ORIGINAL ARTICLE

Microaxial Flow Pump or Standard Care in Infarct-Related Cardiogenic Shock

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ABSTRACT

BACKGROUND

The effects of temporary mechanical circulatory support with a microaxial flow pump on mortality among patients with ST-segment elevation myocardial infarction (STEMI) complicated by cardiogenic shock remains unclear.

METHODS

In an international, multicenter, randomized trial, we assigned patients with STEMI and cardiogenic shock to receive a microaxial flow pump (Impella CP) plus standard care or standard care alone. The primary end point was death from any cause at 180 days. A composite safety end point was severe bleeding, limb ischemia, hemolysis, device failure, or worsening aortic regurgitation.

RESULTS

A total of 360 patients underwent randomization, of whom 355 were included in the final analysis (179 in the microaxial-flow-pump group and 176 in the standard-care group). The median age of the patients was 67 years, and 79.2% were men. Death from any cause occurred in 82 of 179 patients (45.8%) in the microaxial-flow-pump group and in 103 of 176 patients (58.5%) in the standard-care group (hazard ratio, 0.74; 95% confidence interval [CI], 0.55 to 0.99; P=0.04). A composite safety end-point event occurred in 43 patients (24.0%) in the microaxial-flow-pump group and in 11 (6.2%) in the standard-care group (relative risk, 4.74; 95% CI, 2.36 to 9.55). Renal-replacement therapy was administered to 75 patients (41.9%) in the microaxial-flow-pump group and to 47 patients (26.7%) in the standard-care group (relative risk, 1.98; 95% CI, 1.27 to 3.09).

CONCLUSIONS

The routine use of a microaxial flow pump with standard care in the treatment of patients with STEMI-related cardiogenic shock led to a lower risk of death from any cause at 180 days than standard care alone. The incidence of a composite of adverse events was higher with the use of the microaxial flow pump. (Funded by the Danish Heart Foundation and Abiomed; DanGer Shock ClinicalTrials.gov number, NCT01633502.)

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*A complete list of the investigators in the DanGer Shock trial is provided in the Supplementary Appendix, available at NEJM.org.

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Cardiogenic shock is a severe complication that occurs in approximately 8 to 10% of patients with ST-segment elevation myocardial infarction (STEMI)[1,2] and is associated with a mortality of 40 to 50%.[2,3] Among patients with STEMI and cardiogenic shock, the time from the onset of symptoms to death is often less than 24 hours in those with progressive cardiac failure.[4] Because cardiogenic shock will develop when the cardiac output is inadequate to meet the metabolic needs of the body, restoration of perfusion with the use of active mechanical circulatory support is theoretically beneficial.[5] Extracorporeal life support provides both blood flow and blood oxygenation; however, its routine use did not improve clinical outcomes in patients with acute myocardial infarction and cardiogenic shock, and extracorporeal life support was associated with excess bleeding complications and limb ischemia.[6,7]

Percutaneous microaxial flow pumps are another type of active mechanical circulatory support. These pumps drain blood from the left ventricle through a catheter and expel it into the ascending aorta.[8] The microaxial flow pump will unload the left ventricle but is dependent on adequate oxygenation of blood and intact right-heart function to ensure adequate filling of the left ventricle.[5,8] Three small randomized trials did not show a clinical benefit of microaxial flow pumps in patients with acute myocardial infarction and cardiogenic shock,[9-11] and registry studies have consistently shown excess bleeding among patients who received a microaxial flow pump.[1,12,13] Thus, there is uncertainty about whether the routine use of a microaxial flow pump is of benefit or harm to patients who have cardiogenic shock associated with STEMI. We performed the Danish–German Cardiogenic Shock (DanGer Shock) trial to test the hypothesis that routine use of a microaxial flow pump in addition to standard guideline-directed therapies in patients with STEMI-related cardiogenic shock results in a lower mortality than standard care alone.

Methods

Trial Design and Oversight

This international, multicenter, randomized, open-label trial was conducted in Denmark, Germany, and the United Kingdom. The main objective of the trial was to assess the efficacy of the microaxial flow pump (Impella CP, Abiomed) in the treatment of patients with STEMI and cardiogenic shock and planned emergency revascularization. The design of the trial has been published previously,[14] and the protocol is available with the full text of this article at NEJM.org.

The trial was initially intended to be conducted in one country (DanShock), and the first patient was enrolled on January 27, 2013. The DanShock steering committee designed the trial. Because of slow enrollment, the trial was expanded in 2019 to include patients in Germany and, in 2021, the United Kingdom. The trial protocol was approved by the ethics committee at each participating site. An independent data and safety monitoring committee oversaw patient safety in the trial and performed a formal interim analysis after the enrollment and complete follow-up of 180 patients. The data and safety monitoring committee evaluated the interim analysis and recommended to continue the trial. An independent contract research organization (KCRI .org) oversaw the accuracy of data entry and trial conduct.

