



# Extracorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock: Results of the ECMO-CS Randomized Clinical Trial

Petr Ostadal<sup>1</sup>, MD, PhD; Richard Rokyta, MD, PhD; Jiri Karasek, MD, PhD; Andreas Kruger, MD, PhD; Dagmar Vondrakova, MD, PhD; Marek Janotka, MD; Jan Naar<sup>2</sup>, MD, PhD; Jana Smalcova<sup>3</sup>, MD; Marketa Hubatova, MSc; Milan Hromadka, MD, PhD; Stefan Volovar, MD; Miroslava Seyfrydova, MD; Jiri Jarkovsky, PhD; Michal Svoboda, MSc; Ales Linhart, MD, PhD; Jan Belohlavek, MD, PhD; for the ECMO-CS Investigators

**BACKGROUND:** Venous-arterial extracorporeal membrane oxygenation (VA-ECMO) is increasingly being used for circulatory support in patients with cardiogenic shock, although the evidence supporting its use in this context remains insufficient. The ECMO-CS trial (Extracorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock) aimed to compare immediate implementation of VA-ECMO versus an initially conservative therapy (allowing downstream use of VA-ECMO) in patients with rapidly deteriorating or severe cardiogenic shock.

**METHODS:** This multicenter, randomized, investigator-initiated, academic clinical trial included patients with either rapidly deteriorating or severe cardiogenic shock. Patients were randomly assigned to immediate VA-ECMO or no immediate VA-ECMO. Other diagnostic and therapeutic procedures were performed as per current standards of care. In the early conservative group, VA-ECMO could be used downstream in case of worsening hemodynamic status. The primary end point was the composite of death from any cause, resuscitated circulatory arrest, and implementation of another mechanical circulatory support device at 30 days.

**RESULTS:** A total of 122 patients were randomized; after excluding 5 patients because of the absence of informed consent, 117 subjects were included in the analysis, of whom 58 were randomized to immediate VA-ECMO and 59 to no immediate VA-ECMO. The composite primary end point occurred in 37 (63.8%) and 42 (71.2%) patients in the immediate VA-ECMO and the no early VA-ECMO groups, respectively (hazard ratio, 0.72 [95% CI, 0.46–1.12];  $P=0.21$ ). VA-ECMO was used in 23 (39%) of no early VA-ECMO patients. The 30-day incidence of resuscitated cardiac arrest (10.3% versus 13.6%; risk difference,  $-3.2$  [95% CI,  $-15.0$  to  $8.5$ ]), all-cause mortality (50.0% versus 47.5%; risk difference,  $2.5$  [95% CI,  $-15.6$  to  $20.7$ ]), serious adverse events (60.3% versus 61.0%; risk difference,  $-0.7$  [95% CI,  $-18.4$  to  $17.0$ ]), sepsis, pneumonia, stroke, leg ischemia, and bleeding was not statistically different between the immediate VA-ECMO and the no immediate VA-ECMO groups.

**CONCLUSIONS:** Immediate implementation of VA-ECMO in patients with rapidly deteriorating or severe cardiogenic shock did not improve clinical outcomes compared with an early conservative strategy that permitted downstream use of VA-ECMO in case of worsening hemodynamic status.

**REGISTRATION:** URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT02301819.

**Key Words:** clinical trial ■ shock, cardiogenic ■ therapy

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Correspondence to: Petr Ostadal, MD, PhD, Cardiovascular Center, Na Homolce Hospital, Roentgenova 2, 15000 Prague, Czech Republic. Email [ostadal.petr@gmail.com](mailto:ostadal.petr@gmail.com)  
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## Clinical Perspective

### What Is New?

- In the ECMO-CS trial (Extracorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock), immediate implementation of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) did not improve outcomes compared with no immediate VA-ECMO in patients with severe or rapidly deteriorating cardiogenic shock.
- A large proportion (39%) of patients in the no early VA-ECMO group subsequently received VA-ECMO or other mechanical circulatory support because of further hemodynamic deterioration.

### What Are the Clinical Implications?

- Even in patients with severe or rapidly deteriorating cardiogenic shock, early hemodynamic stabilization using inotropes and vasopressors with implementation of mechanical circulatory support only in case of further hemodynamic deterioration provided outcomes that were not different from immediate insertion of VA-ECMO.

## Nonstandard Abbreviations and Acronyms

<b>ECMO-CS</b>	Extracorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock
<b>HR</b>	hazard ratio
<b>MCS</b>	mechanical circulatory support
<b>SCAI</b>	Society for Cardiovascular Angiography and Interventions
<b>VA-ECMO</b>	veno-arterial extracorporeal membrane oxygenation

**C**ardiogenic shock is a critical condition with various pathogeneses, phenotypes, and presentations.<sup>1</sup> Despite advances in cardiovascular acute and intensive care, early mortality from cardiogenic shock remains high.<sup>2,3</sup>

Multiple mechanical circulatory support systems have been developed during the past few decades that can be used for hemodynamic stabilization in this patient population.<sup>4</sup> However, currently available mechanical circulatory support (MCS) devices have not been demonstrated to improve survival in cardiogenic shock.<sup>4</sup> Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is increasingly being used in patients with severe circulatory collapse. Compared with other MCS devices, VA-ECMO can provide full circulatory support and pulmonary gas exchange and rapidly restore organ perfusion in the case of right-, left-, or biventricular failure.<sup>4</sup>

