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PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock

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ABSTRACT

BACKGROUND

In patients who have acute myocardial infarction with cardiogenic shock, early revascularization of the culprit artery by means of percutaneous coronary intervention (PCI) improves outcomes. However, the majority of patients with cardiogenic shock have multivessel disease, and whether PCI should be performed immediately for stenoses in nonculprit arteries is controversial.

METHODS

In this multicenter trial, we randomly assigned 706 patients who had multivessel disease, acute myocardial infarction, and cardiogenic shock to one of two initial revascularization strategies: either PCI of the culprit lesion only, with the option of staged revascularization of nonculprit lesions, or immediate multivessel PCI. The primary end point was a composite of death or severe renal failure leading to renal-replacement therapy within 30 days after randomization. Safety end points included bleeding and stroke.

RESULTS

At 30 days, the composite primary end point of death or renal-replacement therapy had occurred in 158 of the 344 patients (45.9%) in the culprit-lesion-only PCI group and in 189 of the 341 patients (55.4%) in the multivessel PCI group (relative risk, 0.83; 95% confidence interval [CI], 0.71 to 0.96; P=0.01). The relative risk of death in the culprit-lesion-only PCI group as compared with the multivessel PCI group was 0.84 (95% CI, 0.72 to 0.98; P=0.03), and the relative risk of renal-replacement therapy was 0.71 (95% CI, 0.49 to 1.03; P=0.07). The time to hemodynamic stabilization, the risk of catecholamine therapy and the duration of such therapy, the levels of troponin T and creatine kinase, and the rates of bleeding and stroke did not differ significantly between the two groups.

CONCLUSIONS

Among patients who had multivessel coronary artery disease and acute myocardial infarction with cardiogenic shock, the 30-day risk of a composite of death or severe renal failure leading to renal-replacement therapy was lower among those who initially underwent PCI of the culprit lesion only than among those who underwent immediate multivessel PCI. (Funded by the European Union 7th Framework Program and others; CULPRIT-SHOCK ClinicalTrials.gov number, NCT01927549.)

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*A complete list of investigators in the Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial is provided in the Supplementary Appendix, available at NEJM.org.

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The mortality associated with cardiogenic shock in acute myocardial infarction can be reduced with the use of early revascularization, predominantly percutaneous coronary intervention (PCI), to restore blood flow to the culprit coronary artery.[1-3] Up to 80% of patients who have cardiogenic shock present with multivessel coronary artery disease,[4] and mortality is higher with multivessel disease than with single-vessel disease.[5-7] The value of performing immediate PCI for clinically important stenoses of major nonculprit coronary arteries is controversial, and to our knowledge, randomized trials that have addressed this issue have not included patients with cardiogenic shock.[8-11]

Several theoretical arguments support immediate revascularization of all coronary arteries with clinically important stenoses or chronic total occlusions in addition to the culprit lesion, particularly in patients with cardiogenic shock. The most notable argument is the potential to improve overall myocardial perfusion and function. However, immediate multivessel PCI might pose additional risks, such as induction of further ischemia, volume overload, and renal impairment due to the use of an increased dose of contrast material. Current evidence from nonrandomized studies involving patients with cardiogenic shock suggests that mortality at short-term follow-up is higher after immediate multivessel PCI than after PCI of the culprit lesion only.[12] Guideline recommendations differentiate between stable and unstable hemodynamic status.[13,14] European guidelines recommend the consideration of immediate PCI of nonculprit lesions in patients with cardiogenic shock. U.S. guidelines give no specific recommendation. However, recent U.S. appropriate-use criteria indicate that it is appropriate to perform immediate revascularization of a nonculprit artery if cardiogenic shock persists after revascularization of the culprit artery.[13-15] The Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial was designed to test the hypothesis that PCI of the culprit lesion only, with the option of staged revascularization of nonculprit lesions, would result in better clinical outcomes than immediate multivessel PCI among patients who have multivessel coronary artery disease and acute myocardial infarction with cardiogenic shock.

Methods

Trial Design and Oversight

The trial design has been published previously.[4] This investigator-initiated, randomized, open-label, European multicenter trial involved patients who had acute ST-segment elevation or non–ST-segment elevation myocardial infarction that was complicated by cardiogenic shock, with planned early revascularization by means of PCI and an identifiable culprit lesion. The protocol (available with the full text of this article at NEJM.org) was designed by the principal investigator and was modified and approved by the steering committee[4]; it was also approved by all relevant ethics committees. The trial was registered at ClinicalTrials.gov 4 months after enrollment of the first patient, as discussed in the Supplementary Appendix (available at NEJM.org).

The institutions that funded the trial had no involvement in the conduct of the trial. A coordinating research organization, Institut für Herzinfarktforschung (Institute for Myocardial Infarction Research), maintained the data and performed independent statistical analysis. The steering committee vouches for the integrity and completeness of the data, and the statistician vouches for the accuracy of the data analysis and the fidelity of the trial to the protocol.

Patients

Patients were eligible for the trial if they had acute myocardial infarction with cardiogenic shock. Additional eligibility criteria were planned early revascularization by means of PCI, multivessel coronary artery disease (defined as at least two major vessels [≥2 mm in diameter] with >70% stenosis of the diameter), and an identifiable culprit lesion. Criteria for cardiogenic shock included a systolic blood pressure of less than 90 mm Hg for longer than 30 minutes or the use of catecholamine therapy to maintain a systolic pressure of at least 90 mm Hg, clinical signs of pulmonary congestion, and signs of impaired organ perfusion with at least one of the following manifestations: altered mental status, cold and clammy skin and limbs, oliguria with a urine output of less than 30 ml per hour, or an arterial lactate level of more than 2.0 mmol per liter.

