and who underwent revascularization, there was no significant difference in mortality between the 37 patients (13.4%) in whom the balloon pump was inserted before revascularization and the 240 patients (86.6%) in whom the balloon pump was inserted after revascularization (mortality, 36.4% and 36.8%, respectively; P=0.96).

There were no significant differences between study groups with respect to process-of-care outcomes (Table S1 in the Supplementary Appendix). There was a trend toward a higher rate of implantation of a ventricular assist device in the control group than in the IABP group. A total of 33 patients (5.5%) received ventricular assist devices, and the mortality among these patients was higher than that among patients who did not receive a ventricular assist device (69.7% vs. 38.8%, P<0.001).

Serum lactate levels were similar in the two groups (Fig. S2 in the Supplementary Appendix). Renal function at baseline and during daily follow-up did not differ significantly between the groups (Fig. S3 in the Supplementary Appendix). C-reactive protein levels were significantly lower at baseline in the control group than in the IABP group but were similar in the two groups at daily follow-up measurements (Fig. S4 in the Supplementary Appendix). The SAPS II score, which was a measure of disease severity, was significantly lower in the IABP group than in the control group at days 2 and 3 but not at baseline or day 4 (Fig. S5 in the Supplementary Appendix).

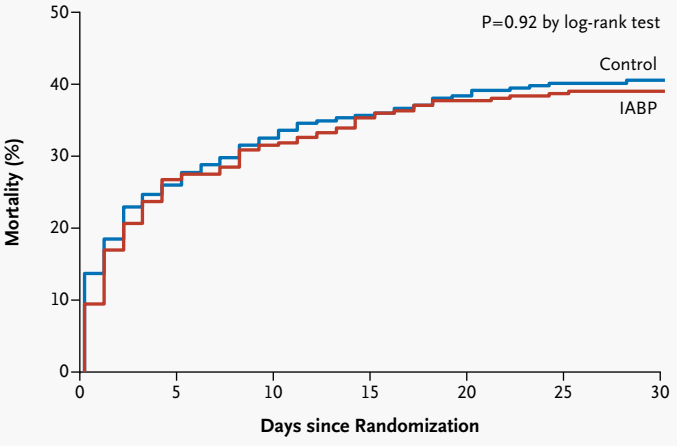


Figure 1. Time-to-Event Curves for the Primary End Point.
Time-to-event curves are shown through 30 days after randomization for the primary end point of all-cause mortality. Event rates represent Kaplan–Meier estimates.

SAFETY

The results with respect to safety end points are shown in Table 3. There were no significant differences between the IABP group and the control group with respect to the rates of stroke, bleeding, sepsis, or peripheral ischemic complications requiring intervention in the hospital. There were also no significant differences in the rates of reinfarction or stent thrombosis.

DISCUSSION

In this large, randomized trial involving patients with cardiogenic shock complicating acute myocardial infarction, for whom early revascularization was planned, intraaortic balloon pump support did not reduce 30-day mortality. These results are reinforced by a lack of significant between-group differences in multiple secondary end points and process-of-care outcomes.

Death in patients with cardiogenic shock can result from one or more of three factors: hemodynamic deterioration, occurrence of multiorgan dysfunction, and development of the systemic inflammatory response syndrome.[10,16] Our trial provides some information regarding the effect of intraaortic balloon counterpulsation on all these factors. There was no immediate improvement in blood pressure or heart rate among patients in whom an intraaortic balloon pump was inserted, as compared with those who did not have a bal-

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Baseline Variable	No. of Patients	IABP	Control	Relative Risk (95% CI)	P Value for Interaction
		30-day mortality (%)			
Sex					0.61
Female	187	44.4	43.2	1.03 (0.74–1.43)	
Male	411	37.3	40.5	0.92 (0.72–1.18)	
Age					0.09
<50 yr	70	19.4	44.1	0.44 (0.21–0.95)	
50–75 yr	334	34.6	36.5	0.95 (0.71–1.27)	
>75 yr	194	53.7	50.0	1.07 (0.81–1.41)	
Diabetes					0.82
Yes	195	42.9	46.7	0.92 (0.67–1.26)	
No	399	37.2	38.9	0.96 (0.74–1.23)	
Hypertension					0.05
Yes	410	42.9	40.4	1.06 (0.84–1.34)	
No	183	28.9	43.0	0.67 (0.45–1.01)	
Type of MI					0.76
STEMI/LBBB	412	41.0	42.9	0.96 (0.77–1.21)	
Non-STEMI	177	37.5	38.3	0.98 (0.67–1.43)	
STEMI type					0.14
Anterior	216	35.4	43.7	0.81 (0.58–1.13)	
Nonanterior	196	48.3	42.2	1.16 (0.85–1.57)	
Previous infarction					0.04
Yes	131	47.9	33.3	1.44 (0.93–2.21)	
No	466	37.3	43.3	0.86 (0.69–1.07)	
Hypothermia					0.31
Yes	226	48.1	44.2	1.09 (0.82–1.44)	
No	372	35.1	39.3	0.89 (0.68–1.16)	
Blood pressure					0.76
<80 mm Hg	161	50.7	46.4	1.09 (0.79–1.50)	
≥80 mm Hg	432	35.9	39.2	0.92 (0.72–1.17)	