According to the current guidelines of the European Society of Cardiology, MCS should be considered for

hemodynamic stabilization in patients experiencing cardiogenic shock (class of recommendation IIa, level of evidence C). VA-ECMO may also be considered in patients with fulminant myocarditis and other conditions causing severe cardiogenic shock.<sup>5</sup> A position statement of the Acute Cardiovascular Care Association of the European Society of Cardiology recommends the use of VA-ECMO in selected patients with refractory cardiogenic shock caused by acute myocardial infarction.<sup>6</sup> Two scientific statements from the American Heart Association recommend consideration of MCS escalation in appropriately selected patients with clinical hypoperfusion or hemodynamic deterioration while on inotropes, selecting the type of MCS according to the specific hemodynamic conditions.<sup>7,8</sup> However, these recommendations are largely based on data from retrospective studies, registry analyses, and expert opinions. The first small randomized study comparing VA-ECMO and conservative therapy in cardiogenic shock included 42 patients and did not find significant differences between the study arms.<sup>9,10</sup> Currently, there are no available data from large, prospective, randomized controlled trials focusing on the use of VA-ECMO in patients with cardiogenic shock; however, several studies are ongoing (EURO-SHOCK [Testing the Value of Novel Strategy and Its Cost Efficacy in Order to Improve the Poor Outcomes in Cardiogenic Shock], ANCHOR [Assessment of ECMO in Acute Myocardial Infarction Cardiogenic Shock], ECLS-SHOCK [Extracorporeal Life Support in Cardiogenic Shock]).<sup>11,12</sup>

The ECMO-CS trial (Extracorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock) aimed to compare immediate implementation of VA-ECMO versus early conservative therapy allowing downstream use of VA-ECMO in case of hemodynamic deterioration, on the background of standard care.

## METHODS

### Trial Organization and Overview

The ECMO-CS trial was a multicenter, randomized, investigator-initiated clinical trial conducted at 4 centers in the Czech Republic. The study protocol was approved by the ethics committees of all participating centers. The trial design has been published.<sup>13</sup> The protocol was designed by the first 2 and the last author and is available as a full-text article in the [Supplemental Material](#). All patients provided informed written consent to participate in the study. If patient status did not permit informed consent, it was provided retrospectively after improvement of their clinical condition. If a patient died, remained unconscious, or had 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 were not used for the analysis. Statistical analyses were performed by an independent academic statistical center (Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic). 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 <https://clinicaltrials.gov> (URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT02301819). The data that support the findings of this study are available from the corresponding author on reasonable request.

## Trial Population

Patients were eligible for randomization if they had either rapidly deteriorating or severe cardiogenic shock, defined by echocardiographic, hemodynamic, and metabolic criteria (Table 1). Exclusion criteria include age <18 years, life expectancy lower than 1 year, high suspicion of pulmonary emboli or cardiac tamponade as a cause of shock, significant bradycardia or tachycardia that could be responsible for hemodynamic instability and was not treated by pacing or cardioversion, cardiac arrest survivors remaining comatose, hypertrophic obstructive cardiomyopathy, peripheral arterial disease precluding arterial cannula insertion in the femoral artery, moderate to severe aortic regurgitation, aortic dissection, uncontrolled bleeding or Thrombolysis in Myocardial Infarction major bleeding within the last 6 months, and known encephalopathy. Details regarding the inclusion and exclusion criteria are provided in the [Supplemental Material](#).

**Table 1. Inclusion Criteria**

Patients must fulfill criteria for rapidly deteriorating or severe cardiogenic shock:
Rapidly deteriorating cardiogenic shock (best corresponds to SCAI stage D-E)
Defined as progressive hemodynamic instability necessitating repeated bolus administration of vasopressors to maintain mean arterial pressure >50 mm Hg + impaired left ventricle systolic function (LVEF <35% or LVEF 35%-55% in case of severe mitral regurgitation or aortic stenosis)
Severe cardiogenic shock (best corresponds to SCAI stage D)
All following criteria should be met:
1. Hemodynamic:
Cardiac index <2.2 L·min <sup>-1</sup> ·m <sup>2</sup> + norepinephrine dose >0.1 µg·kg <sup>-1</sup> ·min <sup>-1</sup> + dobutamine dose >5 µg·kg <sup>-1</sup> ·min <sup>-1</sup>
or
Systolic blood pressure <100 mm Hg + norepinephrine dose >0.2 µg·kg <sup>-1</sup> ·min <sup>-1</sup> + dobutamine dose >5 µg·kg <sup>-1</sup> ·min <sup>-1</sup> + (LVEF < 35% or LVEF 35%-55% + severe mitral regurgitation or aortic stenosis)
2. Metabolic:
Lactate—2 consecutive values ≥3 mmol/L (with at least 30 min between samples), with nondecreasing trend on steady doses of inotropes or vasopressors
or
SvO <sub>2</sub> —2 consecutive values <50% (with at least 30 min between measurements), with nonincreasing trend on steady doses of inotropes or vasopressors
3. Hypovolemia must be excluded:
Central venous pressure >7 mm Hg or pulmonary capillary wedge pressure >12 mm Hg

LVEF indicates left ventricle ejection fraction; SCAI, Society for Cardiovascular Angiography and Interventions; and SvO<sub>2</sub>, venous oxygen saturation.

