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RESEARCH ARTICLE

Extracorporeal membrane oxygenation in the therapy of cardiogenic shock: 1-year outcomes of the multicentre, randomized ECMO-CS trial

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Aims Among patients with cardiogenic shock, immediate initiation of extracorporeal membrane oxygenation (ECMO) did not demonstrate any benefit at 30 days. The present study evaluated 1-year clinical outcomes of the Extracorporeal Membrane Oxygenation in the therapy of Cardiogenic Shock (ECMO-CS) trial.

Methods and results The ECMO-CS trial randomized 117 patients with severe or rapidly progressing cardiogenic shock to immediate initiation of ECMO or early conservative strategy. The primary endpoint for this analysis was 1-year all-cause mortality. Secondary endpoints included a composite of death, resuscitated cardiac arrest or implantation of another mechanical circulatory support device, duration of mechanical ventilation, and the length of intensive care unit (ICU) and hospital stays. In addition, an unplanned post-hoc subgroup analysis was performed. At 1 year, all-cause death occurred in 40 of 58 (69.0%) patients in the ECMO arm and in 40 of 59 (67.8%) in the early conservative arm (hazard ratio [HR] 1.02, 95% confidence interval [CI] 0.66–1.58; $p = 0.93$). The composite endpoint occurred in 43 (74.1%) patients in the ECMO group and in 47 (79.7%) patients in the early conservative group (HR 0.83, 95% CI 0.55–1.25; $p = 0.29$). The durations of mechanical ventilation, ICU stay and hospital stay were comparable between groups. Significant interaction with treatment strategy and 1-year mortality was observed in subgroups according to baseline mean arterial pressure (MAP) indicating lower mortality in the subgroup with low baseline MAP (<63 mmHg: HR 0.58, 95% CI 0.29–1.16; $p_{interaction} = 0.017$).

Conclusions Among patients with severe or rapidly progressing cardiogenic shock, immediate initiation of ECMO did not improve clinical outcomes at 1 year compared to the early conservative strategy. However, immediate ECMO initiation might be beneficial in patients with advanced haemodynamic compromise.

Keywords Clinical trial • Cardiogenic shock • Therapy • Extracorporeal membrane oxygenation

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Introduction

Cardiogenic shock is a critical condition caused by primary cardiac dysfunction resulting in inadequate cardiac output with tissue hypoperfusion.[1] Despite advances and developments in acute cardiovascular and intensive care, mortality rates for cardiogenic shock remain high.[2,3] During past years, mechanical circulatory support (MCS), especially veno-arterial extracorporeal membrane oxygenation (ECMO), has been increasingly used to restore total circulatory output, increase blood pressure, and improve tissue perfusion in these patients. Initiation of MCS became standard therapeutic strategy recommended by guidelines from the European Society of Cardiology (class IIa recommendation)[1] and the American Heart Association, American College of Cardiology and Heart Failure Society of America (class IIb recommendation).[4] These recommendations were based almost exclusively on findings from observational studies (level of evidence C).[1,4]

Recently, four randomized clinical trials and their meta-analysis reported that early initiation of ECMO in patients with cardiogenic shock did not improve clinical outcomes, including all-cause mortality at 30 days.[5–9] However, longer observation is needed to carefully evaluate the effect of ECMO in cardiogenic shock, considering that many patients remain hospitalized 30 days after the index event and that early haemodynamic improvement, similar to ischaemic or bleeding complications associated with the use of ECMO, may impact long-term outcome.[6] To date, long-term results from multicentre randomized trials comparing ECMO and standard care in cardiogenic shock have not been available. Therefore, we present 1-year pre-defined follow-up of the Extracorporeal Membrane Oxygenation in the therapy of Cardiogenic Shock (ECMO-CS) trial. In addition, an unplanned post-hoc subgroup analysis was performed.

Methods

Study overview

The ECMO-CS trial was an investigator-initiated, multicentre randomized trial conducted at four experienced centres in the Czech Republic. All patients provided informed written consent to participate in the study. If patient's status did not permit a written informed consent, it was provided retrospectively after improvement of their clinical condition. If a patient died, remained unconscious, or experienced significant brain dysfunction, informed consent was obtained from the patient's next of kin. If informed consent was not obtained, all acquired data were removed from the database and not used in the analysis. The authors confirm the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The ECMO-CS trial was supported by a grant from the Czech Health Research Council (No. 15-27994A) and was registered at ClinicalTrials.gov (NCT02301819).

