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

Running title: *Ostadal et al.; ECMO in cardiogenic shock*

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Abstract

Background: Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is increasingly being used for circulatory support in cardiogenic shock patients, although the evidence supporting its use in this context remains insufficient. The aim of the Extracorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock (ECMO-CS) trial was to compare immediate implementation of VA-ECMO vs. 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 standard(s) of care. In the early conservative group, VA-ECMO could be used downstream in case of worsening hemodynamic status. The primary endpoint 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 due to the absence of informed consent, 117 subjects were included in the analysis, of whom 58 randomized to immediate VA-ECMO and 59 to no immediate VA-ECMO. The composite primary endpoint occurred in 37 (63.8%) and 42 (71.2%) of patients in the immediate VA-ECMO and the no early VA-ECMO groups, respectively (hazard ratio, 0.72; 95% confidence intervals [CI], 0.46 to 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.% vs. 13.6%; risk difference [RD], -3.2; 95% CI, -15.0 to 8.5), all-cause mortality (50.0% versus 47.5%; RD, 2.5; 95% CI, -15.6 to 20.7), serious adverse events (60.3% vs. 61.0%; RD, -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.

Conclusion: 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.

Clinical Trial Registration:
URL: https://www.clinicaltrials.gov; Unique identifier NCT02301819.

Nonstandard Abbreviations and Acronyms

VA-ECMO	Veno-arterial extracorporeal membrane oxygenation
ECMO-CS	Extracorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock Trial
LVEF	Left ventricular ejection fraction
SCAI	Society for Cardiovascular Angiography and Interventions

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Clinical Perspective

What is new?

- In the ECMO-CS (Extracorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock) Trial, 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 due to 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 than immediate insertion of VA-ECMO.

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Introduction

Cardiogenic shock is a critical condition with various etiologies, phenotypes, and presentations [1]. Despite advances in cardiovascular acute and intensive care, early mortality from cardiogenic shock remains high [2, 3].

Multiple mechanical circulatory support systems have been developed over the past few decades that can be used for hemodynamic stabilization in this patient population [4]. However, currently available mechanical circulatory support (MCS) devices have not been demonstrated to improve survival in cardiogenic shock. [4]. 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 bi-ventricular failure. [4]

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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 [5]. 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 [6]. 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 MCS type of according to the specific hemodynamic condition(s) [7, 8]. 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

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significant differences between the study arms [9, 10]. 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 (Testing the Value of Novel Strategy and Its Cost Efficacy in Order to Improve the Poor Outcomes in Cardiogenic Shock [EURO-SHOCK], Assessment of ECMO in Acute Myocardial Infarction Cardiogenic Shock [ANCHOR], Extracorporeal Life Support in Cardiogenic Shock [11]) [11, 12].

The aim of the Extracorporeal Membrane Oxygenation in the therapy of Cardiogenic Shock (ECMO-CS) trial was to compare immediate implementation of VA-ECMO vs. 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 four centers in the Czech Republic. The study protocol was approved by the Ethics Committees of all participating centers. The trial design has been published [13]. The protocol was designed by the first two and the last author, and is available as a full text article at 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

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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). The data that support the findings of this study are available from the corresponding author upon 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 one 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 artery disease precluding arterial cannula insertion in the femoral artery, moderate to severe aortic regurgitation, aortic dissection, uncontrolled bleeding or TIMI major bleeding within last 6 months, and known encephalopathy. Details regarding the inclusion and exclusion criteria are provided in the Supplemental Material.

Trial procedures

Patients who fulfilled the trial entry criteria were randomly assigned in a 1:1 ratio to one of two 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 (i.e., percutaneous coronary or non-coronary intervention, cardiac surgery) or mechanical circulatory support. In the early conservative group, VA-ECMO could be used downstream in case of further worsening of

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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 endpoint 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 endpoints 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 endpoints (including the safety endpoints) 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 50% reduction of primary endpoint at two-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 Pearson Chi Square test or Fisher's exact test. Continuous variables were presented as median (interquartile range) and compared using 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 log-rank test. Calculation of the 95% confidence intervals for point estimates of end point occurrence probability are based on the

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cumulative risk function (or logarithmic transformation of the survival function). Hazard ratios (HR) with 95% confidence intervals were calculated using a Cox proportional hazard model with Efron approximation for tie holding. Furthermore, 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 AFT model) was prepared. Differences in end point proportions between the two categories were investigated using risk difference (RD) with 95% confidence intervals. Because of the potential for type 1 error due to 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) and R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Hypotheses were tested at a significance level of 5%.