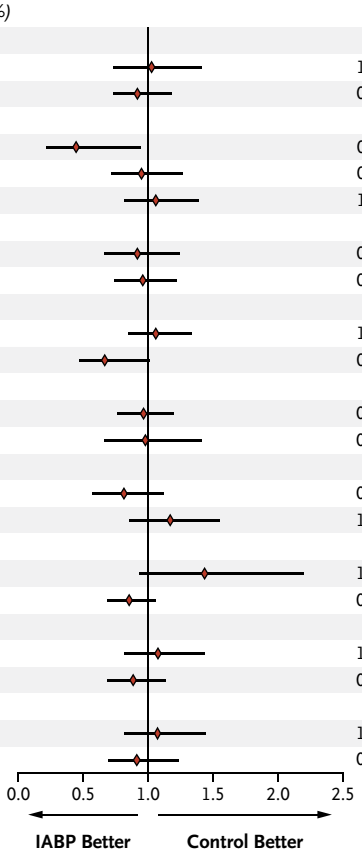


Figure 2. Subgroup Analyses of the Primary End Point.

The forest plot shows the relative risk (with 95% confidence intervals) of the primary end point according to subgroups. Included are all patients with 30-day follow-up data. LBBB denotes left bundle-branch block, MI myocardial infarction, and STEMI ST-segment elevation myocardial infarction.

loon pump inserted. Although there was a positive effect of intraaortic balloon counterpulsation on multiorgan dysfunction at day 2 and day 3, as assessed with the use of the SAPS II, this effect was not evident at day 4. There were also no significant effects on C-reactive protein level or serum lactate level, which were assessed as measures of inflammation and tissue oxygenation.

Experimental and clinical studies have indicated that intraaortic balloon counterpulsation results in a hemodynamic benefit as a result of afterload reduction and diastolic augmentation with improvement in coronary perfusion.[17] However, the effects on cardiac output are modest and might not be sufficient to reduce mortality.[17] In a recent, small, randomized trial, there were no significant differences in cardiac power output, left ventricular stroke-work index, or systemic vascular resistance between patients assigned to intraaortic balloon counterpulsation and those assigned to a control group.[18]

The use of intraaortic balloon counterpulsation before coronary revascularization may make the revascularization procedure safer by improving left ventricular unloading.[19] However, in the current trial, there was no mortality benefit in the subgroup of patients in whom the intraaortic balloon pump was inserted before the start of revascularization, as compared with those in whom it was inserted after revascularization. In another recent randomized trial involving patients with large anterior infarctions but without cardiogenic shock, insertion of a balloon pump before PCI, as compared with control treatment (no intraaor-

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tic balloon pump), did not reduce the infarct size.[20] Other randomized trials involving patients without cardiogenic shock, several of which were performed before the advent of coronary stenting, also showed no clinical benefit from the use of balloon counterpulsation.[9]

In this trial, we sought to minimize crossover from the control group to the IABP group. To do so, we selected hospitals that do not require the routine use of the intraaortic balloon pump in this clinical setting, and we specified that balloon pumps should be used in the control group only for patients in whom mechanical complications developed. Despite these efforts, 30 crossovers occurred; 26 of these were inconsistent with the protocol, and 12 of these 26 were based entirely on the discretion of the investigator. These 12 patients had baseline characteristics that were similar to those of patients who did not cross over, which suggests that no clear objective criteria led to the protocol violation. In addition, the crossovers occurred mainly in five centers, which further suggests that there was a subjective basis for the decision to initiate intraaortic balloon pump therapy.