## Trial Procedures

Patients who fulfilled the trial entry criteria were randomly assigned in a 1:1 ratio to 1 of 2 arms: immediate VA-ECMO or early conservative therapy; the study was unblinded. An automated, web-based system was used for randomization with permuted blocks, with stratification according to the type of cardiogenic shock (rapidly deteriorating or severe), and the trial center. Except for immediate VA-ECMO implementation in the intervention group, all other diagnostic and therapeutic procedures were performed as per current standard(s) of care, including other cardiovascular interventions (ie, percutaneous coronary or noncoronary intervention, cardiac surgery) or mechanical circulatory support. In the early conservative group, VA-ECMO could be used downstream in case of further worsening of hemodynamic status, defined as rise of serum lactate by 3 mmol/L in comparison with the lowest value during the past 24 hours. The indications and strategies for left ventricular venting during the VA-ECMO support and also strategies for prevention or treatment of leg ischemia were not defined in the protocol and were left to the discretion of the physicians at the participating centers.

## Trial End Points

The primary end point was the composite of death from any cause, resuscitated circulatory arrest, and implementation of another mechanical circulatory support (including VA-ECMO in the conservative arm) at 30 days. Prespecified secondary end points included all-cause mortality at 30 days, neurological outcome (according to the Cerebral Performance Category scale) at 30 days, clinically significant bleeding, leg ischemia, pneumonia, sepsis, and technical complications. The end points (including the safety end points) were reported by investigators without independent adjudication.

## Power Analysis and Sample Size Calculation

With the sample size of 120 individuals (60 individuals in each arm), the study had 80% power to detect a 50% reduction of the primary end point at a 2-sided  $\alpha$  of 0.05.

## Statistical Analysis

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 until 30 days. Categorical variables are presented as percentages and compared using the Pearson chi-square test or Fisher exact test. Continuous variables were presented as median (interquartile range) and compared using the *t* test or Mann-Whitney test.

The time to the occurrence of the primary composite end point (or death) was analyzed using the Kaplan-Meier method and compared using a log-rank test. Calculation of the 95% CIs for point estimates of end point occurrence probability are based on the cumulative risk function (or logarithmic transformation of the survival function). Hazard ratios (HR) with 95% CIs were calculated using a Cox proportional hazard model with Efron approximation for tie holding. Furthermore, the multivariate Cox model was used with adjustment for significantly different variables in baseline characteristics. In case that proportionality of risk was not met, sensitivity analysis (Weibull accelerated failure time model) was prepared. Differences in

end point proportions between the 2 categories were investigated using risk difference with 95% CIs. Because of the potential for type 1 error as a result of 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) and R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Hypotheses were tested at a significance level of 5%.

## RESULTS

### Patients

Between September 2014 and January 2022, a total of 122 patients were randomly assigned to immediate VA-ECMO or no immediate VA-ECMO. After excluding 5 patients because of absence of informed consent (all of them died, and informed consent could not be obtained from next of kin), 58 subjects were included in the immediate VA-ECMO group and 59 in the early conservative therapy group (Figure S1). The baseline characteristics of the 2 study groups at the time of randomization were balanced (Table 2). The median age was 67 years (60–74 years) in the immediate VA-ECMO group and 65 years (58–71 years) in the early conservative group. In the immediate VA-ECMO group, fewer patients were smokers. Arterial blood lactate level at randomization was 5.3 mmol/L (3.1–8.4 mmol/L) in the immediate VA-ECMO group and 4.7 mmol/L (3.3–7.4 mmol/L) in the early conservative group. More than 70% of patients in both groups were on mechanical ventilation. Furthermore, 86.2% of subjects in the immediate VA-ECMO group and 84.7% in the early conservative group received norepinephrine, and a substantial proportion of both groups received dobutamine, milrinone, and vasopressin. The vasoactive-inotropic score was 59.9 (32.8–121.5) in the immediate VA-ECMO group and 61.0 (28.0–124.9) in the early conservative group (Table 2). The most common cause of cardiogenic shock in both arms was ST-segment-elevation acute myocardial infarction followed by decompensation of chronic heart failure (Table 2). Use of therapeutic interventions, including percutaneous coronary intervention and cardiac surgery, did not differ between the study groups (Table S1). Although previous cardiac surgery was not an exclusion criterion, only primarily nonsurgical patients were enrolled in the trial, although some of them subsequently required cardiac surgery during hospitalization.

### End Points

The composite primary end point occurred in 37 (63.8%) patients in the immediate VA-ECMO group and 42 (71.2%) in the early conservative group (Table 3). The Kaplan-Meier probability estimate at 30 days was 68.9% in the immediate VA-ECMO group and 71.8% in the early con-

servative group (HR, 0.72 [95% CI, 0.46–1.12];  $P=0.21$ ) (Figure 1).

All-cause mortality at 30 days was comparable between the 2 groups (50.0% versus 47.5%; HR, 1.110 [95% CI, 0.660–1.866]) (Table 3, Figure 2). In the immediate VA-ECMO group, fewer patients required another MCS device (17.2% versus 42.4%, respectively; HR, 0.380 [95% CI, 0.182–0.793]). Resuscitated cardiac arrest occurred in 10.3% of the immediate VA-ECMO group and 13.6% of the early conservative group (HR, 0.790 [95% CI, 0.274–2.277]) (Table 3). Similarly, the incidences of death from any cause or resuscitated cardiac arrest, implementation of another MCS device, or serious adverse events were comparable between treatment arms (Table 3). The results remained similar after adjustment for smoking status with the respect to composite primary end point (HR, 0.681 [95% CI, 0.426–1.088]) and death from any cause (HR, 0.916 [95% CI, 0.528–1.590]).