The trial was funded by the Danish Heart Foundation and Abiomed. Representatives of the funders did not take part in the trial design and did not participate in the analysis or interpretation of data or in the writing of the manuscript. The first draft of the manuscript was written by the first author with input from the last author. All site principal investigators and designated site personnel had access to the Web-based REDCap database, in which data from the individual sites were entered and could be accessed. KCRI had access to data entered at all sites. The DanGer Shock steering committee initially interpreted the results, and all the authors contributed to the writing and approval of the final version of the manuscript to be submitted for publication. All authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Representatives of Abiomed had an opportunity to review and comment on the final manuscript.

Patients

Patients 18 years of age or older with STEMI and cardiogenic shock were eligible for enrollment.

Cardiogenic shock was defined as hypotension (systolic blood pressure below 100 mm Hg or an ongoing need for vasopressor support), end-organ hypoperfusion with an arterial lactate level of 2.5 mmol per liter or greater, and a left ventricular ejection fraction of less than 45%. Patients who had been resuscitated from out-of-hospital cardiac arrest and remained comatose on arrival to the cardiac catheterization laboratory and patients with overt right ventricular failure were excluded. A complete list of inclusion and exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org.

RANDOMIZATION AND TRIAL PROCEDURES

The consent process is described in the Supplementary Appendix. Patients underwent randomization in the catheterization laboratory, either before or after a revascularization procedure or up to 12 hours after leaving the cardiac catheterization laboratory, depending on when cardiogenic shock was recognized. Randomization was performed with the use of an Web-based randomization system (TrialPartner by DEFACTUM, Department of Public Health at Aarhus University). Randomization was stratified according to the timing of randomization relative to the revascularization procedure and localization of STEMI (anterior vs. nonanterior).

The patients in each trial group underwent a revascularization procedure and received pressor support if indicated. In the patients assigned to receive the microaxial flow pump, the device was to be placed immediately after randomization and run at the highest possible performance level for at least 48 hours unless complications occurred, as specified in the protocol. In the event of hemodynamic instability, treatment could be escalated to additional mechanical circulatory support after randomization in either trial group. In the microaxial-flow-device group, treatment could be escalated to the placement of an Impella 5.0 Impella RP device or extracorporeal life support. In the standard-care group, extracorporeal life support was recommended, although placement of an Impella 5.0 device was allowed. Any use of an Impella CP device for hemodynamic instability in the standard-care group (i.e., crossover) was considered to be a protocol violation. Hemodynamic criteria and guidance for weaning of the microaxial flow pump are provided in Appendix A in the protocol.

TRIAL END POINTS

The primary end point was death from any cause at 180 days. The first secondary end point was escalation of treatment to additional mechanical circulatory support (short- or long-term), heart transplantation, or death from any cause, whichever came first (composite cardiac end point). The second secondary end point was days alive and out of the hospital, which was calculated as the number of days from discharge to death or data censoring at 180 days minus the number of days of readmission in the case of hospitalization after discharge. Prespecified exploratory end points were the results of the primary and secondary end-point analyses in the as-treated population and a composite end point of unplanned readmission for a cardiovascular cause or death after discharge.

Adverse events were moderate or severe bleeding according to Global Use of Strategies to Open Occluded Arteries criteria,[15] limb ischemia, stroke, receipt of renal-replacement therapy, and sepsis with positive blood cultures. A composite safety end point included severe bleeding, limb ischemia, hemolysis, device failure, and worsening of aortic regurgitation. A complete list of adverse events and definitions is provided in the trial protocol.

STATISTICAL ANALYSIS

Details of the statistical methods are provided in the statistical analysis plan, available with the protocol.[16] Sample size was estimated on the basis of an assumed mortality of 60% in the standard-care group and 42% in the microaxial-flow-pump group at 180 days. With a two-sided alpha level of 0.05, a minimum of 162 patients per trial group and a total of 165 deaths in the entire trial population would provide the trial with 80% power to reject the null hypothesis in favor of the alternative hypothesis. To account for possible loss to follow-up, we planned to randomly assign a total of 360 patients to a trial group.

Death from any cause at 180 days was analyzed in the intention-to-treat population with the use of an unadjusted Cox proportional-hazards model. The assumption of proportional hazards was assessed with the use of log–log likelihood plots and by plotting Kaplan–Meier observed survival curves and Cox model–predicted curves according to trial group. The effect of the intervention at 180 days is expressed as a hazard ratio with a 95% confidence interval and presented in

a Kaplan–Meier plot. The primary end-point analysis was performed with a two-sided alpha level of 0.048 to adjust for one formal interim analysis. Predefined subgroup analyses were performed according to biologic sex (female vs. male), age (≤69 vs. >69 years), arterial lactate level (≤4.5 vs. >4.5 mmol per liter), mean arterial blood pressure (≤63 vs. >63 mm Hg), left ventricular ejection fraction (≤25% vs. >25%), location of STEMI (nonanterior vs. anterior), number of diseased vessels (one vs. two or more), year of randomization (2013–2018 vs. 2019–2023), and Society for Cardiovascular Angiography and Interventions (SCAI) shock classification at randomization (stage C vs. stage D or E; stages range from A to E, with higher stages indicating greater severity), which uses the definitions suggested by the Cardiogenic Shock Working Group (CSWG) that are based on blood pressure and arterial lactate levels.[17] In addition, a post hoc subgroup analysis of treatment effect across countries of enrollment was performed.