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Results

Patients

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Between September 2014 and January 2022, a total of 122 patients were randomly assigned to immediate VA-ECMO vs no immediate VA-ECMO. After excluding 5 patients due to 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 two study groups at the time of randomization were balanced (Table 2). The median age was 67 (60 to 74) years in the immediate VA-ECMO group and 65 years (58 to 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 to 8.4 mmol/L) in the immediate VA-ECMO group and 4.7 mmol/L (3.3 to 7.4 mmol/L) in the early conservative group. More than 70% of patients in both groups were on mechanical ventilation.

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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 to 121.5) in the immediate VA-ECMO group and 61.0 (28.0 to 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 study groups (Table S1). Although previous cardiac surgery was not an exclusion criterion, finally only primarily non-surgical patients were enrolled in the trial, although some of them subsequently required cardiac surgery during hospitalization.

End points

The composite primary endpoint 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 conservative group (HR, 0.72; 95% confidence intervals [CI], 0.46 to 1.12; P=0.21) (Figure 1).

All-cause mortality at 30 days was comparable between the two groups (50.0% versus [vs.] 47.5%; HR, 1.110; 95% CI, 0.660 to 1.866) (Table 3, Figure 2). In the immediate VA-ECMO group, fewer patients required another MCS device (17.2% vs. 42.4%, respectively; HR, 0.380; 95% CI, 0.182 to 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 to 2.277 (Table 3). Similarly, the incidence of death from any cause or resuscitated cardiac arrest, death from any cause, resuscitated cardiac arrest, implementation of another MCS device or serious adverse events were comparable between treatment arms (Table 3).

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The results remained similar after adjustment for smoking status with the respect to composite primary endpoint (HR, 0.681; 95 CI, 0.426 to 1.088) and death from any cause (HR, 0.916; 95% CI, 0.528 to 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 to 2.238). Beside the 23 patients with VA-ECMO implementation in the early conservative arm, one patient received long-term MCS (HeartMate, Abbott) and three patients required an Impella (Abiomed, US). In the early VA-ECMO arm two patients received short-term surgical mechanical support (Centrimag, Abbott, US), three patients underwent long-term mechanical support implantation (HeartMate, Abbott, US) and two patients required an Impella (Abiomed, US).

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 SCAI stage D-E) and 72 experienced severe cardiogenic shock (corresponding to SCAI stage D). The incidence of primary composite end point was 72.2% in those with severe cardiogenic shock and 60.0% in those with rapidly deteriorating

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cardiogenic shock (Figure S3); similar results were also observed for all-cause mortality (54.2% vs. 40.0%, respectively) (Figure S4). The incidence of primary end point and all-cause death was comparable 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 endpoint and all-cause death was comparable between the immediate VA-ECMO and the early conservative groups (Table S4). Similar results were observed also in the subgroup of 43 subjects with cardiogenic shock of non-myocardial infarction etiology (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 (RD, -0.7; 95% CI, -18.4 to 17.0). The incidence of sepsis and pneumonia were comparable between the two 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).

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Discussion

Among patients with rapidly progressing or severe cardiogenic shock, immediate implementation of VA-ECMO did not improve 30 days clinical outcomes. Immediate 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 [1, 14]. The definitions of cardiogenic shock vary widely based on 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 [2, 3, 5, 15]. The severity of cardiogenic shock was recently classified in a statement from the Society for Cardiovascular Angiography and Interventions (SCAI) and endorsed by other major cardiovascular societies [1]. The aim of our study was 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—or should be—considered according to the current guidelines or scientific statements [5-8]. Based on 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 [9, 10]. However, our study compared immediate VA-ECMO implementation with an early conservative therapy and allowed downstream use of VA-ECMO in the early conservative

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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 [2]. The use of balloon pump was not associated with a reduction in 30-day all-cause mortality (39.7% versus. 41.3%; P=0.69) [2] and based on these results routine use of balloon pumps is not recommended [5-8]. More evidence for the use of mechanical circulatory support in cardiogenic shock may be derived from the results of the four large ongoing randomized clinical trials (EURO-SHOCK, ANCHOR, ECLS-SHOCK, DanGer Shock) [8, 12, 16, 17]. 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 DanGer Shock trial compares Impella and conservative therapy. In contrast to our study, VA-ECMO (or Impella) use is not recommended in the conservative arms in these trials [9, 11, 16, 17].