Exclusion criteria were resuscitation for longer

than 30 minutes, no intrinsic heart action, an assumed severe deficit in cerebral function with fixed dilated pupils, an indication for primary urgent coronary-artery bypass grafting, single-vessel coronary artery disease, a mechanical cause of cardiogenic shock, the onset of shock more than 12 hours before randomization, an age of more than 90 years, shock with a noncardiogenic cause, massive pulmonary embolism, known severe renal insufficiency (creatinine clearance, <30 ml per minute), and other severe concomitant disease associated with a life expectancy of less than 6 months. For all eligible patients, written informed consent was obtained with the use of a prespecified process that varied slightly according to country (see the Supplementary Appendix).[4] Patients with cardiogenic shock who were not eligible for randomization were entered into the prospective CULPRIT-SHOCK registry.

RANDOMIZATION AND TREATMENT

Patients underwent randomization immediately after diagnostic angiography. Randomization was performed centrally with the use of an Internet-based program with randomly changing blocks of four or six and stratification according to center.

Patients were randomly assigned, in a 1:1 ratio, to one of two initial revascularization strategies: either PCI of the culprit lesion only, with the option of staged revascularization of nonculprit lesions, or immediate multivessel PCI. In all the patients, PCI of the culprit lesion was performed first, with the use of standard interventional techniques. In patients in the culprit-lesion-only PCI group, all other lesions were to be left untreated at the time of the initial procedure. Staged revascularization procedures were encouraged on the basis of the presence of residual ischemic lesions (evaluated by means of noninvasive testing or with the use of fractional flow reserve [FFR]), symptoms, and clinical and neurologic status. In patients in the multivessel PCI group, PCI of all major coronary arteries with more than 70% stenosis of the diameter was to be performed. This included efforts to recanalize chronic total occlusions during the acute phase; the recommended maximum dose of contrast material was 300 ml.

All other interventional therapeutic measures were allowed, independent of the assigned treatment strategy. In particular, the use of mechanical circulatory support was left to the discretion of the operator. Further therapy was provided in the intensive care unit (ICU) in accordance with generally accepted intensive care guidelines. If renal-replacement therapy was deemed to be necessary, the method, duration, and reason for initiation (in accordance with predefined criteria) were documented.

PRIMARY AND SECONDARY END POINTS

The primary end point was a composite of death from any cause or severe renal failure leading to renal-replacement therapy within 30 days after randomization. Renal-replacement therapy (dialysis, hemofiltration, or hemodiafiltration) was considered for otherwise untreatable volume overload, hyperkalemia (potassium level, >6.0 mmol per liter), severe uremia (blood urea level, >50 mg per deciliter), or persistent severe metabolic acidosis (pH, <7.2).[4]

Clinical secondary end points included the individual components of the primary end point, recurrent myocardial infarction, rehospitalization for congestive heart failure, and repeat revascularization. Other secondary end points included time to hemodynamic stabilization, the use of catecholamine therapy and the duration of such therapy, the duration of the ICU stay, the Simplified Acute Physiology Score II (SAPS-II), and the use of mechanical ventilation and the duration of such therapy. For the assessment of renal and myocardial injury, serial measurements of estimated creatinine clearance and creatine kinase and troponin levels were obtained. Procedural success was included as a secondary end point but was not clearly prespecified, and therefore the results are not reported.

Safety end points included bleeding, which was defined as type 2, 3, or 5 on the Bleeding Academic Research Consortium (BARC) scale (with type 2 indicating any overt, actionable sign of bleeding; type 3 bleeding with a decrease in the hemoglobin level of >3 g per deciliter, any transfusion, cardiac tamponade, or intracranial or ocular involvement; and type 5 fatal bleeding), as well as occurrence of stroke.[4,16] Detailed definitions of the outcome measures and specific information regarding the reporting of individual prespecified end points are provided in the Supplementary Appendix.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Culprit-Lesion-Only PCI Group (N=344)	Multivessel PCI Group (N=342)
Age — yr		
Median	70	70
Interquartile range	60–78	60–77
Male sex — no./total no. (%)	257/343 (74.9)	267/342 (78.1)
Weight — kg		
Median	80	80
Interquartile range	70–90	75–90
Height — cm		
Median	174	175
Interquartile range	168–180	170–180
Body-mass index†		
Median	26.6	26.7
Interquartile range	24.2–29.4	24.7–29.4
Cardiovascular risk factors — no./total no. (%)		
Current smoking	85/334 (25.4)	89/325 (27.4)
Hypertension	200/339 (59.0)	206/335 (61.5)
Hypercholesterolemia	112/338 (33.1)	116/333 (34.8)
Diabetes mellitus	102/337 (30.3)	116/335 (34.6)
Previous myocardial infarction — no./total no. (%)	60/339 (17.7)	53/335 (15.8)
Previous stroke — no./total no. (%)	29/341 (8.5)	20/336 (6.0)
Known peripheral artery disease — no./total no. (%)	43/341 (12.6)	37/337 (11.0)
Previous PCI — no./total no. (%)	64/339 (18.9)	63/335 (18.8)
Previous coronary-artery bypass grafting — no./total no. (%)	20/341 (5.9)	13/337 (3.9)
Signs of impaired organ perfusion — no./total no. (%)		
Altered mental status	237/341 (69.5)	224/341 (65.7)
Cold, clammy skin and limbs	233/338 (68.9)	236/335 (70.4)
Oliguria	80/334 (24.0)	93/326 (28.5)
Arterial lactate >2.0 mmol/liter	216/334 (64.7)	224/330 (67.9)
Fibrinolysis <24 hr before randomization — no./total no. (%)	19/341 (5.6)	15/341 (4.4)
Resuscitation before randomization — no./total no. (%)	177/341 (51.9)	189/342 (55.3)
ST-segment elevation myocardial infarction — no./total no. (%)	206/335 (61.5)	209/330 (63.3)
Anterior ST-segment elevation myocardial infarction — no./total no. (%)	108/205 (52.7)	114/206 (55.3)
Left bundle-branch block — no./total no. (%)	52/335 (15.5)	47/331 (14.2)
Systolic blood pressure — mm Hg		
Median	100	100
Interquartile range	83–120	85–130
Diastolic blood pressure — mm Hg		
Median	60	61
Interquartile range	50–80	50–80
Mean blood pressure — mm Hg		
Median	76	76
Interquartile range	63–92	63–93