Study design and endpoints

The trial design and protocol were published previously.[6,10] Briefly, patients fulfilling the inclusion criteria for severe or rapidly progressing cardiogenic shock of various aetiologies (online supplementary *Tables S1* and *S2*) were randomly assigned to immediate initiation of ECMO or to an early conservative strategy. Importantly, in the early conservative arm, ECMO could be used in case of conservative therapy failure and further haemodynamic worsening with elevation in serum lactate level by 3 mmol/L compared with the lowest value during the past 24 h.[6,10] Thirty-day results of the trial were published previously.[6] The primary endpoint for this analysis was 1-year all-cause mortality. Secondary endpoints included a composite of death from any cause, resuscitated cardiac arrest and implementation of another MCS device, duration of mechanical ventilation, and the length of intensive care unit (ICU) and hospital stays. Furthermore, a post-hoc subgroup analysis was performed, including subgroups according to age, sex, presentation with ST-elevation myocardial infarction, percutaneous coronary intervention for the index event, baseline mean arterial pressure, left ventricular ejection fraction, lactate level, and vasoactive-inotropic score.

Statistical analysis

Sample size determination was based on the assumption of the incidence of the primary outcome (composite of death from any cause, resuscitated cardiac arrest and implementation of another type of MCS device at 30 days) and was published previously.[6] Analyses were performed according to the intention-to-treat principle and included data from all patients and for all events that occurred from the time of randomization up to 1 year. Categorical variables are expressed as percentages and compared using Pearson's chi-squared test or Fisher's exact test. Continuous variables are presented as median (interquartile range [IQR]) and compared using the *t*-test or Mann–Whitney test as appropriate. Time to death was analysed using the Kaplan–Meier method and compared using the log-rank test. Calculation of 95% confidence intervals (CIs) for point estimates of endpoint occurrence probability was based on the cumulative risk function (or logarithmic transformation of the survival function). Hazard ratios (HRs) with corresponding 95% CIs were calculated using a Cox proportional hazard model with Efron approximation for tie holding. Odds ratios (OR) with corresponding 95% CIs were calculated using Baptista–Pike test. Due to the potential for type 1 error in multiple comparisons, findings for the secondary outcomes and subgroup analyses should be interpreted as exploratory. The analysis was performed using SPSS version 28 (IBM Corporation, Armonk, NY, USA), R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) and Prism 8 (GraphPad Inc., San Diego, CA, USA). Hypotheses were tested at a significance level of 5% (i.e. differences with $p < 0.05$ were considered to be statistically significant).

Results

Patients

Between September 2014 and January 2022, 122 patients were randomly assigned to one of two groups: immediate ECMO, or early conservative therapy. After excluding five patients due to the absence of informed consent (all of them died and informed consent could not be obtained from the next of kin), 58 subjects were included in the immediate ECMO group and 59 in the early conservative therapy group, for whom 1-year data were available for all (online supplementary *Figure S1*). The baseline characteristics of the two study groups at the time of randomization were balanced (*Table 1*).