The secondary composite cardiac end point was analyzed with the use of an unadjusted Cox proportional-hazards model, and the treatment effect is expressed as a hazard ratio with a 95% confidence interval. Days alive and out of the hospital within 180 days is expressed as the mean between-group difference with a 95% confidence interval. Adverse events were summarized for each trial group, and the results are given as a relative risk with a 95% confidence interval.

The widths of the confidence interval have not been adjusted for multiplicity and may not be used in place of hypothesis testing, except for the primary end-point analysis. No data were missing in the primary end-point analysis, and missing values for other variables were not imputed. Statistical analyses were performed with the use of SPSS software, version 28.0 (IBM).

RESULTS

PATIENTS

From January 2013 through July 2023, a total of 1211 patients underwent screening, and 360 patients were enrolled at 14 centers — 4 centers in Denmark (215 patients), 9 in Germany (135 patients), and 1 in the United Kingdom (10 patients). Five patients were excluded after randomization because consent could not be obtained (1 patient in the microaxial-flow-pump group and 4 in the standard-care group). The final analysis included 355 patients — 179 in the microaxial-flow-pump group and 176 in the standard-care group (Fig. S1 in the Supplementary Appendix). Randomization was performed before percutaneous coronary intervention (PCI) in 201 patients (56.6%), in the cardiac catheterization laboratory but after PCI in 96 patients (27.0%), and after departure from the catheterization laboratory in 58 patients (16.3%).

The characteristics of the patients at baseline appeared to be well balanced between the trial groups (Table 1). The median age of the patients was 67 years, and 79.2% were men. The median arterial lactate level was 4.5 mmol per liter (interquartile range, 3.3 to 7.1), the median systolic blood pressure was 82 mm Hg (interquartile range, 72 to 91), and the median left ventricular ejection fraction was 25% (interquartile range, 15 to 30).

MANAGEMENT OF STEMI AND CARDIOGENIC SHOCK

Details regarding the management of STEMI in the cardiac catheterization laboratory and the intensive care unit are provided in Table 2 and Tables S1 and S2. Culprit-vessel PCI was performed in 343 patients (96.6%), and emergency coronary-artery bypass grafting was performed in 5 patients (1.4%) (Table 1 and Table 2). Among 179 patients assigned to the microaxial-flow-pump group, the device was placed successfully in 170 patients (95.0%), and 3 patients (1.7%) crossed over to receive standard care only. In 6 patients (3.3%), device placement was attempted but was unsuccessful. Device placement was attempted in 88 of 99 patients (88.9%) in the microaxial-flow-pump group who had undergone randomization before revascularization and was successful in 84 of these patients (95.5%); in the other 11 patients (11.1%), the device was placed after PCI of the culprit lesion despite their having undergone randomization before revascularization. In the standard-care group, 3 patients (1.7%) received a microaxial flow pump and were thus considered to be crossover patients (Table 2). In the microaxial-flow-pump group, treatment was escalated to another mechanical circulatory support system in 28 patients (15.6%), and in the standard-care group, treatment was escalated to another support system in 37 patients (21.0%) (Table 2).

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline and Timing of Randomization.*

Characteristic	Microaxial Flow Pump plus Standard Care (N=179)	Standard Care Alone (N=176)
Median age (IQR) — yr	67 (58–76)	69 (61–76)
Male sex — no. (%)	142 (79.3)	139 (79.0)
Medical history — no. (%)		
Hypertension	89 (49.7)	94 (53.4)
Diabetes	33 (18.4)	47 (26.7)
Myocardial infarction	29 (16.2)	28 (15.9)
Heart failure	16 (8.9)	17 (9.7)
Chronic kidney disease	17 (9.5)	18 (10.2)
Median systolic blood pressure (IQR) — mm Hg	84 (72–91)	82 (72–91)
Median of the mean arterial blood pressure (IQR) — mm Hg	63 (55–72)	64 (55–73)
Median heart rate (IQR) — beats/min	94 (77–110)	95 (76–111)
Median arterial lactate level (IQR) — mmol/liter	4.6 (3.4–7.1)	4.5 (3.2–6.9)
Median left ventricular ejection fraction (IQR) — %	25 (20–31)	25 (15–30)
Resuscitation before randomization — no. (%)	39 (21.8)	33 (18.8)
Intubation before randomization — no. (%)	35 (19.6)	28 (15.9)
Transfer from outside hospital — no. (%)	51 (28.5)	48 (27.3)
Anterior myocardial infarction — no. (%)	126 (70.4)	129 (73.3)
SCAI–CSWG stage at admission — no. (%)†		
C	100 (55.9)	97 (55.1)
D	51 (28.5)	50 (28.4)
E	28 (15.6)	29 (16.5)
No. of diseased vessels on coronary angiography — no. (%)		
0	1 (0.6)	0
1	52 (29.1)	47 (26.7)
2	70 (39.1)	64 (36.4)
3	56 (31.3)	65 (36.9)
Timing of randomization		
Median time from symptom onset to randomization (IQR) — hr	4.8 (2.4–12.8)	3.8 (2.2–9.4)
Randomization performed before revascularization — no. (%)	99 (55.3)	102 (58.0)
Randomization performed in the catheterization laboratory but after revascularization — no. (%)	48 (26.8)	48 (27.3)
Randomization performed ≤12 hr after departure from the catheterization laboratory — no. (%)	32 (17.9)	26 (14.8)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range.