Table 1. (Continued.)

Characteristic	Culprit-Lesion-Only PCI Group (N = 344)	Multivessel PCI Group (N = 342)
Heart rate — beats/min		
Median	90	91
Interquartile range	73–109	72–107
Creatinine — mg/dl‡		
Median	1.17	1.20
Interquartile range	0.90–1.66	0.90–1.68
Creatinine clearance — ml/min		
Median	64	66
Interquartile range	42–95	43–93
No. of affected vessels — no./total no. (%)		
1	3/343 (0.9)	2/342 (0.6)
2	122/343 (35.6)	124/342 (36.3)
3	218/343 (63.6)	216/342 (63.2)
Vessel related to the infarction — no./total no. (%)		
Left anterior descending artery	132/343 (38.5)	156/342 (45.6)
Left circumflex artery	76/343 (22.2)	70/342 (20.5)
Right coronary artery	102/343 (29.7)	89/342 (26.0)
Left main artery	31/343 (9.0)	22/342 (6.4)
Bypass graft	2/343 (0.6)	5/342 (1.5)
≥1 Chronic total occlusion — no./total no. (%)	77/344 (22.4)	82/342 (24.0)
Left ventricular ejection fraction — %		
Median	33	30
Interquartile range	25–40	21–40

* PCI denotes percutaneous coronary intervention.
† Body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ To convert the values for creatinine to micromoles per liter, multiply by 88.4.

STATISTICAL ANALYSIS

To calculate the sample size, we estimated an event rate of the composite primary end point of death or renal-replacement therapy of 38% in the culprit-lesion-only PCI group and 50% in the multivessel PCI group.[4] A sequential statistical design was chosen; one interim analysis was performed after 50% of all the patients who could be evaluated had completed 30 days of follow-up. The global type I error level was 0.05. We calculated that a sample of 684 patients would give the trial 80% power to rule out the null hypothesis of no difference between the two treatment groups in the event rate for the primary end point (at a two-sided alpha level of 0.048 for the final analysis). To allow for a withdrawal rate of 3%, 706 patients were recruited. The software used for sample-size calculation was nQuery Advisor, version 7.0 (Statistical Solutions).

All data were analyzed according to the intention-to-treat principle. In addition, sensitivity analyses were performed in the per-protocol and as-treated populations (defined in Fig. S1 in the Supplementary Appendix) to evaluate data robustness. For the primary end point, chi-square testing was performed to compare event rates. Binary secondary end points were assessed by means of Fisher's exact tests or chi-square tests, and quantitative secondary end points were assessed by means of Mann–Whitney U tests. No correction for multiple testing was performed. Analyses were performed in subgroups that were defined accord-

Table 2. Procedural Characteristics.

Variable	Culprit-Lesion-Only PCI Group (N=344)	Multivessel PCI Group (N=342)	P Value
Arterial access — no./total no. (%)			
Femoral	287/343 (83.7)	277/342 (81.0)	0.36
Radial	61/343 (17.8)	66/342 (19.3)	0.61
Brachial	2/343 (0.6)	1/342 (0.3)	>0.99
Stent in culprit lesion — no./total no. (%)			
Any	326/343 (95.0)	324/342 (94.7)	0.86
Bare metal	20/326 (6.1)	17/324 (5.2)	0.63
Drug eluting	305/326 (93.6)	308/324 (95.1)	0.41
Bioresorbable scaffold in culprit lesion — no./total no. (%)	2/326 (0.6)	3/324 (0.9)	0.69
Aspiration thrombectomy of culprit lesion — no./total no. (%)	60/343 (17.5)	39/342 (11.4)	0.02*
TIMI grade for blood flow — no./total no. (%)†			
Before PCI of culprit lesion			
0	189/339 (55.8)	178/337 (52.8)	
I	37/339 (10.9)	45/337 (13.4)	
II	56/339 (16.5)	50/337 (14.8)	
III	57/339 (16.8)	64/337 (19.0)	0.49
After PCI of culprit lesion			
0	13/342 (3.8)	16/338 (4.7)	
I	12/342 (3.5)	8/338 (2.4)	
II	28/342 (8.2)	21/338 (6.2)	
III	289/342 (84.5)	293/338 (86.7)	0.46
Immediate PCI of nonculprit lesions — no./total no. (%)	43/344 (12.5)	310/342 (90.6)	<0.001
Immediate complete revascularization achieved — no./total no. (%)	26/344 (7.6)	277/342 (81.0)	<0.001
Total dose of contrast material — ml			<0.001
Median	190	250	
Interquartile range	140–250	200–350	
Total duration of fluoroscopy — min			<0.001
Median	13	19	
Interquartile range	7–20	12–29	
Staged PCI of nonculprit lesions — no./total no. (%)	60/344 (17.4)	8/341 (2.3)	<0.001
Staged coronary-artery bypass grafting — no./total no. (%)	1/344 (0.3)	0/341	>0.99
Mechanical circulatory support — no./total no. (%)			
Any	99/344 (28.8)	95/342 (27.8)	0.77
Intraaortic balloon pump	25/99 (25.3)	26/95 (27.4)	0.74
Impella 2.5 percutaneous ventricular assist device	16/99 (16.2)	18/95 (18.9)	0.61
Impella CP percutaneous ventricular assist device	30/99 (30.3)	18/95 (18.9)	0.07
TandemHeart percutaneous ventricular assist device	2/99 (2.0)	0/95	0.50
Extracorporeal membrane oxygenation	18/99 (18.2)	27/95 (28.4)	0.09
Other	12/99 (12.1)	8/95 (8.4)	0.40
Heart transplantation — no./total no. (%)	1/343 (0.3)	0/340	>0.99
Mild hypothermia — no./total no. (%)	111/344 (32.3)	118/340 (34.7)	0.50