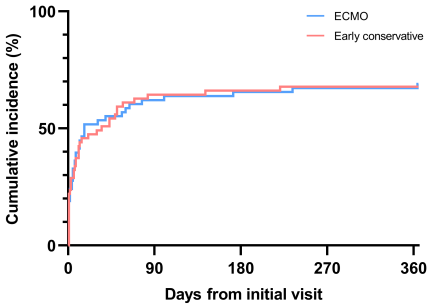
Table 1 Baseline characteristics

Characteristic	All ($n = 117$)	ECMO ($n = 58$)	Early conservative ($n = 59$)
Sex, *n* (%)			
Male	86 (73.5)	43 (74.1)	43 (72.9)
Female	31 (26.5)	15 (25.9)	16 (27.1)
Age, years, median (IQR)	66 (59–73)	67 (60–74)	65 (58–71)
Medical history, *n* (%)			
Chronic coronary syndrome	39 (34.2)	21 (37.5)	18 (31.0)
Chronic heart failure	27 (23.7)	14 (25.0)	13 (22.4)
Dilated cardiomyopathy	15 (13.3)	6 (10.9)	9 (15.5)
Chronic renal failure	16 (14.2)	7 (12.5)	9 (15.8)
Peripheral artery disease	10 (8.8)	3 (5.5)	7 (11.9)
Hypertension	73 (64.0)	35 (62.5)	38 (65.5)
Diabetes	37 (32.5)	16 (28.6)	21 (36.2)
Current smoker	41 (36.9)	14 (25.9)	27 (47.4)
Clinical parameters at randomization, median (IQR)			
Blood lactate, mmol/L	5.0 (3.2–8.0)	5.3 (3.1–8.4)	4.7 (3.3–7.4)
Systolic blood pressure, mmHg	85.0 (80.0–100.0)	84.0 (80.0–95.0)	89.0 (79.5–105.0)
Mean arterial pressure, mmHg	63.3 (55.3–72.0)	63.3 (56.7–68.7)	64.5 (54.3–75.3)
Heart rate, bpm	102.0 (84.0–120.0)	110.0 (86.5–130.0)	100.0 (82.0–110.0)
Therapy at randomization			
Intra-aortic balloon pump, *n* (%)	15 (13.3)	6 (10.9)	9 (15.5)
Mechanical ventilation, *n* (%)	81 (72.3)	41 (74.5)	40 (70.2)
Renal replacement therapy, *n* (%)	7 (6.2)	4 (7.3)	3 (5.2)
Norepinephrine, *n* (%)	100 (85.5)	50 (86.2)	50 (84.7)
Norepinephrine dose, µg/kg/min, median (IQR)	0.50 (0.23–1.24)	0.48 (0.23–1.36)	0.50 (0.27–1.19)
Epinephrine, *n* (%)	4 (3.4)	1 (1.7)	3 (5.1)
Epinephrine dose, µg/kg/min, median (IQR)	0.26 (0.14–0.80)	0.21 (0.21–0.21)	0.30 (0.07–1.30)
Dobutamine, *n* (%)	64 (54.7)	31 (53.4)	33 (55.9)
Dobutamine dose, µg/kg/min, median (IQR)	5.1 (4.9–8.0)	6.1 (5.0–9.7)	5.1 (4.7–7.6)
Milrinone, *n* (%)	38 (32.5)	22 (37.9)	16 (27.1)
Milrinone dose, µg/kg/min, median (IQR)	0.40 (0.30–0.50)	0.40 (0.30–0.50)	0.40 (0.37–0.51)
Vasopressin, *n* (%)	41 (35.0)	19 (32.8)	22 (37.3)
Vasopressin dose, U/kg/min, median (IQR)	0.0017 (0.0010–0.0025)	0.0020 (0.0010–0.0030)	0.0017 (0.0012–0.0022)
Levosimendan, *n* (%)	32 (29.4)	20 (37.0)	12 (21.8)
Vasoactive-inotropic score, median (IQR)	61.0 (30.0–124.0)	59.9 (32.8–121.5)	61.0 (28.0–124.9)
Cause of cardiogenic shock, *n* (%)			
ST-elevation myocardial infarction	59 (50.4)	30 (51.7)	29 (49.2)
Non-ST-elevation myocardial infarction	14 (12.0)	7 (12.1)	7 (11.9)
Decompensation of chronic heart failure	27 (23.1)	14 (24.1)	13 (22.0)
Mechanical complications of myocardial infarction	3 (2.6)	1 (1.7)	2 (3.4)
Aortic stenosis	9 (7.7)	5 (8.6)	4 (6.8)
Mitral regurgitation	4 (3.4)	1 (1.7)	3 (5.1)
Myocarditis	1 (0.9)	–	1 (1.7)

ECMO, extracorporeal membrane oxygenation; IQR, interquartile range.

Endpoints

At 1 year, death from any cause occurred in 40 of 58 (69.0%) patients in the ECMO arm and in 40 of 59 (67.8%) in the early conservative arm (HR 1.02, 95% CI 0.66–1.58; $p = 0.93$) (*Figure 1*, *Table 2*). The major cause of death was refractory shock followed by multi-organ failure in both groups (online supplementary *Table S3*). All survivors had good neurological outcome. The composite endpoint of death from any cause, resuscitated cardiac arrest, and implantation of another MCS device occurred in 43 (74.1%) patients in the immediate ECMO group and 47 (79.7%) in the early conservative group (HR 0.83, 95% CI 0.55–1.25; $p = 0.29$ (*Figure 2*, *Table 2*). Resuscitated cardiac arrest occurred in 6 (10.3%) patients in the immediate ECMO group and 8 (13.6%) in the early conservative group (OR 0.74, 95% CI 0.23–2.42) (*Table 2*). In the immediate ECMO group, fewer patients required another MCS device (11 [19.0%] vs. 29 [49.2%]; OR 0.28, 95% CI 0.13–0.64) (*Table 1*). The another MCS in the ECMO arm was intra-aortic balloon pump in four cases, two patients received Impella (Abiomed, Danvers, MA, USA) and two patients received



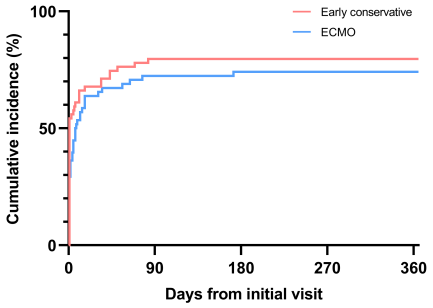
No. at risk					
ECMO	58	22	20	19	18
Early conservative	59	22	20	20	19

Figure 1 Cumulative incidence of all-cause death. ECMO, extracorporeal membrane oxygenation.