† Society for Cardiovascular Angiography and Interventions–Cardiogenic Shock Working Group (SCAI–CSWG) stage was defined according to Kapur et al.[17] and is based on the arterial lactate level and arterial blood pressure at randomization. Stage C was defined as a lactate level of 2.5 to 4.99 mmol per liter, a systolic blood pressure of 60 mm Hg or higher, and a mean arterial pressure of 50 mm Hg or higher; stage D was defined as a lactate level of 5 to 10 mmol per liter, a systolic blood pressure of 60 mm Hg or higher, and a mean arterial pressure of 50 mm Hg or higher; and stage E was defined as a lactate level of greater than 10 mmol per liter, a systolic blood pressure below 60 mm Hg, or a mean arterial pressure below 50 mm Hg.

Table 2. In-Hospital Management of Cardiogenic Shock.*

Management	Microaxial Flow Pump plus Standard Care (N=179)	Standard Care Alone (N=176)
Revascularization		
PCI — no. (%)	171 (95.5)	172 (97.7)
Non–culprit vessel PCI — no./no. of patients with multivessel disease (%)	59/127 (46.5)	55/129 (42.6)
Immediate CABG — no. (%)	1 (0.6)	4 (2.3)
Median time from admission to balloon inflation (IQR) — min	58 (36–114)	45 (31–81)
Mechanical circulatory support		
Placement of Impella CP device — no. (%)†	170 (95.0)	3 (1.7)
Randomization occurred before PCI and microaxial flow pump placed before PCI — no./total no. (%)	84/99 (84.8)	3/3 (100)
Median time from randomization to placement of microaxial flow pump (IQR) — min	14 (8–29)	15 (8–31)
Median duration of microaxial flow pump support (IQR) — hr	59 (30–87)	60 (31–92)
Mechanical hemolysis — no./total no. (%)	21/170 (12.4)	1/3 (33.3)
Device malfunction — no./total no. (%)‡	2/170 (1.2)	1/3 (33.3)
Successful weaning from microaxial flow pump — no./total no. (%)	138/170 (81.2)	1/3 (33.3)
Escalation to additional mechanical circulatory support		
Placement of Impella 5.0 device — no. (%)	7 (3.9)	5 (2.8)
Placement of Impella CP for venting during venoarterial ECMO therapy — no. (%)	0	4 (2.3)
Placement of Impella 2.5 device — no. (%)	0	1 (0.6)
Placement of Impella RP device — no. (%)	0	0
Venoarterial ECMO — no. (%)	21 (11.7)	33 (18.8)
Median time from randomization to placement of venoarterial ECMO (IQR) — hr	14 (4–54)	2 (1–5)
Placement of permanent LVAD — no. (%)	10 (5.6)	4 (2.3)
Any escalation to additional mechanical circulatory support — no. (%)	28 (15.6)§	37 (21.0)¶
Intensive care management		
Mechanical ventilation — no. (%)	133 (74.3)	116 (65.9)
Median duration of mechanical ventilation (IQR) — days	5 (2–10)	3 (1–10)
Medication use — no. (%)		
Any vasopressor	159 (88.8)	146 (83.0)
Norepinephrine	156 (87.2)	142 (80.7)
Dopamine	51 (28.5)	41 (23.3)
Epinephrine	67 (37.4)	66 (37.5)
Any inotrope	124 (69.3)	109 (61.9)
Dobutamine	62 (34.6)	59 (33.5)
Milrinone	63 (35.2)	58 (33.0)
Levosimendan	40 (22.3)	39 (22.2)

Table 2. (Continued.)