In the early conservative group, 23 (39%) patients required downstream VA-ECMO support, of whom 12 (52.2%) died. Of the 36 patients in the early conservative group who did not subsequently receive VA-ECMO, 16 (44.4%) died. The mean time from randomization to insertion of VA-ECMO in the early conservative arm was 1.9 days. In the subgroup of 81 patients treated with VA-ECMO in the immediate VA-ECMO arm (58 subjects) or the early conservative arm (23 subjects), 41 (50.6%) patients died, as compared with 16 patients (44.4%) in the early conservative group who did not subsequently receive VA-ECMO (“as-treated” comparison; HR, 1.254 [95% CI, 0.703–2.238]). Besides the 23 patients with VA-ECMO implementation in the early conservative arm, 1 patient received long-term MCS (HeartMate, Abbott, Plymouth, MN), and 3 patients required an Impella (Abiomed, Danvers, MA). In the early VA-ECMO arm, 2 patients received short-term surgical mechanical support (Centrimag, Abbott, Plymouth, MN), 3 patients underwent long-term mechanical support implantation (HeartMate), and 2 patients required an Impella.

At 30 days, 13 patients in each group remained hospitalized, and 7 in each group were discharged home; 9 subjects in the early VA-ECMO group and 11 patients in the early conservative group were transferred to long-term care or rehabilitation (Table S2). Neurological status at 30 days was comparable between the groups (Table S2, Figure S2).

### Type and Etiology of Cardiogenic Shock

A total of 45 patients fulfilled the criteria for rapidly deteriorating cardiogenic shock (corresponding to Society for Cardiovascular Angiography and Interventions [SCAI] stage D-E), and 72 experienced severe cardiogenic shock (corresponding to SCAI stage D). The incidence

**Table 2. Baseline Characteristics**

Characteristic	All	VA-ECMO	Conservative	P value
	N=117	N=58	N=59	
Sex, n (%)				
Male	86 (73.5)	43 (74.1)	43 (72.9)	0.878
Female	31 (26.5)	15 (25.9)	16 (27.1)	
Age, y (IQR)	66 (59-73)	67 (60-74)	65 (58-71)	0.356
Medical history, n (%)				
Chronic coronary syndrome	39 (34.2)	21 (37.5)	18 (31.0)	0.467
Chronic heart failure	27 (23.7)	14 (25.0)	13 (22.4)	0.745
Dilated cardiomyopathy	15 (13.3)	6 (10.9)	9 (15.5)	0.471
Chronic renal failure	16 (14.2)	7 (12.5)	9 (15.8)	0.616
Peripheral arterial disease	10 (8.8)	3 (5.5)	7 (11.9)	0.324
Hypertension	73 (64.0)	35 (62.5)	38 (65.5)	0.737
Diabetes	37 (32.5)	16 (28.6)	21 (36.2)	0.384
Current smoker	41 (36.9)	14 (25.9)	27 (47.4)	0.019
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)	0.960
Systolic blood pressure, mmHg	85.0 (80.0-100.0)	84.0 (80.0-95.0)	89.0 (79.5-105.0)	0.282
Mean arterial pressure, mmHg	63.3 (55.3-72.0)	63.3 (56.7-68.7)	64.5 (54.3-75.3)	0.289
Heart rate, beats/min	102.0 (84.0-120.0)	110.0 (86.5-130.0)	100.0 (82.0-110.0)	0.076
Therapy at randomization, n (%)				
Intra-aortic balloon pump	15 (13.3)	6 (10.9)	9 (15.5)	0.471
Mechanical ventilation	81 (72.3)	41 (74.5)	40 (70.2)	0.605
Renal replacement therapy	7 (6.2)	4 (7.3)	3 (5.2)	0.712
Norepinephrine	100 (85.5)	50 (86.2)	50 (84.7)	
Norepinephrine dose, $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , median (IQR)	0.50 (0.23-1.24)	0.48 (0.23-1.36)	0.50 (0.27-1.19)	0.741
Epinephrine	4 (3.4)	1 (1.7)	3 (5.1)	
Epinephrine dose, $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , median (IQR)	0.26 (0.14-0.80)	0.21 (0.21-0.21)	0.30 (0.07-1.30)	0.999
Dobutamine	64 (54.7)	31 (53.4)	33 (55.9)	
Dobutamine dose, $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , median (IQR)	5.1 (4.9-8.0)	6.1 (5.0-9.7)	5.1 (4.7-7.6)	0.492
Milrinone	38 (32.5)	22 (37.9)	16 (27.1)	
Milrinone dose, $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , median (IQR)	0.40 (0.30-0.50)	0.40 (0.30-0.50)	0.40 (0.37-0.51)	0.389
Vasopressin	41 (35.0)	19 (32.8)	22 (37.3)	
Vasopressin dose, $\text{U}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , median (IQR)	0.0017 (0.0010-0.0025)	0.0020 (0.0010-0.0030)	0.0017 (0.0012-0.0022)	0.824
Levosimendan	32 (29.4)	20 (37.0)	12 (21.8)	0.081
Vasoactive-inotropic score, median (IQR)	61.0 (30.0-124.0)	59.9 (32.8-121.5)	61.0 (28.0-124.9)	0.976
Cause of cardiogenic shock, n (%)				
ST-segment-elevation myocardial infarction	59 (50.4)	30 (51.7)	29 (49.2)	0.854
Non-ST-segment-elevation myocardial infarction	14 (12.0)	7 (12.1)	7 (11.9)	0.999
Decompensation of chronic heart failure	27 (23.1)	14 (24.1)	13 (22.0)	0.829
Mechanical complications of myocardial infarction	3 (2.6)	1 (1.7)	2 (3.4)	0.999
Other	14 (12.0)	6 (10.3)	8 (13.6)	0.777