Table 2 Incidence of the composite endpoint and individual components of the composite endpoint

Endpoint	ECMO ($n = 58$)	Conservative ($n = 59$)	HR/OR (95% CI)
Death	40 (69.0)	40 (67.8)	1.02 (0.66–1.58)
Another mechanical circulatory support	11 (19.0)	29 (49.2)	0.28 (0.13–0.64)
Resuscitated cardiac arrest	6 (10.3)	8 (13.6)	0.74 (0.23–2.42)
Composite of death from any cause, implantation of another mechanical circulatory support, resuscitated cardiac arrest	43 (74.1)	47 (79.7)	0.83 (0.55–1.25)

Data are presented as *n* (%).
CI, confidence interval; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; OR, odds ratio.



No. at risk					
ECMO	58	17	16	16	15
Early conservative	59	13	13	13	12

Figure 2 Cumulative incidence of the composite endpoint (all-cause death, resuscitated circulatory arrest, implantation of another mechanical circulatory support device). ECMO, extracorporeal membrane oxygenation.

short-term surgical mechanical left ventricular support (CentriMag, Abbott Laboratories, Abbott Park, IL, USA) – all these devices were implanted to unload the left ventricle; three patients were bridged to long-term mechanical support implantation (HeartMate, Abbott Laboratories, Abbott Park, IL, USA). In the early conservative arm, 23 patients required ECMO, three individuals received balloon pump and one subject received Impella in addition to ECMO for unloading, four patients had Impella alone and in three patients was implanted long-term left ventricular support HeartMate (one of them was on ECMO). From the 40 deaths in the early conservative arm, 19 occurred in patients with MCS.

The median duration of mechanical ventilation was 6 days (IQR 1–18 days) in the ECMO arm and 6 days (IQR 1–21 days) in the early conservative arm ($p = 0.66$) (online supplementary *Figure S2*). The median duration of ICU stay was 13 days (IQR 3–29 days) in the ECMO arm and 11 days (IQR 3–30 days) in the early conservative arm ($p = 0.62$) (online supplementary *Figure S3*). The median length of hospital stay was 17 days (IQR 3–31 days) in the ECMO arm and 11 days (IQR 3–41 days) in the early conservative arm ($p = 0.80$) (online supplementary *Figure S4*).

Three patients in the ECMO arm experienced stroke, all of them died (two from refractory shock, one from multi-organ failure); none stroke was observed in the early conservative arm. Renal replacement therapy was needed in 16 of 58 (27.6%) patients in the ECMO arm (12 of them died) and in 10 of 59 (16.9%) patients in the early conservative arm (8 of them died).

Subgroup analysis

Relative risks for 1-year all-cause mortality were consistent across subgroups according to age, sex, presentation with ST-elevation myocardial infarction, percutaneous coronary intervention for index event, left ventricular ejection fraction, lactate level and vasoactive-inotropic score. Significant interaction with treatment strategy and 1-year mortality was observed in subgroups according to baseline mean arterial pressure (<63 mmHg: HR 0.58, 95% CI 0.29–1.16 vs. ≥63 mmHg: HR 1.74, 95% CI 0.93–3.23; $p_{interaction} = 0.017$; median baseline mean arterial pressure in the ECMO-CS trial was 63 mmHg) (*Figure 3*). The interaction was even more pronounced in subgroups according to baseline mean arterial pressure of 60 mmHg (online supplementary *Figure S5*). Those with mean arterial pressure <63 mmHg had a comparable (numerically higher) vasoactive-inotropic score as subjects with a mean arterial pressure ≥63 mmHg (66 [IQR 36–144] vs. 51 [IQR 24–113]; $p = 0.12$) (online supplementary *Figure S6*) and similar pattern was observed for inotropic score (7.1 [IQR 4.7–9.6] vs. 5.0 [IQR 4.2–8.0], $p = 0.13$).