Management	Microaxial Flow Pump plus Standard Care (N=179)	Standard Care Alone (N=176)
Staged in-hospital revascularization procedures		
PCI — no. (%)	7 (3.9)	10 (5.7)
CABG — no. (%)	0	3 (1.7)
Median duration of ICU admission (IQR) — days	6 (2–15)	3 (0–10)
Still in ICU at day 30 — no. (%)	22 (12.3)	11 (6.2)
Median duration of hospitalization (IQR) — days	12 (4–27)	7 (1–19)
Still in hospital at day 30 — no. (%)	41 (22.9)	19 (10.8)

* CABG denotes coronary-artery bypass grafting, ECMO extracorporeal membrane oxygenation, ICU intensive care unit, IQR interquartile range, LVAD left ventricular assist device, and PCI percutaneous coronary intervention.
† Seven patients in the standard-care group received an Impella CP: the device was placed in three patients because of hemodynamic instability and in four patients as an unloading strategy during venoarterial ECMO therapy. The microaxial flow pump was not placed in nine patients assigned to the microaxial-flow-pump group: three patients had hemodynamic improvement or a logistic reason for not receiving the device (these patients crossed over to receive standard care only), implantation was unsuccessful in four patients because of poor vascular access, one patient received a diagnosis of aortic dissection type A, and one patient died before placement.
‡ Device malfunction in which the microaxial flow pump stopped unexpectedly occurred in two patients (one patient assigned to the microaxial-flow-pump group and one patient assigned to standard-care group), and device malfunction of the purge system occurred in one patient assigned to the microaxial-flow-pump group.
§ In the microaxial-flow-pump group, any escalation to additional mechanical circulatory support included an Impella CP (first) plus venoarterial ECMO in 14 patients, an Impella CP (first) plus venoarterial ECMO plus an Impella 5.0 in 4 patients, an Impella CP (first) plus venoarterial ECMO plus a durable LVAD in 3 patients, an Impella CP (first) plus an Impella 5.0 plus a durable LVAD in 3 patients, and an Impella CP (first) plus a durable LVAD in 4 patients.
¶ In the standard-care group, any escalation to additional mechanical circulatory support included venoarterial ECMO alone in 21 patients, venoarterial ECMO (first) plus an Impella CP for venting in 4 patients, an Impella CP first (crossover) plus venoarterial ECMO in 1 patient, venoarterial ECMO plus an Impella 5.0 in 3 patients, venoarterial ECMO plus an Impella 5.0 plus a durable LVAD in 1 patient, venoarterial ECMO plus a durable LVAD in 3 patients, an Impella CP (crossover) in 2 patients, an Impella 5.0 in 1 patient, and a durable LVAD in 1 patient.

PRIMARY AND SECONDARY END POINTS

Death from any cause at 180 days (primary end point) occurred in 82 of 179 patients (45.8%) in the microaxial-flow-pump group and in 103 of 176 patients (58.5%) in the standard-care group (hazard ratio, 0.74; 95% confidence interval [CI], 0.55 to 0.99; P=0.04) (Fig. 1A). The results of subgroup analyses are shown in Figure 2 and Fig. S2. The number needed to treat to avoid 1 death was 8. Causes of death are shown in Table S3.

In the secondary end-point analyses, a composite cardiac end-point event occurred in 94 of 179 patients (52.5%) in the microaxial-flow-pump group and in 112 of 176 patients (63.6%) in the standard-care group (hazard ratio, 0.72; 95% CI, 0.55 to 0.95) (Table 3 and Fig. 1B). The mean number of days alive and out of the hospital was 82 in the microaxial-flow-pump group and 73 in standard-care group (mean between-group difference, 8; 95% CI, –8 to 25) (Table 3 and Fig. S3). The reasons for readmission between hospital discharge and 6 months are provided in Table S4. The results of exploratory analyses are provided in Figures S4, S5, and S6.

ADVERSE EVENTS

A composite safety end-point event occurred in 43 patients (24.0%) in the microaxial-flow-pump group and in 11 (6.2%) in the standard-care group (relative risk, 4.74; 95% CI, 2.36 to 9.55) (Table 3 and Fig. S7). In the microaxial-flow-pump group, the number needed to harm was 6. The relative risk (microaxial-flow-pump group vs. standard-care group) of moderate or severe bleeding was 2.06 (95% CI, 1.15 to 3.66); of limb ischemia, 5.15 (95% CI, 1.11 to 23.84); of renal-replacement therapy, 1.98 (95% CI, 1.27 to 3.09); and of sepsis with a positive blood culture, 2.79 (95% CI, 1.20 to 6.48). The results of all safety analyses are provided in Table 3 and Figure S7.