Table 2. (Continued.)

Variable	Culprit-Lesion-Only PCI Group (N=344)	Multivessel PCI Group (N=342)	P Value
Mechanical ventilation — no./total no. (%)	273/344 (79.4)	282/339 (83.2)	0.20
Duration of mechanical ventilation — days			0.97
Median	3	3	
Interquartile range	1–7	1–7	
Duration of intensive care treatment — days			0.61
Median	5	5	
Interquartile range	2-12	2-11	
Antiplatelet and anticoagulant drugs administered in the catheterization laboratory — no./total no. (%)			
Aspirin	259/344 (75.3)	240/341 (70.4)	0.15
Clopidogrel	65/344 (18.9)	61/341 (17.9)	0.73
Prasugrel	47/344 (13.7)	41/341 (12.0)	0.52
Ticagrelor	76/344 (22.1)	83/341 (24.3)	0.49
Glycoprotein IIb/IIIa inhibitor	74/344 (21.5)	73/341 (21.4)	0.97
Cangrelor	8/344 (2.3)	11/341 (3.2)	0.47
Unfractionated heparin	276/344 (80.2)	281/341 (82.4)	0.47
Low-molecular-weight heparin	50/344 (14.5)	49/341 (14.4)	0.95
Bivalirudin	16/344 (4.7)	24/341 (7.0)	0.18
Subsequent medications in those who survived until hospital discharge — no./total no. (%)			
Statin	184/195 (94.4)	152/165 (92.1)	0.40
Beta-blocker	181/195 (92.8)	148/165 (89.7)	0.29
Angiotensin-converting–enzyme inhibitor or angiotensin II type 1 receptor antagonist	176/195 (90.3)	140/165 (84.8)	0.12
Aspirin	191/195 (97.9)	163/165 (98.8)	0.54
Clopidogrel	89/195 (45.6)	73/165 (44.2)	0.79
Prasugrel	67/195 (34.4)	56/165 (33.9)	0.93
Ticagrelor	78/195 (40.0)	65/165 (39.4)	0.91
Catecholamine therapy — no./total no. (%)	304/344 (88.4)	309/339 (91.2)	0.23
Duration of catecholamine therapy — days			0.43
Median	2	2	
Interquartile range	1–4	1–5	
Time to hemodynamic stabilization — days			0.56
Median	3	3	
Interquartile range	1–6	1–6	

* The difference between the two groups in the rate of aspiration thrombectomy would most likely not remain significant after adjustment for multiple testing.
† Thrombolysis in Myocardial Infraction (TIMI) grades for blood flow range from 0 to III, with higher grades indicating better flow. TIMI grades were reported by the investigator.

ing to sex, age (<50 years, 50 to 75 years, or >75 years), location of the infarction (anterior or nonanterior), number of affected vessels (two or three), type of myocardial infarction (ST-segment elevation or non–ST-segment elevation), and the presence or absence of diabetes, arterial hypertension, previous infarction, and chronic total occlusion.

RESULTS

PATIENTS

From April 2013 through April 2017, a total of 1075 patients with cardiogenic shock were screened at 83 European centers, and 706 of those patients (65.6%) were randomly assigned to the culprit-lesion-only PCI group (351 patients) or the multivessel PCI group (355 patients). Data could be evaluated for 344 patients in the culprit-lesion-only PCI group and for 342 patients in the multivessel PCI group (Fig. S1 in the Supplementary Appendix). Baseline characteristics were well balanced between the two treatment groups (Table 1).

TREATMENT

Procedural characteristics are shown in Table 2. Crossover from the culprit-lesion-only PCI group to the multivessel PCI group was reported in 43 patients (12.5%); reasons for crossover are shown in Table S1 in the Supplementary Appendix. Staged revascularization was performed in 61 of the 344 patients (17.7%) in the culprit-lesion-only PCI group. Crossover from the multivessel PCI group to the culprit-lesion-only PCI group was reported in 32 patients (9.4%); reasons for crossover are shown in Table S2 in the Supplementary Appendix.

The Thrombolysis in Myocardial Infarction (TIMI) grades for blood flow obtained before and after PCI of the culprit artery did not differ significantly between the two groups. More patients underwent aspiration thrombectomy in the culprit-lesion-only group than in the multivessel PCI group. The overall dose of contrast material was significantly higher and the duration of fluoroscopy was significantly longer in the multivessel PCI group than in the culprit-lesion-only group. There was no significant difference between the two groups with respect to the use of adjunctive medications or devices for mechanical circulatory support. Most patients were treated with multiple antiplatelet and anticoagulant drugs, including aspirin, $P2Y_{12}$ inhibitors, glycoprotein IIb/IIIa inhibitors, and unfractionated heparin.