Discussion

In a 1-year follow-up of the randomized ECMO-CS trial, we report three key findings. First, among patients with rapidly progressing or severe cardiogenic shock, immediate initiation of ECMO did not improve 1-year clinical outcomes. Second, long-term all-cause mortality of cardiogenic shock remains very high and markedly

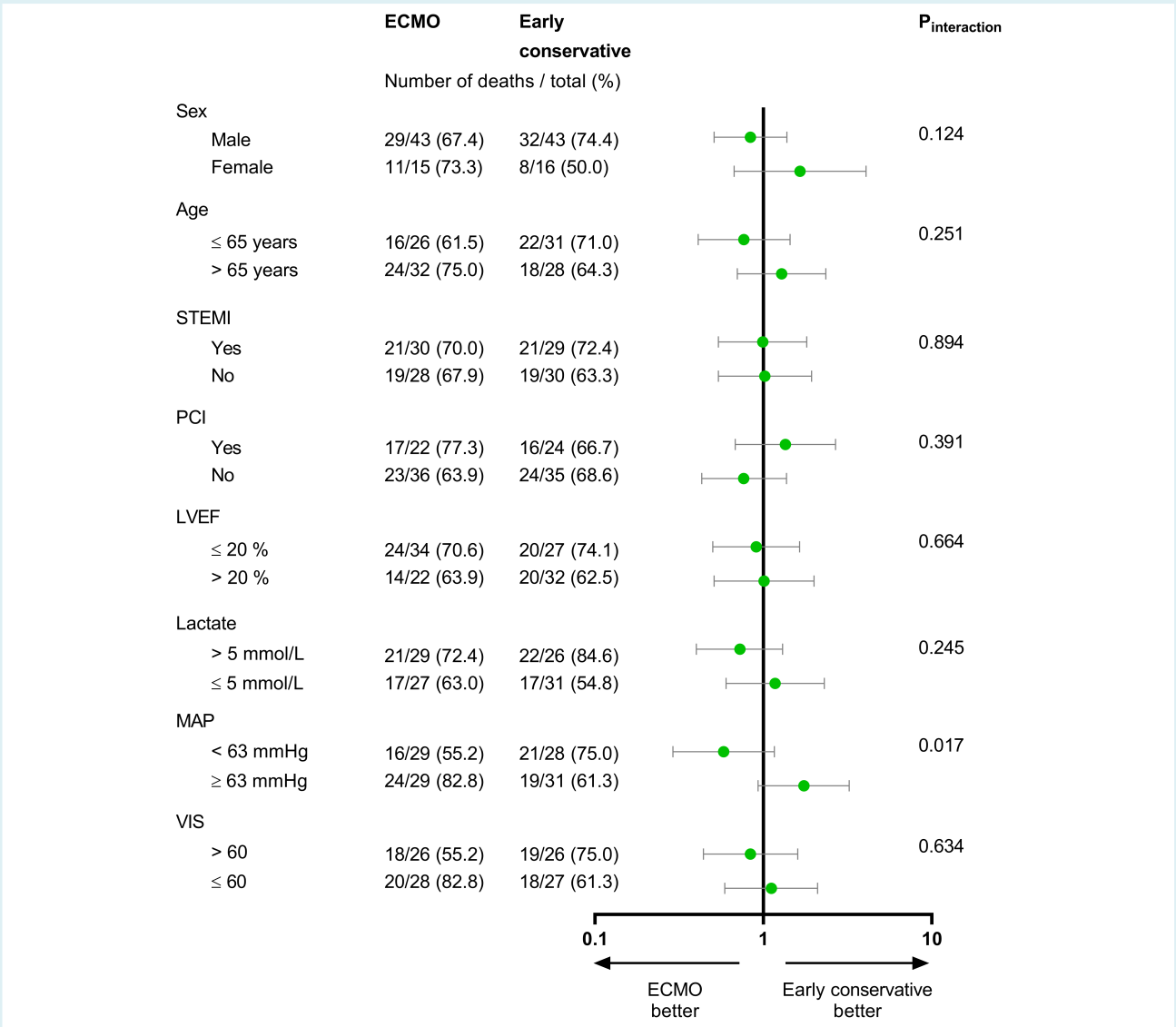


Figure 3 Relative risk for 1-year all-cause death in subgroups. ECMO, extracorporeal membrane oxygenation; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; VIS, vasoactive inotropic score.

higher than 30-day mortality. Third, patients with persistent severe hypotension on inotropes and vasopressors may benefit from early implementation of ECMO.