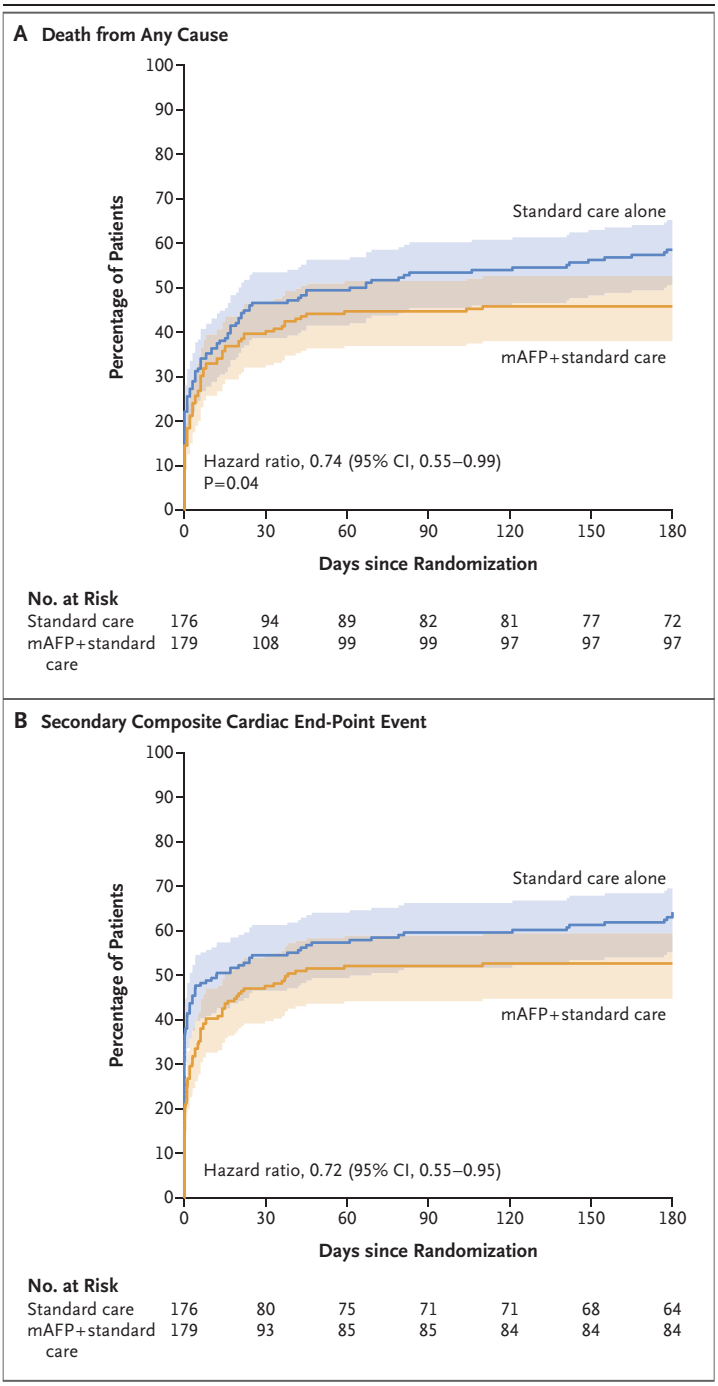

Figure 1. Time to Death from Any Cause at 180 Days and Time to Treatment Escalation, Heart Transplantation, or Death from Any Cause.

Shown are time-to-event curves for death from any cause at 180 days (Panel A) and for a composite cardiac end-point event (escalation of treatment to additional mechanical circulatory support [short-term or long-term]), heart transplantation, or death from any cause, whichever came first) in the intention-to-treat population. The hazard ratios are from the unadjusted analysis, and the shaded areas indicate 95% confidence intervals. The 95% confidence intervals in Panel B have not been adjusted for multiplicity, and the width of the confidence intervals should not be used to estimate treatment effects. The abbreviation mAFP denotes microaxial flow pump.

DISCUSSION

In our trial involving patients with STEMI and cardiogenic shock, the risk of death from any cause at 180 days was lower among those who received mechanical circulatory support with a microaxial flow pump in addition to standard care than among those who received standard care alone. Adverse events occurred more frequently among the patients in the microaxial-flow-pump group than among those in the standard-care group.

This trial differs from other contemporary randomized trials of mechanical circulatory support in that it was conducted in a more homogenous patient population. The enrollment criterion of a mandatory elevation in arterial lactate level in the absence of a cardiac arrest led to the identification of a patient population with profound left ventricular failure and a high incidence of adverse events, as reflected by the substantial mortality that was observed beyond 30 days of follow-up. Such late mortality among patients has been described in the National Cardiogenic Shock Initiative, in which mortality increased from 32% at 30 days to 47% at 1 year,[18] and is also in agreement with other registry data.[19,20] We excluded patients who remained comatose after cardiac arrest. Because cardiac arrest increases anaerobic metabolism and the accumulation of lactate, it is often impossible to differentiate between the metabolic derangement caused by cardiac arrest and that caused by underlying left ventricular failure due to myocardial injury.[21] It is important to note that the cause of death in patients with these conditions differs, with hypoxic brain injury being the leading cause of death among those with cardiac arrest and persistent cardiac failure being the leading cause among those without cardiac arrest.[4] Therefore, patients with out-of-hospital cardiac arrest who were resuscitated but had a Glasgow Coma Scale score lower than 8 (range, 3 to 15, with higher scores indicating better status) were excluded from the current

trial, as opposed to most other trials involving patients with acute myocardial infarction and cardiogenic shock, among whom the prevalence of cardiac arrest before randomization was high.[6,10]

Results of a subgroup analysis suggested that the benefit of a microaxial flow pump may be greater if the patient's blood pressure was low before randomization, a finding that is in line with experimental data that suggest that a microaxial flow pump does not perform well if the left ventricular afterload is increased by vasoconstriction.[22] The microaxial flow pump also unloads the left ventricle with a decrease in wall stress, thereby reducing myocardial oxygen consumption.[5,23] Experimental studies have shown that unloading the left ventricle reduces myocardial injury.[23,24] Whether this therapeutic effect occurred in our trial is not known but is being addressed in a trial involving patients with anterior STEMI without cardiogenic shock.[25]