PRIMARY AND SECONDARY END POINTS

One patient in the multivessel PCI group was lost to follow-up before 30 days. Therefore, 344 patients in the culprit-lesion-only PCI group and 341 patients in the multivessel PCI group were included in the analysis of the primary and secondary end points (Fig. S1 in the Supplementary Appendix).

At 30 days, the rate of the composite primary end point of death or renal-replacement therapy was significantly lower in the culprit-lesion-only PCI group than in the multivessel PCI group (45.9% vs. 55.4%; relative risk, 0.83; 95% confidence interval [CI], 0.71 to 0.96; P=0.01) (Table 3 and Fig. 1A). Only minor variation in the relative risk was observed when the analysis was performed in the per-protocol population (44.8% in the culprit-lesion-only PCI group vs. 55.1% in the multivessel PCI group; relative risk, 0.81; 95% CI, 0.69 to 0.96; P=0.01) or the as-treated population (46.0% in the culprit-lesion-only PCI group vs. 55.1% in the multivessel PCI group; relative risk, 0.83; 95% CI, 0.72 to 0.97; P=0.02). Prespecified subgroup analyses revealed consistent results across all the subgroups (Fig. 2).

The rate of death from any cause was significantly lower in the culprit-lesion-only PCI group than in the multivessel PCI group (43.3% vs. 51.6%; relative risk, 0.84; 95% CI, 0.72 to 0.98; P=0.03) (Table 3 and Fig. 1B). The causes of death are shown in Table S3 in the Supplementary Appendix. The rate of renal-replacement therapy did not differ significantly between the culprit-lesion-only PCI group and the multivessel PCI group (11.6% and 16.4%, respectively; relative risk, 0.71; 95% CI, 0.49 to 1.03; P=0.07) (Table 3 and Fig. 1C). The rates of recurrent myocardial infarction, rehospitalization for congestive heart failure, bleeding, and stroke did not differ significantly between the two groups (Table 3). Event rates for the primary end point and its components among patients in the CULPRIT-SHOCK registry are shown in Table S4 in the Supplementary Appendix.

The time to hemodynamic stabilization, the use of catecholamine therapy and the duration of such therapy, the duration of the ICU stay, and the use of mechanical ventilation and the duration of such therapy did not differ significantly between the two groups (Table 2). There was also no significant difference between the two groups in the SAPS-II score. The creatinine clearance and levels of arterial lactate, troponin, and creatine kinase were similar in the two treatment groups. (See Figs. S2 through S6 in the Supplementary Appendix.)

Table 3. Clinical Outcomes at 30 Days.

Outcome	Culprit-Lesion-Only PCI Group (N=344)	Multivessel PCI Group (N=341)	Relative Risk (95% CI)	P Value
	no./total no. (%)			
Primary end point: death from any cause or renal-replacement therapy	158/344 (45.9)	189/341 (55.4)	0.83 (0.71–0.96)	0.01
Death from any cause*	149/344 (43.3)	176/341 (51.6)	0.84 (0.72–0.98)	0.03
Renal-replacement therapy	40/344 (11.6)	56/341 (16.4)	0.71 (0.49–1.03)	0.07
Indication for renal-replacement therapy				
Hyperkalemia	7/40 (17.5)	9/56 (16.1)		
Metabolic acidosis	18/40 (45.0)	20/56 (35.7)		
Uremia	13/40 (32.5)	20/56 (35.7)		
Volume overload	12/40 (30.0)	17/56 (30.4)		
Other cause	6/40 (15.0)	4/56 (7.1)		
Recurrent myocardial infarction	4/344 (1.2)	3/341 (0.9)	1.32 (0.30–5.86)	1.00
Rehospitalization for congestive heart failure	1/344 (0.3)	1/342 (0.3)	0.99 (0.10–9.50)	0.99
Death, recurrent myocardial infarction, or rehospitalization for congestive heart failure	151/344 (43.9)	179/342 (52.3)	0.84 (0.72–0.98)	0.03
Staged or urgent repeat revascularization	74/344 (21.5)	13/341 (3.8)	7.43 (3.61–15.31)	<0.001
Stroke	12/344 (3.5)	10/341 (2.9)	1.19 (0.52–2.72)	0.68
BARC type 2, 3, or 5 bleeding†				
Any	57/344 (16.6)	75/341 (22.0)	0.75 (0.55–1.03)	0.07
BARC 2	14/57 (24.6)	23/75 (30.7)		
BARC 3a	21/57 (36.8)	28/75 (37.3)		
BARC 3b	17/57 (29.8)	19/75 (25.3)		
BARC 3c	0/57	2/75 (2.7)		
BARC 5a	4/57 (7.0)	1/75 (1.3)		
BARC 5b	1/57 (1.8)	2/75 (2.7)		

* Causes of death are shown in Table S3 in the Supplementary Appendix.