Other causes of cardiogenic shock include myocarditis, aortic stenosis, and mitral regurgitation. IQR indicates interquartile range; and VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

of primary composite end point was 72.2% in those with severe cardiogenic shock and 60.0% in those with rapidly deteriorating cardiogenic shock (Figure S3); similar

results were also observed for all-cause mortality (54.2% versus 40.0%, respectively) (Figure S4). The incidence of primary end point and all-cause death was comparable

**Table 3. Incidence of the Composite Primary End Point, Individual Components of the Composite Primary End Point and Secondary Composite Outcomes**

End point, n (%)	VA-ECMO	Conservative	Risk difference (95% CI)	Hazard ratio (95% CI)
	N=58	N=59		
Composite primary outcome—composite of death from any cause, implantation of another mechanical circulatory support, resuscitated cardiac arrest	37 (63.8)	42 (71.2)	-7.4 (-24.3 to 9.5)	0.721 (0.463 to 1.123)
Death	29 (50.0)	28 (47.5)	2.5 (-15.6 to 20.7)	1.110 (0.660 to 1.866)
Another mechanical circulatory support	10 (17.2)	25 (42.4)	-25.1 (-41.1 to -9.2)	0.380 (0.182 to 0.793)
Resuscitated cardiac arrest	6 (10.3)	8 (13.6)	-3.2 (-15.0 to 8.5)	0.790 (0.274 to 2.277)
Composite of death from any cause or resuscitated cardiac arrest	31 (53.4)	32 (54.2)	-0.8 (-18.9 to 17.3)	1.037 (0.633 to 1.700)
Composite of death from any cause, implantation of another mechanical circulatory support, resuscitated cardiac arrest, and serious adverse event	51 (87.9)	50 (84.7)	3.2 (-9.2 to 15.6)	

VA-ECMO indicates veno-arterial extracorporeal membrane oxygenation.

between the immediate VA-ECMO and the early conservative therapy groups in both cardiogenic shock types (Figure 3, Table S3).

In the subgroup of 74 patients with cardiogenic shock caused by acute myocardial infarction, the incidence of the primary end point and all-cause death was comparable between the immediate VA-ECMO and the early conservative groups (Table S4). Similar results were observed in the subgroup of 43 subjects with cardiogenic shock of nonmyocardial infarction pathogenesis (Table S4).

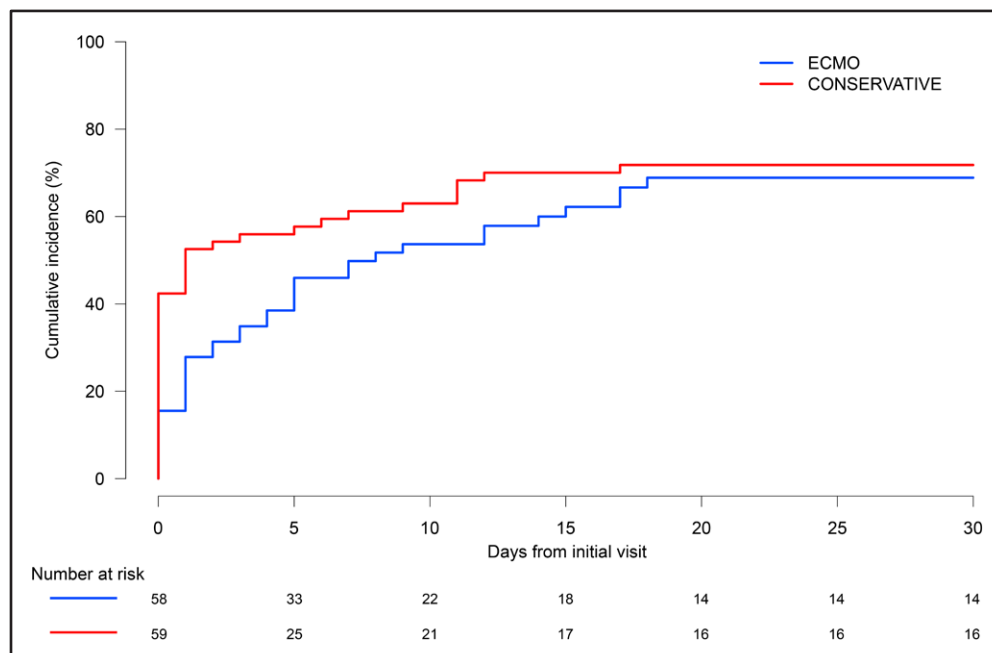
**Safety**

Serious adverse events occurred in 35 (60.3%) patients in the immediate VA-ECMO group and 36 (61.0%) in the

early conservative group (risk difference, -0.7 [95% CI, -18.4 to 17.0]). The incidence of sepsis and pneumonia was comparable between the 2 groups; stroke, leg ischemia, and bleeding were numerically higher in the VA-ECMO group (Table 4). Similarly, the incidence of serious adverse events was comparable between the subgroup of 81 patients treated with immediate VA-ECMO in any of the arms and the subgroup of 36 patients in the early conservative arm without downstream VA-ECMO use (“as-treated” analysis) (Table S5).