The potential benefit from early ECMO implementation in cardiogenic shock was recently addressed in four randomized controlled trials. The first was the small, single-centre, ExtraCorporeal Life Support for acute myocardial infarction complicated by cardiogenic shock (ECLS-SHOCK I) trial, including 42 patients with acute myocardial infarction, most of them after successful resuscitation for cardiac arrest (90–100%).[5] The second was the present ECMO-CS trial, with 117 patients with cardiogenic shock of various aetiologies excluding patients after cardiac arrest.[6] The third was the Testing the Value of Novel Strategy and Its Cost Efficacy in Order to Improve the Poor Outcomes in Cardiogenic Shock (EURO SHOCK) trial, which was terminated early after enrolment of 35 patients with acute myocardial infarction (49% after resuscitation).[7] The fourth and, to date, the largest, Extracorporeal Life Support in Cardiogenic Shock (ECLS-SHOCK II) trial, included 417 patients with acute myocardial infarction, 78% of whom after resuscitation for cardiac arrest.[8] Neutral effect on 30-day outcomes was observed in all above trials and confirmed in the individual patient data meta-analysis (exclusively including subjects with acute myocardial infarction-related cardiogenic shock).[5–9] However, in the ECMO-CS trial, a substantial proportion of patients remained hospitalized at 30 days, partly on mechanical ventilation with uncertain prognosis and, therefore, longer-term follow-up is justified to evaluate the clinical outcomes.[6] Importantly, whereas the 30-day mortality in the

ECMO-CS trial was 49% (and 47% in the meta-analysis),[6,9] at 1 year, mortality increased to 68% with numerous deaths after 30 days. Of note, 91% of all deaths occurred within 90 days and 96% in 180 days; this observation may be useful for planning future clinical trials focused on MCS in cardiogenic shock.

Current evidence regarding the long-term effect of MCS in patients with cardiogenic shock from randomized controlled trials is limited. Consistent with results from the present study, Lackermair *et al.*,[11] in the ECLS-SHOCK I trial, did not observe significant difference in 1-year survival with and without ECMO. However, long-term mortality in that trial was very low (19–38%) compared to our study, as well as with the recent large trials in cardiac arrest survivors, and even lower than the 30-day mortality reported in other randomized trials with ECMO in cardiogenic shock.[6–8,11–13] On the other hand, the long-term mortality rate in the present study (68%) is greater than that from the Hypothermia During ECMO (HYPO-ECMO) trial[14] and registries,[15] indicating that the ECMO-CS cohort was extremely sick, which can be explained by the enrolment of subjects with cardiogenic shock of various aetiologies including decompensated chronic heart failure and therapy with higher doses of vasopressors that was required for enrolment. Comparable long-term mortality to the ECMO-CS trial was also observed in the recent Danish–German Cardiogenic Shock (DanGer Shock) trial.[16]

In contrast to other three studies comparing ECMO and standard care, patients who underwent resuscitation for cardiac arrest were not eligible for the ECMO-CS trial. The reason for exclusion of cardiac arrest survivors in the ECMO-CS trial included differences in haemodynamic profile, guideline-recommended therapy and, particularly, cause of death compared with other patients with cardiogenic shock.[17,18] Comatose cardiac arrest survivors were also excluded in the DanGer Shock trial, currently the only study that demonstrates benefit of MCS (Impella) in acute myocardial infarction-related cardiogenic shock.[16]

In the ECMO-CS trial, downstream use of ECMO in the conservative arm was permitted in case of failure of conservative therapy and further haemodynamic worsening defined per protocol as elevation of blood lactate level by 3 mmol/L. In fact, a substantial proportion of patients in the early conservative arm (39%) received ECMO later in the course of the treatment. Therefore, the results of the ECMO-CS trial should be interpreted as a comparison of immediate ECMO with an early conservative strategy, not as a comparison of ECMO versus no ECMO. It is noteworthy that despite the use of ECMO was not recommended in the conservative arms of the EURO SHOCK and ECLS-SHOCK II trials, 6% and 12% of patients respectively, also received ECMO in these studies and also other types of MCS in the ECLS-SHOCK II trial.[7,8]

Subgroup analysis suggested a significant interaction between treatment strategy and 1-year mortality in subgroups according to baseline blood pressure. It is important to note that at the time of baseline mean arterial pressure measurement, all patients were already treated with inotropes and vasopressors based on the inclusion criteria. Subjects with a baseline mean arterial pressure <63 mmHg had a better chance to benefit from an early ECMO strategy compared to those with higher mean arterial pressure. Mean arterial pressure is significantly associated with severity of shock and prognosis,[19] implying that patients with more advanced cardiogenic shock at presentation might benefit from early ECMO. Moreover, a numerically higher vasoactive-inotropic score or inotropic score in patients with lower mean arterial pressure indicates that the reason for low blood pressure was not inadequate conservative therapy. Based on this hypothesis-generated finding, severe hypotension despite conservative therapy with inotropes and vasopressors might help to identify patients who may benefit from ECMO. This observation in the ECMO-CS study where cardiac arrest survivors have been excluded may contrast with the ECLS-SHOCK II population, where the majority of patients suffered cardiac arrest before being diagnosed with cardiogenic shock and therefore their hypotension might have been caused by post-resuscitation syndrome, rather than primary cardiac dysfunction. And, consequently, a chance for ECMO to improve outcome in post-resuscitation syndrome may substantially differ resulting in no benefit in any of the subgroups in the ECLS-SHOCK II trial.[8] On the other hand, Moller *et al.*[16] in the DanGer Shock trial report similar observation in subgroup analysis as in the present study – benefit from Impella in patients with baseline mean arterial pressure ≤63 mmHg and no benefit in subjects with mean arterial pressure >63 mmHg.