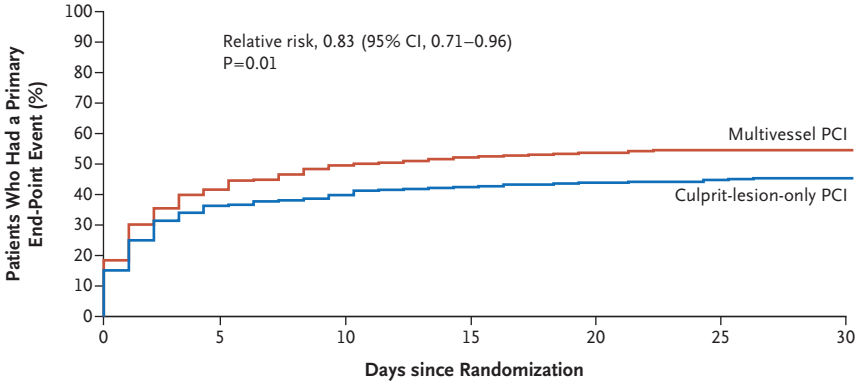
† On the Bleeding Academic Research Consortium (BARC) scale, type 2 indicates any overt, actionable sign of bleeding; type 3a, overt bleeding with a decrease in the hemoglobin level of 3 to less than 5 g per deciliter or any transfusion; type 3b, overt bleeding with a decrease in the hemoglobin level of 5 g or more per deciliter, cardiac tamponade, or surgical intervention; type 3c, intracranial hemorrhage or intraocular bleeding; type 5a, probable fatal bleeding; and type 5b, definite fatal bleeding.

DISCUSSION

In this randomized, multicenter trial involving patients with multivessel coronary artery disease and acute myocardial infarction with cardiogenic shock, PCI of the culprit lesion only (with the option of staged revascularization of nonculprit lesions) was superior to immediate multivessel PCI with respect to a composite end point of death or renal-replacement therapy at 30 days. The difference was driven mainly by significantly lower mortality in the culprit-lesion-only PCI group.

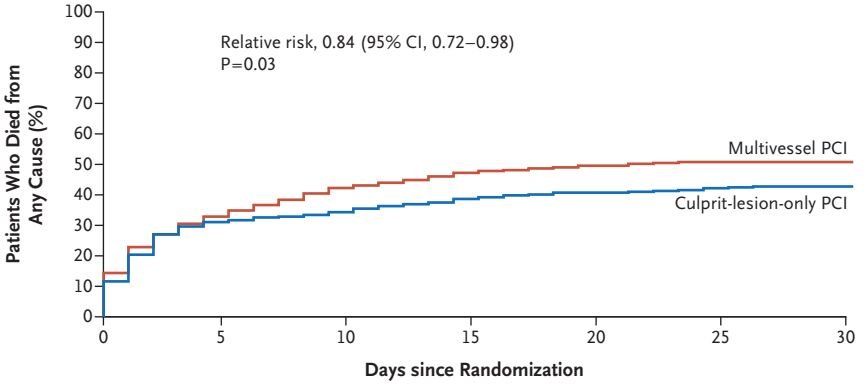
Multivessel coronary artery disease is present in the vast majority of patients who have acute myocardial infarction with cardiogenic shock and is associated with higher mortality than single-vessel disease.[5] Thus, mortality at 30 days was higher in this trial than in other randomized trials involving patients with cardiogenic shock, despite similar inclusion criteria regarding cardiogenic shock.[2,17-19] Although PCI of the culprit lesion is the established standard of care, the management of nonculprit lesions is the subject of intense debate. Complete revascularization has been thought

A Composite Primary End Point



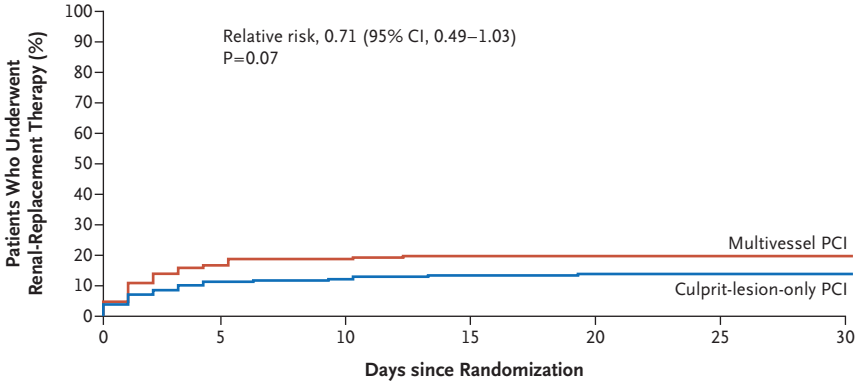
No. at Risk							
Multivessel PCI	341	199	172	162	156	153	152
Culprit-lesion-only PCI	344	219	207	198	192	189	184

B Death from Any Cause



No. at Risk							
Multivessel PCI	341	229	197	179	170	166	165
Culprit-lesion-only PCI	344	237	226	211	203	198	193

C Renal-Replacement Therapy



No. at Risk							
Multivessel PCI	341	199	172	162	156	153	152
Culprit-lesion-only PCI	344	219	207	198	192	189	184

Figure 1 (facing page). Event Rates of the Primary End Point and Its Components at 30 Days.

Shown are Kaplan–Meier time-to-event curves for the primary end point of a composite of death from any cause or severe renal failure leading to renal-replacement therapy (Panel A), as well as the individual components of death from any cause (Panel B) and renal-replacement therapy (Panel C), within 30 days after randomization. PCI denotes percutaneous coronary intervention.

to be beneficial in improving ventricular function and hemodynamic status.[13] However, the results of this trial and of nonrandomized studies have shown lower mortality with PCI of the culprit lesion only than with multivessel PCI.[12]

The lack of benefit of immediate multivessel PCI in this trial might be related to the significantly higher dose of contrast material that was used in the multivessel PCI group than in the culprit-lesion-only PCI group and a consequent decline in renal function. However, the incidence of severe renal failure leading to renal-replacement therapy did not differ significantly between the two groups. The higher dose of contrast material that was used in the multivessel PCI group than in the culprit-lesion-only PCI group may have also led to acute left ventricular volume overload and a subsequent negative effect on myocardial function and recovery. In addition, the prolonged duration of the multivessel PCI procedure may be hazardous at a time when the patient is hemodynamically compromised.