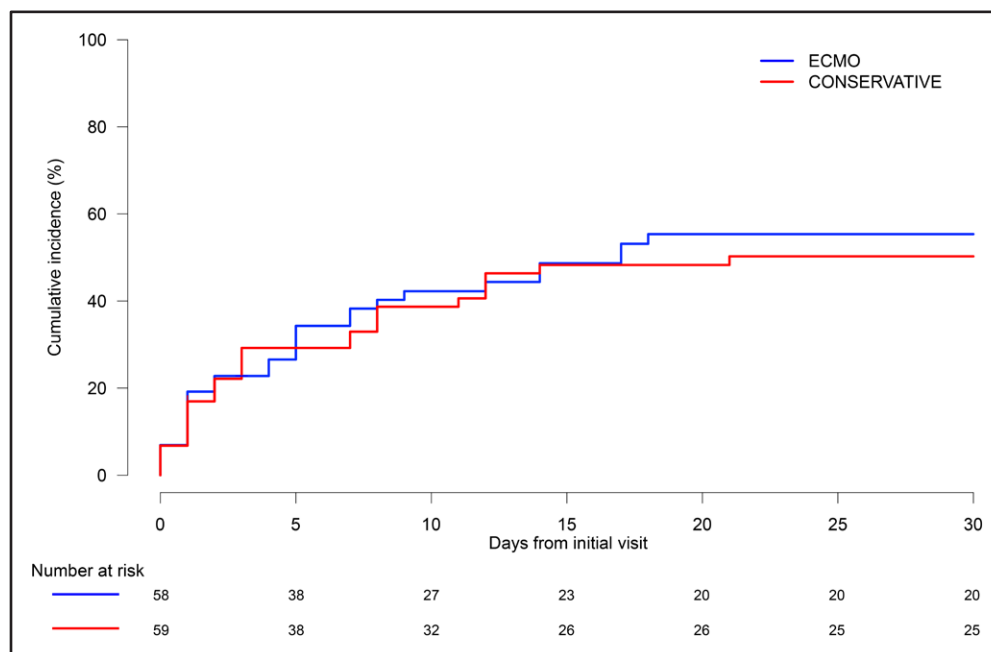
**DISCUSSION**

Among patients with rapidly progressing or severe cardiogenic shock, immediate implementation of VA-ECMO did not improve 30-day clinical outcomes. Immediate



**Figure 1. Cumulative incidence of the composite primary end point.**

ECMO indicates extracorporeal membrane oxygenation.



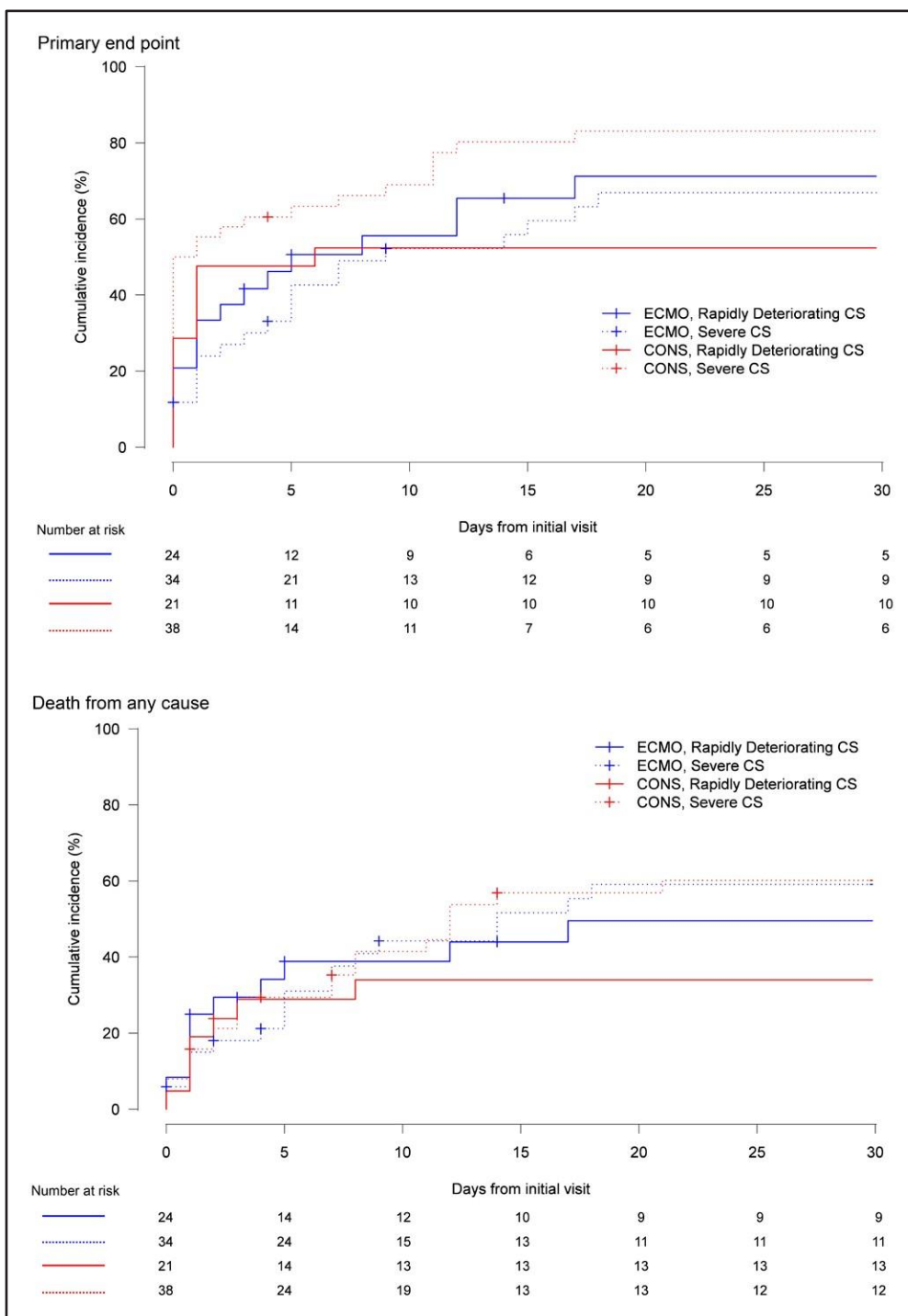
**Figure 2. Cumulative incidence of all-cause death.** ECMO indicates extracorporeal membrane oxygenation.