Our study had several limitations. First, all participants were Caucasian, given that the trial recruited participants exclusively in the Czech Republic, which may limit the generalizability of our results to other racial or ethnic groups. There was also no upper age limit for enrolment but exclusion criteria included life expectancy <1 year. Second, the trial was designed and the sample size was calculated to find a difference in a composite primary outcome at 30 days. Therefore, all other results must be considered exploratory, including analysis of secondary outcomes and, especially, the post-hoc subgroup analysis. Third, as mentioned above, the trial did not compare ECMO with conservative therapy but immediate ECMO with an early conservative strategy permitting 'bailout' ECMO implementation in case of failure of conservative treatment and further haemodynamic worsening. The results should, therefore, be interpreted accordingly. Moreover, the baseline arterial pressure and inotrope/vasopressor doses correspond with the status at randomization. Unfortunately, the time from onset of symptoms or onset of shock was not recorded and was not included in the inclusion/exclusion criteria. The ECMO-CS trial also randomized patients who were transferred from other hospitals or departments because of cardiogenic shock. Therefore, we cannot identify subjects where ECMO was used as 'salvage' therapy and 'early implantation' refers to the time from presentation. Fourth, the trial was unblinded and the endpoints were not adjudicated. Finally, inclusion criteria were based on shock severity defined by intensity of vasoactive therapy, haemodynamic or metabolic parameters, and the evidence of cardiac pump failure, not on specific aetiologies. However, exclusion criteria included several specific conditions that may cause or influence cardiogenic shock, including high suspicion of pulmonary embolism, cardiac tamponade, bradycardia, tachycardia, aortic regurgitation, or obstructive hypertrophic cardiomyopathy. Moreover, as mentioned above, those who survived cardiac arrest were also excluded.

Therefore, our results cannot be generalized to all aetiologies of shock and to all concomitant conditions.

In conclusion, among patients with severe or rapidly progressing cardiogenic shock, immediate initiation of ECMO did not improve clinical outcomes at 1 year compared with early conservative strategy. However, an early ECMO strategy may be beneficial in patients with severe shock despite conservative therapy with inotropes and vasopressors.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Conflict of interest: P.O. has received speaker's honoraria from Abiomed, Edwards, Fresenius and Getinge. J.B. has received speaker's honoraria from Abiomed, Getinge and Resuscitec. All other authors have nothing to disclose.