The findings of this trial are in contrast with the results of trials involving hemodynamically stable patients with myocardial infarction, which have shown a lower rate of major adverse cardiac events with either angiographically guided or FFR-guided early multivessel PCI than with PCI of the culprit lesion only.[8-11,20] However, these findings were driven mainly by the difference in the rate of repeat revascularization, which was counted as part of a composite end point, because repeat revascularization was usually performed during follow-up as staged revascularization procedures in patients who initially underwent PCI of the culprit lesion only. In our trial, staged revascularization was encouraged and not counted as a disadvantage of the culprit-lesion-only PCI strategy. In previous trials involving hemodynamically stable patients with myocardial infarction, there were no significant differences between the two treatment strategies in mortality or the rate of recurrent infarction. Among patients with cardiogenic shock, the acute hazards of a prolonged procedure time (including the increased dose of contrast material) seem to outweigh any potential negative aspects of repeat revascularization.

In contrast with previous trials involving highly selected patients with stable infarction, this trial did not specify the presence of a chronic total occlusion as an exclusion criterion.[8-11] This allowed for inclusion of a real-world cohort of patients with multivessel disease and cardiogenic shock. Chronic total occlusion is frequently present in patients with cardiogenic shock and is associated with adverse clinical outcomes.[21,22] Exclusion of patients with a chronic total occlusion would have led to a major selection bias and a lower-risk cohort. Therefore, in the multivessel PCI group, immediate recanalization of a chronic total occlusion was recommended. However, it was also advised to pursue recanalization attempts cautiously and to limit the total dose of contrast material to 300 ml. Complete revascularization was achieved in 81% of the patients in the multivessel PCI group. A previous trial involving patients with stable infarction showed no benefit of recanalization for chronic total occlusion of nonculprit lesions.[23]

This trial has several limitations. First, blinding was not possible because of the nature of the intervention. Management of cardiogenic shock involves a complex series of clinical decisions, and it is not possible to fully eliminate some bias during the actual course of treatment. Second, some patients could not be evaluated because of difficulties in obtaining final informed consent. The withdrawal rate was at the exact anticipated level of 3%. Third, 75 patients crossed over from their assigned treatment to the other treatment. Of these patients, 14 in the culprit-lesion-only PCI group underwent immediate multivessel PCI for multiple reasons, including lack of hemodynamic improvement, plaque shifts, and the presence of newly detected lesions after treatment of the culprit lesion; these reasons suggest that the treatment strategy may require adaptation to the specific clinical circumstances.

In conclusion, this randomized, multicenter trial showed that, among patients who had multi-