VA-ECMO therapy was not associated with an increased incidence of adverse events, and a substantial proportion of patients in the early conservative therapy group required VA-ECMO later during their hospital stay.

Despite recent advances in diagnostic tools and therapeutic interventions, cardiogenic shock continues to have high mortality. Cardiogenic shock is a clinical syndrome with various etiologies, phenotypes, and presentations.<sup>1,14</sup> The definitions of cardiogenic shock vary widely on the basis of the presence of hypotension and hypoperfusion, whereas more accurate hemodynamic criteria, confirmation of structural heart disease, or evidence for sufficient heart filling are frequently not required for diagnosis.<sup>2,3,5,15</sup> The severity of cardiogenic shock was recently classified in a statement from the SCAI and endorsed by other major cardiovascular societies.<sup>1</sup> Our study aimed to compare immediate VA-ECMO with an early conservative therapy in patients with rapidly deteriorating or severe cardiogenic shock, defined according to hemodynamic criteria, evidence of structural heart disease, and parameters of tissue hypoperfusion that best correspond to stage D-E of the SCAI classification. Therefore, the ECMO-CS trial population matches well with the conditions in which mechanical circulatory support may be—or should be—considered according to the current guidelines or scientific statements.<sup>5–8</sup> On the basis of the study protocol, for ethical reasons, VA-ECMO could be used in the early conservative group later in case of clearly defined further hemodynamic worsening, which was also considered a clinically relevant end point. VA-ECMO was used for this indication in a substantial proportion of patients.

Although the incidence of the composite primary end point in our study was higher than anticipated, we failed to demonstrate that immediate implementation of VA-ECMO in severe or rapidly deteriorating cardiogenic shock improved outcomes compared with an early conservative approach. This observation is, in part, in good agreement with the first, small randomized trial reporting equal outcomes with VA-ECMO compared with medical therapy.<sup>9,10</sup> However, our study compared immediate VA-ECMO implementation with an early conservative therapy and allowed downstream use of VA-ECMO in the early conservative group. The allowance of VA-ECMO insertion in the early conservative arm in case of further hemodynamic worsening on inotropes and vasopressors makes interpretation of the results more difficult. However, there are ethical reasons to allow MCS if pharmacological stabilization fails, which is a frequent clinical scenario.

Currently, there is no evidence from randomized controlled trials supporting the use of mechanical circulatory support in cardiogenic shock. The large IABP-Shock II trial (Intra-Aortic Balloon Pump in Cardiogenic Shock II) randomized 600 patients with acute myocardial infarction complicated with cardiogenic shock to routine intra-aortic balloon pump use or conservative care.<sup>2</sup> The use of the balloon pump was not associated with a reduction in 30-day all-cause mortality (39.7% versus 41.3%;  $P=0.69$ ),<sup>2</sup> and on the basis of these results, routine use of balloon pumps is not recommended.<sup>5–8</sup> More evidence for the use of mechanical circulatory support in cardiogenic shock may be derived from the results of the 4 large ongoing randomized clinical trials (EURO-SHOCK,



**Figure 3. Cumulative incidence of primary composite end point and all-cause death according to the type of cardiogenic shock and treatment arms.**

ECMO indicates early veno-arterial extracorporeal membrane oxygenation (VA-ECMO) arm; CONS, early conservative arm. Rapidly deteriorating CS, rapidly deteriorating cardiogenic shock (corresponds to Society for Cardiovascular Angiography and Interventions [SCAI] stage D-E); and Severe CS, severe cardiogenic shock (corresponds to the SCAI stage D).