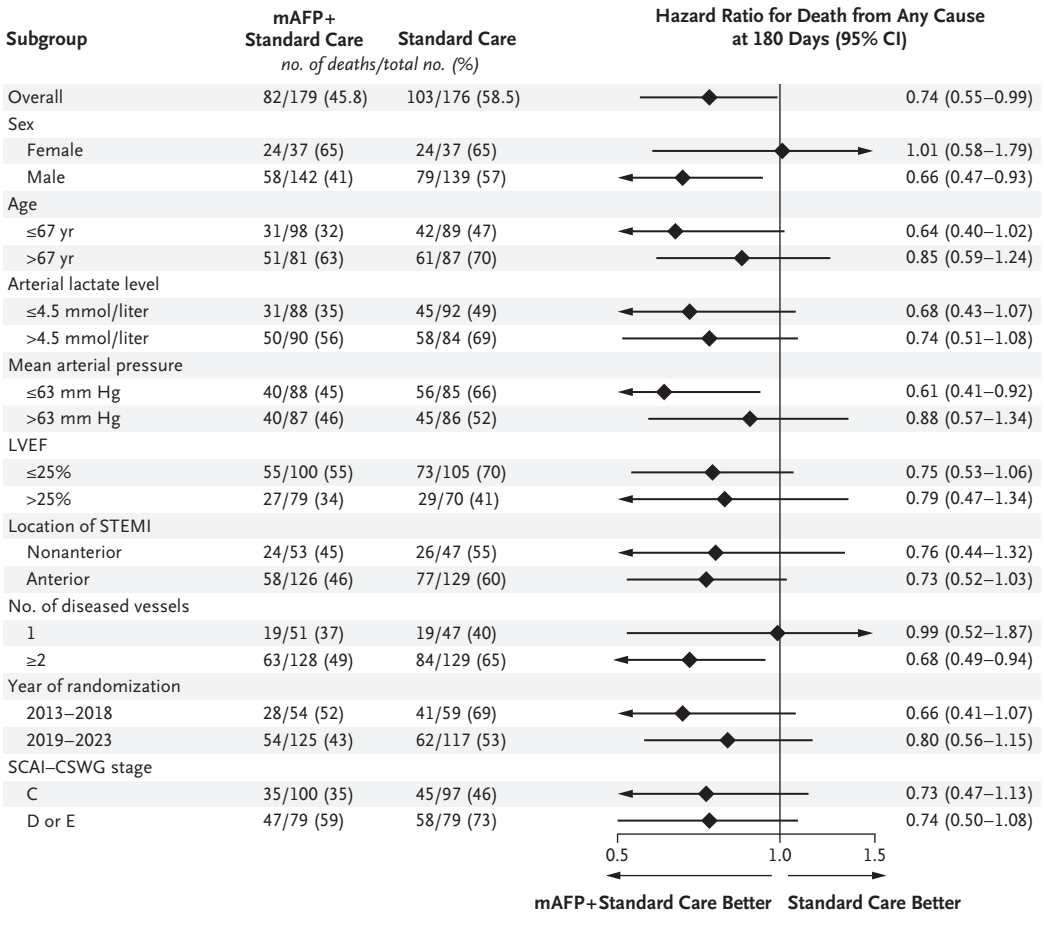

Figure 2. Subgroup Analysis of the Primary End Point.

Shown is a forest plot of the hazard ratio of death from any cause at 180 days in prespecified subgroups. The mean arterial pressure at randomization was available for 346 patients. Society for Cardiovascular Angiography and Interventions–Cardiogenic Shock Working Group (SCAI–CSWG) stage was defined according to Kapur et al.[17] and is based on the arterial lactate level and arterial blood pressure at randomization. Stage C was defined as a lactate level of 2.5 to 4.99 mmol per liter, a systolic blood pressure of 60 mm Hg or higher, and a mean arterial pressure of 50 mm Hg or higher; stage D was defined as a lactate level of 5 to 10 mmol per liter, a systolic blood pressure of 60 mm Hg or higher, and a mean arterial pressure of 50 mm Hg or higher; and stage E was defined as a lactate level of greater than 10 mmol per liter, a systolic blood pressure below 60 mm Hg, or a mean arterial pressure below 50 mm Hg. The widths of the confidence intervals were not adjusted for multiplicity and may not be interpreted in terms of hypothesis testing. LVEF denotes left ventricular ejection fraction, and STEMI ST-segment elevation myocardial infarction.