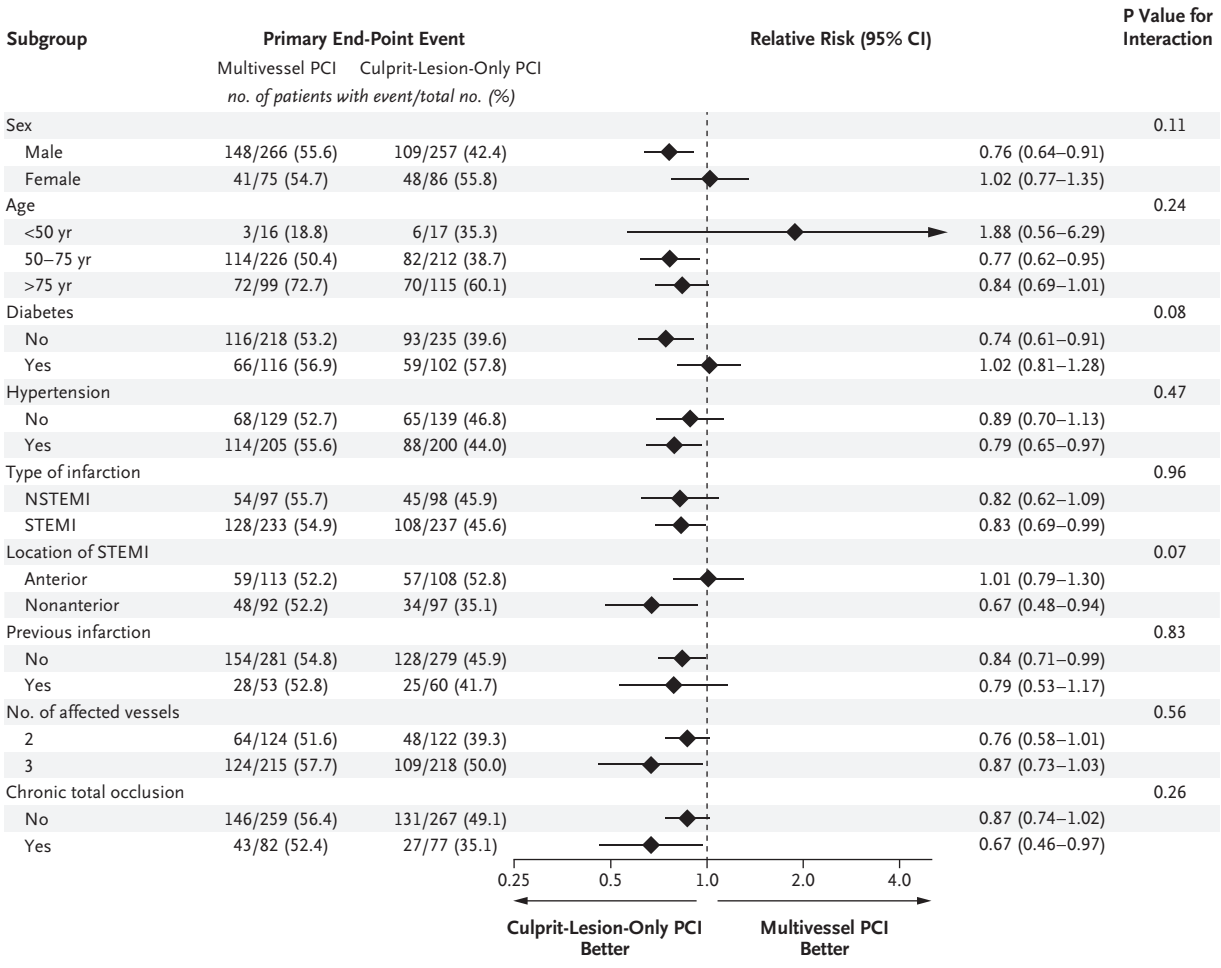


Figure 2. Subgroup Analyses of the Primary End Point at 30 Days.

NSTEMI denotes non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.

vessel coronary artery disease and acute myocardial infarction with cardiogenic shock, the risk of a composite of death or renal-replacement therapy was lower among those who initially underwent PCI of the culprit lesion only than among those who underwent multivessel PCI. This outcome was mainly driven by lower mortality among patients who underwent culprit-lesion-only PCI.

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

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APPENDIX

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REFERENCES

1. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. JAMA 2006;295:2511-5.
2. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. N Engl J Med 1999;341:625-34.
3. Thiele H, Ohman EM, Desch S, Eitel I, de Waha S. Management of cardiogenic shock. Eur Heart J 2015;36:1223-30.
4. Thiele H, Desch S, Piek JJ, et al. Multivessel versus culprit lesion only percutaneous revascularization plus potential staged revascularization in patients with acute myocardial infarction complicated by cardiogenic shock: design and rationale of CULPRIT-SHOCK trial. Am Heart J 2016;172:160-9.
5. Sanborn TA, Sleeper LA, Webb JG, et al. Correlates of one-year survival inpatients with cardiogenic shock complicating acute myocardial infarction: angiographic findings from the SHOCK trial. J Am Coll Cardiol 2003;42:1373-9.
6. Webb JG, Lowe AM, Sanborn TA, et al. Percutaneous coronary intervention for cardiogenic shock in the SHOCK trial. J Am Coll Cardiol 2003;42:1380-6.
7. Wong SC, Sanborn T, Sleeper LA, et al. Angiographic findings and clinical correlates in patients with 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: Suppl A:1077-83.
8. Smits PC, Abdel-Wahab M, Neumann F-J, et al. Fractional flow reserve–guided multivessel angioplasty in myocardial infarction. N Engl J Med 2017;376:1234-44.
9. Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. N Engl J Med 2013;369:1115-23.
10. Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. J Am Coll Cardiol 2015;65:963-72.
11. Engstrøm T, Kelbæk H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3–PRIMULTI): an open-label, randomised controlled trial. Lancet 2015; 386:665-71.
12. de Waha S, Jobs A, Eitel I, et al. Multivessel versus culprit lesion only percutaneous coronary intervention in cardiogenic shock complicating acute myocardial infarction: a systematic review and meta-analysis. Eur Heart J Acute Cardiovasc Care 2017 July 1 (Epub ahead of print).
13. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2017 August 26 (Epub ahead of print) (https://doi.org/10.1093/eurheartj/ehx393).
14. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. J Am Coll Cardiol 2016;67:1235-50.
15. Patel MR, Calhoon JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2016 appropriate use criteria for coronary revascularization in patients with acute coronary syndromes: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and the Society of Thoracic Surgeons. J Am Coll Cardiol 2017;69:570-91.
16. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123: 2736-47.

17. Alexander JH, Reynolds HR, Stebbins AL, et al. Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock: the TRIUMPH randomized controlled trial. JAMA 2007; 297:1657-66.
18. Thiele H, Zeymer U, Neumann F-J, et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of the randomised, open-label trial. Lancet 2013; 382:1638-45.
19. Thiele H, Zeymer U, Neumann F-J, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med 2012;367:1287-96.
20. Sardella G, Lucisano L, Garbo R, et al. Single-staged compared with multistaged PCI in multivessel NSTEMI patients: the SMILE Trial. J Am Coll Cardiol 2016;67:264-72.
21. van der Schaaf RJ, Claessen BE, Vis MM, et al. Effect of multivessel coronary disease with or without concurrent chronic total occlusion on one-year mortality in patients treated with primary percutaneous coronary intervention for cardiogenic shock. Am J Cardiol 2010; 105:955-9.
22. Hoebers LP, Vis MM, Claessen BE, et al. The impact of multivessel disease with and without a co-existing chronic total occlusion on short- and long-term mortality in ST-elevation myocardial infarction patients with and without cardiogenic shock. Eur J Heart Fail 2013;15: 425-32.
23. Henriques JPS, Hoebers LP, Råmunddal T, et al. Percutaneous intervention for concurrent chronic total occlusions in patients with STEMI: the EXPLORE Trial. J Am Coll Cardiol 2016;68:1622-32.