ANCHOR, ECLS-SHOCK, DanGer Shock).<sup>8,12,16,17</sup> All these trials are focused on cardiogenic shock caused by acute myocardial infarction. The ECLS-SHOCK and EURO-SHOCK trials compare VA-ECMO and conservative therapy, the ANCHOR trial compares VA-ECMO plus

intra-aortic balloon pump and conservative therapy, and the DanGer Shock trial compares the Impella and conservative therapy. In contrast with our study, VA-ECMO (or Impella) use is not recommended in the conservative arms in these trials.<sup>9,11,16,17</sup>



**Table 4. Adverse Events**

Adverse event, n (%)	VA-ECMO	Conservative	Risk difference (95% CI)	P value
	N = 58	N = 59		
Serious adverse events	35 (60.3)	36 (61.0)	-0.7 (-18.4 to 17.0)	0.941
Bleeding	18 (31.0)	12 (20.3)	10.7 (-5.0 to 26.4)	0.185
Leg ischemia	8 (13.8)	3 (5.1)	8.7 (-1.8 to 19.2)	0.107
Stroke	3 (5.2)	0 (0.0)	5.2 (-0.5 to 10.9)	0.119
Pneumonia	18 (31.0)	18 (30.5)	0.5 (-16.2 to 17.3)	0.951
Sepsis	23 (39.7)	23 (39.0)	0.7 (-17.0 to 18.4)	0.941
Technical complications	1 (1.7)	0 (0.0)	1.7 (-1.6 to 5.1)	0.496
Bleeding, leg ischemia, stroke	22 (37.9)	14 (23.7)	14.2 (-2.3 to 30.7)	0.096
No. of adverse events				
0	23 (39.7)	23 (39.0)		0.179
1	9 (15.5)	11 (18.6)		
2	11 (19.0)	19 (32.2)		
3	6 (10.3)	4 (6.8)		
≥4	8 (13.8)	2 (3.4)		

VA-ECMO indicates veno-arterial extracorporeal membrane oxygenation.

The incidence of adverse events in our study was similar in the early VA-ECMO and early conservative therapy groups. This observation contradicts several other studies reporting a higher occurrence of complication(s) with VA-ECMO in patients with cardiogenic shock.<sup>18–21</sup> However, safety outcomes in the present study could also be influenced by the fact that a substantial proportion of the early conservative group also received VA-ECMO or another MCS device later, and the interpretation is difficult because of the limited sample size.

Our trial has limitations. First, all patients who participated were white, 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 also was no upper age limit for enrollment, 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. Therefore, all other results must be considered hypothesis-generating. The small sample size also precluded subgroup analyses. The sample size was calculated based on the assumption of a 54% incidence of the primary end point in the conservative group (assuming 40% mortality,<sup>2</sup> a 20% incidence of the implantation of another mechanical circulatory support of whom 60% would survive, and 2% incidence of successfully resuscitated cardiac arrest without MCS in the conservative group) and 50% reduction of primary end point in the VA-ECMO group. We acknowledge that a presumed reduction in the primary end point of 50% may be excessive, but considering the meta-analysis reporting a 33% reduction in 30-day mortality with ECMO versus balloon pump<sup>22</sup> and a lower need for other mechanical support in the early VA-ECMO

group, we believe it was justified; however, it precludes adequate evaluation of clinically important benefits from early VA-ECMO below this threshold. Thus, larger studies are needed to evaluate smaller, but clinically relevant, degrees of risk reduction with VA-ECMO in patients with cardiogenic shock. Third, as mentioned above, the trial did not compare VA-ECMO with conservative therapy but immediate VA-ECMO with early conservative strategy permitting “bailout” VA-ECMO therapy in case of hemodynamic worsening. The results should, therefore, be interpreted accordingly. Furthermore, the definition of shock progression allowing VA-ECMO placement in the early conservative arm is not perfect. It was based on the rise of lactate that cannot cover all characteristics of the extremely complex hemodynamic situation and is also influenced by lactate clearance. Also, strategies for venting of the possibly overloaded left ventricle by increased afterload caused by VA-ECMO were not specified in the protocol, and these interventions, if needed, were performed at the discretion of the attending physicians and according to local practice at the individual participating centers. Inadequate use of left ventricular unloading might impair the outcomes in the immediate VA-ECMO arm. However, intra-aortic balloon pump was used in 6 patients in the immediate VA-ECMO arm already at randomization, and another 7 patients received a percutaneous or surgical left-ventricular assist device later; therefore, a substantial proportion of VA-ECMO-treated patients underwent unloading. Fourth, the trial was unblinded, and the end points were not adjudicated. Last, inclusion criteria for the study were based on shock severity defined by intensity of vasoactive therapy, hemodynamic or metabolic parameters, and the evidence of

cardiac pump failure, not on the specific etiologies. 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 hypertrophic obstructive cardiomyopathy. Moreover, cardiac arrest survivors remaining comatose were also excluded. Therefore, our results cannot be generalized to all etiologies of shock and to all concomitant conditions and should be interpreted in the context of the inclusion criteria.

In conclusion, immediate implementation of VA-ECMO in patients with rapidly deteriorating or severe cardiogenic shock (corresponding to SCAI stage D-E) was feasible but did not improve clinical outcomes compared with an early conservative approach permitting downstream use of VA-ECMO in cases of hemodynamic worsening.

## ARTICLE INFORMATION

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### Affiliations

Department of Cardiology, Na Homolce Hospital, Prague, Czech Republic (P.O., A.K., D.V., M.J., J.N.). Department of Cardiology, University Hospital and Faculty of Medicine Pilsen, Charles University, Pilsen, Czech Republic (R.R., M. Hromadka, S.V., M. Seyfrydova). Hospital Liberec, Liberec, Czech Republic (J.K.). 2nd Department of Medicine—Department of Cardiovascular Medicine, First Faculty of Medicine, Charles University and General University Hospital, Prague, Liberec, Czech Republic (J.K., J.S., M. Hubatova, A.L., J.B.). Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Brno, Czech Republic (J.J., M. Svoboda). Institute of Biostatistics and Analyses, Ltd, Brno, Czech Republic (M. Svoboda).

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### Supplemental Material

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