Table 3. End Points and Adverse Events in the Intention-to-Treat Population.*

Event	Microaxial Flow Pump plus Standard Care (N=179)	Standard Care Alone (N=176)	Effect Size (95% CI)†
Primary end point: death from any cause at 180 days — no. (%)	82 (45.8)	103 (58.5)	0.74 (0.55 to 0.99)‡
Secondary end point			
Composite cardiac end point — no. (%)§	94 (52.5)	112 (63.6)	0.72 (0.55 to 0.95)
No. of days alive and out of the hospital (range)¶	82 (0 to 177)	73 (0 to 179)	8 (–8 to 25)
Adverse events			
Composite safety end point — no. (%)‖	43 (24.0)	11 (6.2)	4.74 (2.36 to 9.55)
Moderate or severe bleeding — no. (%)**	39 (21.8)	21 (11.9)	2.06 (1.15 to 3.66)
Limb ischemia — no. (%)	10 (5.6)	2 (1.1)	5.15 (1.11 to 23.84)
Renal-replacement therapy — no. (%)	75 (41.9)	47 (26.7)	1.98 (1.27 to 3.09)
Stroke — no. (%)	7 (3.9)	4 (2.3)	1.75 (0.50 to 6.01)
Cardioversion after ventricular tachycardia or fibrillation — no. (%)	59 (33.0)	52 (29.5)	1.17 (0.75 to 1.83)
Sepsis with positive blood culture†† — no. (%)	21 (11.7)	8 (4.5)	2.79 (1.20 to 6.48)

* The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used in place of hypothesis testing. The results of exploratory end-point analyses are provided in Figures S4, S5, and S6 in the Supplementary Appendix.
† The effect size is given as a hazard ratio for death from any cause at 180 days and for a composite cardiac event, as a mean between-group difference for days alive and out of the hospital, and as a relative risk for adverse events, including the composite safety end point.
‡ P=0.04.
§ The composite cardiac end point was escalation of treatment to additional mechanical circulatory support (short- or long-term), heart transplantation, or death of any cause, whichever came first.
¶ Days alive and out of the hospital were calculated as the number of days from discharge to death or data censoring at 180 days minus the number of days of readmission in the case of hospitalization after discharge.
‖ The composite safety end point was the occurrence of severe bleeding, limb ischemia, hemolysis, device failure, or worsening aortic regurgitation.
** Bleeding was recorded according to the Global Use of Strategies to Open Occluded Arteries criteria.[15]
†† Sepsis was defined as organ dysfunction or tissue hypoperfusion (manifesting as hypotension, elevated lactate, or decreased urine output) in addition to positive blood cultures for infection.

The incidence of complications was higher among the patients who received a microaxial flow pump than among those who received standard care alone, a finding that was in agreement with registry data.[1,12] An unexpected finding was a considerably higher use of renal-replacement therapy in the microaxial-flow-pump group than in the standard-care group; in the former, the use of renal-replacement therapy was higher than that observed in the extracorporeal life support trial.[6] The finding of excess need for renal-replacement therapy in the microaxial-flow-pump group may be attributable to the fact that more patients died early in the standard-care group, which may have introduced a survival bias owing to a competing risk. The microaxial flow pump can also cause mechanical hemolysis. The subsequent increase in the level of plasma-free hemoglobin can induce nephropathy leading to acute kidney failure, which may be aggravated further by bleeding and sepsis.[26]

The composite safety end point (severe bleeding, limb ischemia, hemolysis, device failure, or worsening of aortic regurgitation) and adverse events such as receipt of renal-replacement therapy and sepsis encompass events that are generally considered to increase overall mortality, especially among patients with severe cardiogenic shock. However, it is reassuring that these severe complications did not overshadow the benefit of treatment with a microaxial flow pump. It remains a priority to address the prevention of serious adverse events that occur as a result of treatment with a microaxial flow pump.

Our trial has limitations. Inclusion and exclusion criteria were strict, and the results from our trial cannot be extrapolated to patients with cardiogenic shock who remain comatose after cardiac arrest, patients with myocardial infarction without ST-segment elevation, patients with SCAI stage C shock without an elevation in the arterial lac-

tate level, and patients with cardiogenic shock who have more prominent biventricular failure. The trial was conducted in a small number of centers in Denmark, Germany, and the United Kingdom, so results may differ in health care systems in other countries. Data on race or ethnic group were not collected. The majority of persons in the countries where the patients were enrolled are White, and our results may not apply to other geographic regions or areas with more racial diversity (Table S5). Our trial was not blinded, and we cannot exclude the possible effect of this factor on therapeutic decisions made by treating physicians. Although specific strategies for intensive care management were recommended in the protocol, the criteria for discharge from the intensive care unit were not. The trial was conducted over a period of 10 years, although most patients underwent randomization after 2019. No significant breakthroughs in improving the treatment outcomes in patients with STEMI and cardiogenic shock were observed during this period; however, the appreciation and understanding of shock during STEMI had changed, and the use of advanced mechanical circulatory support had increased. In both trial groups, the frequency of escalation to additional mechanical circulatory support was similar to that in contemporary registries[1,18] and randomized trials.[7]

In our trial, the routine use of a microaxial flow pump in the treatment of patients with STEMI-related cardiogenic shock led to a lower risk of death from any cause at 180 days than standard care alone. The incidence of a composite of adverse events was higher with the use of the microaxial flow pump.

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

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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