The trial protocol allowed for the insertion of a ventricular assist device on the basis of the investigator's clinical judgment. Currently, there are no well-defined clinical criteria for the insertion of ventricular assist devices, and scientific evidence is scarce. Only three randomized trials involving a total of 100 patients have compared ventricular assist with intraaortic balloon counterpulsation.[21] The use of ventricular assist devices was low in our trial. However, there was a trend toward a higher rate of implantation of ventricular assist devices in the control group than in the IABP group. This finding might have been a consequence of the lack of well-defined criteria for device insertion and an assumption by the investigators that ventricular assist was more likely to be necessary when the patient did not receive balloon pump support.[22] Ventricular assist devices provide greater hemodynamic benefit than balloon counterpulsation but are associated with a higher rate of adverse events and no proven survival benefit.[5,21,23] On the basis of existing data, current guidelines do not recommend ventricular assist devices as first-line therapy for patients with acute myocardial infarction and cardiogenic shock.[8]

Our trial had a number of limitations. First, blinding was not possible because of the nature of the intervention. To minimize bias, we made use of a central randomization system, and the members of the clinical events committee were unaware of the group assignments. Second, we did not obtain hemodynamic measurements or assess laboratory inflammatory markers other than blood pressure, heart rate, and C-reactive protein levels, although data on these variables are available from previous trials.[24-27] Third, the slightly lower mortality in our trial — approximately 40%, as compared with 42 to 48% in other randomized trials and registries — might suggest that our trial included a higher percentage of patients with mild or moderately severe cardiogenic shock, a factor that could preclude generalization of the results to patients with the most severe forms of cardiogenic shock.[1-4,28] However, on the basis of a post hoc analysis, there was no mortality benefit of intraaortic balloon counterpulsation among patients with a systolic blood pressure of less than 80 mm Hg. Fourth, given the negative overall result, we cannot definitively rule out a type II error; however, the minor absolute difference in mortality, together with the lack of benefit with respect to secondary end points, makes any clinically meaningful positive effect unlikely. Finally, we do not yet have any information about longer-term outcomes. Since intraaortic balloon counterpulsation was used for a median of only 3 days, it seems unlikely that any beneficial effect will become evident later than 30 days. Nevertheless, further assessments are planned at 6 months and at 12 months for further corroboration of the 30-day findings.

In conclusion, we conducted a randomized, controlled trial of intraaortic balloon pump support in patients with cardiogenic shock complicating myocardial infarction for whom early revascularization was planned. Use of intraaortic balloon counterpulsation, as compared with conventional therapy, did not reduce 30-day mortality.

Supported by grants from the German Research Foundation, the German Heart Research Foundation, the German Cardiac Society, Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte, and the University of Leipzig–Heart Center and by unrestricted grants from Maquet Cardiopulmonary and Teleflex Medical.

Dr. Thiele reports receiving consulting fees from Eli Lilly, grant support on behalf of his institution from Eli Lilly and Terumo, and lecture fees from AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, the Medicines Company, and Terumo; Dr. Zeymer, serving on the board of Daiichi Sankyo and Eli Lilly and receiving consulting and lecture fees from Daiichi Sankyo, Eli Lilly, and the Medicines Company; Dr. Richardt, receiving lecture fees from Maquet Cardiovascular; Dr. Böhm, receiving consulting fees from AstraZeneca, Bayer, Boehringer

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Ingelheim, Daiichi Sankyo, Medtronic, Merck, Novartis, Pfizer, Sanofi Aventis, and Servier and lecture fees from AstraZeneca, AWD.pharma Dresden, Bayer, Berlin-Chemie, Boehringer Ingelheim, Daiichi Sankyo, Merck, Novartis, Pfizer, Sanofi Aventis, and Servier; Dr. Schneider, serving on the ethics committee of Landesärztekammer Baden-Württemberg, receiving payment for manuscript preparation from Biosense Webster, Grupo Ferrer, and Nycomed, and receiving money on behalf of the clinical research organization at his institution from Abbott Vascular, AstraZeneca, Bayer Schering, Bayer Vital, Biotronik, Bristol-Myers Squibb, Boehringer Ingelheim, Cordis, Daiichi Sankyo, Diagenics, Enverdis, Eli Lilly, GlaxoSmithKline, Guidant, IKKF, Impulse Dynamics, Medtronic, Merck, Novartis, Roche Diagnostics, Sanofi Aventis, Schering-Plough, Siemens, St. Jude Medical, Takeda Pharma, Trommsdorff, and Vifor Pharma; and Dr. Werdan, serving on the board of Biotest and Servier, receiving grant support on behalf of his institution from Biotest and Servier, and receiving lecture fees from Biotest, Brahms, Maquet Cardiovascular, and Servier. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients who agreed to participate in this trial and the staff who helped recruit patients.

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