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
2. Thiele H, Akin I, Sandri M, de Waha-Thiele S, Meyer-Saraei R, Fuernau G, *et al.*; CULPRIT-SHOCK Investigators. One-year outcomes after PCI strategies in cardiogenic shock. *N Engl J Med* 2018;**379**:1699–1710. https://doi.org/10.1056/NEJMoa1808788
3. Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, *et al.*; CULPRIT-SHOCK Investigators. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med* 2017;**377**:2419–2432. https://doi.org/10.1056/NEJMoa1710261
4. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* 2022 AHA/ACC/HFSA Guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;**145**:e895–e1032. https://doi.org/10.1161/CIR.0000000000001063
5. Brunner S, Guenther SPW, Lackermair K, Peterss S, Orban M, Boulesteix AL, *et al.* Extracorporeal life support in cardiogenic shock complicating acute myocardial infarction. *J Am Coll Cardiol* 2019;**73**:2355–2357. https://doi.org/10.1016/j.jacc.2019.02.044
6. Ostadal P, Rokyta R, Karasek J, Kruger A, Vondrakova D, Janotka M, *et al.*; ECMO-CS Investigators. Extracorporeal membrane oxygenation in the therapy of cardiogenic shock: Results of the ECMO-CS randomized clinical trial. *Circulation* 2023;**147**:454–464. https://doi.org/10.1161/CIRCULATIONAHA.122.062949
7. Banning AS, Sabate M, Orban M, Gracey J, López-Sobrino T, Massberg S, *et al.* Venoarterial extracorporeal membrane oxygenation or standard care in patients with cardiogenic shock complicating acute myocardial infarction: The multicentre, randomised EURO SHOCK trial. *EuroIntervention* 2023;**19**:482–492. https://doi.org/10.4244/EIJ-D-23-00204
8. Thiele H, Zeymer U, Akin I, Behnes M, Rassaf T, Mahabadi AA, *et al.*; ECLS-SHOCK Investigators. Extracorporeal life support in infarct-related cardiogenic shock. *N Engl J Med* 2023;**389**:1286–1297. https://doi.org/10.1056/NEJMoa2307227
9. Zeymer U, Freund A, Hochadel M, Ostadal P, Belohlavek J, Rokyta R, *et al.* Venoarterial extracorporeal membrane oxygenation in patients with infarct-related cardiogenic shock: An individual patient data meta-analysis of randomised trials. *Lancet* 2023;**402**:1338–1346. https://doi.org/10.1016/S0140-6736(23)01607-0
10. Ostadal P, Rokyta R, Kruger A, Vondrakova D, Janotka M, Smíd O, *et al.* Extra corporeal membrane oxygenation in the therapy of cardiogenic shock (ECMO-CS): Rationale and design of the multicenter randomized trial. *Eur J Heart Fail* 2017;**19**:124–127. https://doi.org/10.1002/ejhf.857
11. Lackermair K, Brunner S, Orban M, Peterss S, Orban M, Theiss HD, *et al.* Outcome of patients treated with extracorporeal life support in cardiogenic shock complicating acute myocardial infarction: 1-year result from the ECLS-SHOCK study. *Clin Res Cardiol* 2021;**110**:1412–1420. https://doi.org/10.1007/s00392-020-01778-8
12. Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA, Meuwissen MM, *et al.* Coronary angiography after cardiac arrest without ST segment elevation: One-year outcomes of the COACT randomized clinical trial. *JAMA Cardiol* 2020;**5**:1358–1365. https://doi.org/10.1001/jamacardio.2020.3670
13. Dankiewicz J, Cronberg T, Lilja G, Jakobsen JC, Levin H, Ullén S, *et al.*; TTM2 Trial Investigators. Hypothermia versus normothermia after out-of-hospital cardiac arrest. *N Engl J Med* 2021;**384**:2283–2294. https://doi.org/10.1056/NEJMoa2100591
14. Levy B, Girerd N, Amour J, Besnier E, Nesseler N, Helms J, *et al.*; HYPO-ECMO Trial Group and the International ECMO Network (ECMONet). Effect of moderate hypothermia vs normothermia on 30-day mortality in patients with cardiogenic shock receiving venoarterial extracorporeal membrane oxygenation: A randomized clinical trial. *JAMA* 2022;**327**:442–453. https://doi.org/10.1001/jama.2021.24776
15. Sterling LH, Fernando SM, Talarico R, Qureshi D, van Diepen S, Herridge MS, *et al.* Long-term outcomes of cardiogenic shock complicating myocardial infarction. *J Am Coll Cardiol* 2023;**82**:985–995. https://doi.org/10.1016/j.jacc.2023.06.026
16. Moller JE, Engstrom T, Jensen LO, Eiskjær H, Mangner N, Polzin A, *et al.*; DanGer Shock Investigators. Microaxial flow pump or standard care in infarct-related cardiogenic shock. *N Engl J Med* 2024;**390**:1382–1393. https://doi.org/10.1056/NEJMoa2312572
17. Josiassen J, Lerche Helgestad OK, Moller JE, Kjaergaard J, Hoejgaard HF, Schmidt H, *et al.* Hemodynamic and metabolic recovery in acute myocardial infarction-related cardiogenic shock is more rapid among patients presenting with out-of-hospital cardiac arrest. *PLoS One* 2020;**15**:e0244294. https://doi.org/10.1371/journal.pone.0244294
18. Nolan JP, Sandroni C, Bottiger BW, Cariou A, Cronberg T, Friberg H, *et al.* European Resuscitation Council and European Society of Intensive Care Medicine Guidelines 2021: Post-resuscitation care. *Resuscitation* 2021;**161**:220–269. https://doi.org/10.1016/j.resuscitation.2021.02.012
19. Burstein B, Tabi M, Barsness GW, Bell MR, Kashani K, Jentzer JC. Association between mean arterial pressure during the first 24 hours and hospital mortality in patients with cardiogenic shock. *Crit Care* 2020;**24**:513. https://doi.org/10.1186/s13054-020-03217-6