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 [18-21]. 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 due to limited sample size.

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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 less than one 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 54% incidence of the primary end point in the conservative group (assuming 40% mortality [2], 20% incidence of the implantation of another mechanical circulatory of whom 60% would survive, and 2% incidence of successfully resuscitated cardiac arrest without MCS in the conservative group) and 50% reduction of primary endpoint in the VA-ECMO group. We acknowledge that a presumed reduction in the primary endpoint of 50% may be excessive, but considering the meta-analysis reporting a 33% reduction in 30-day mortality with ECMO vs. balloon pump [22] 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

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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. Finally, 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.

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Disclosures

Dr. Ostadal received speaker's honoraria from Getinge, Edwards, Xenios. Dr. Belohlavek received speaker's honoraria from Getinge. No other authors reported disclosures.

Supplemental Materials

List of investigators

Inclusion and exclusion criteria

Tables S1-S5

Figures S1-S4

Study protocol

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Table 1. Inclusion criteria

Patients must fulfil 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 mmHg + impaired left ventricle systolic function (Left ventricle ejection fraction (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 (CI) < 2.2 L/min/m2 + norepinephrine dose > 0.1 µg/kg/min + dobutamine dose > 5 µg/kg/min	
	or		
		Systolic blood pressure < 100 mmHg + norepinephrine dose > 0.2 µg/kg/min + dobutamine dose > 5 µg/kg/min + (LVEF < 35% or LVEF 35-55% + severe mitral regurgitation or aortic stenosis)	
	2. Metabolic:		
		Lactate – two consecutive values ≥ 3 mmol/L (with at least 30 min between samples), with non-decreasing trend on steady doses of inotropes and/or vasopressors	
	or		
		SvO_2 – two consecutive values < 50% (with at least 30 min between measurements), with non-increasing trend on steady doses of inotropes and/or vasopressors	
	3. Hypovolemia must be excluded:		
		Central venous pressure > 7 mmHg or pulmonary capillary wedge pressure > 12 mmHg	

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Table 2. Baseline characteristics

Characteristic	All	VA-ECMO	Conservative	P-value
	N = 117	N = 58	N = 59	
Sex - no. (%)				
Male	86 (73.5 %)	43 (74.1 %)	43 (72.9 %)	0.878
Female	31 (26.5 %)	15 (25.9 %)	16 (27.1 %)	
Age - years (IQR)	66 (59; 73)	67 (60; 74)	65 (58; 71)	0.356
Medical history - no. (%)				
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
Periphery artery 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 - no. (%)				
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 [µg/kg/min]	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 %)	

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Epinephrine dose [µg/kg/min]	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 [µg/kg/min]	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 [µg/kg/min]	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 [U/kg/min]	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				
ST-elevation myocardial infarction	59 (50.4 %)	30 (51.7 %)	29 (49.2 %)	0.854
Non-ST-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, interquartile range

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Table 3. Incidence of the composite primary end point, individual components of the composite primary end point and secondary composite outcomes

End point - no. (%)	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; 1.123)
Death	29 (50.0 %)	28 (47.5 %)	2.5 (-15.6 to 20.7)	1.110 (0.660; 1.866)
Another mechanical circulatory support	10 (17.2 %)	25 (42.4 %)	-25.1 (-41.1 to -9.2)	0.380 (0.182; 0.793)
Resuscitated cardiac arrest	6 (10.3 %)	8 (13.6 %)	-3.2 (-15.0 to 8.5)	0.790 (0.274; 2.277)
Composite of death from any cause or resuscitated cardiac arrest	31 (53.4 %)	32 (54.2 %)	-0.8 (-18.9; 17.3)	1.037 (0.633; 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; 15.6)	
CI, confidence interval				

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Table 4. Adverse events

Adverse event - no. (%)	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; 30.7)	0.096
Number 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%)		

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Figure Legends

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

Figure 2. Cumulative incidence of all-cause death.

Figure 3. Cumulative incidence of primary composite end point and all-cause death according to the type of cardiogenic shock and treatment arms. VA-ECMO, early VA-ECMO arm; CONS, early conservative arm. Rapidly deteriorating CS, rapidly deteriorating cardiogenic shock (corresponds to the SCAI stage D-E); Severe CS, severe cardiogenic shock (corresponds to the SCAI stage D).

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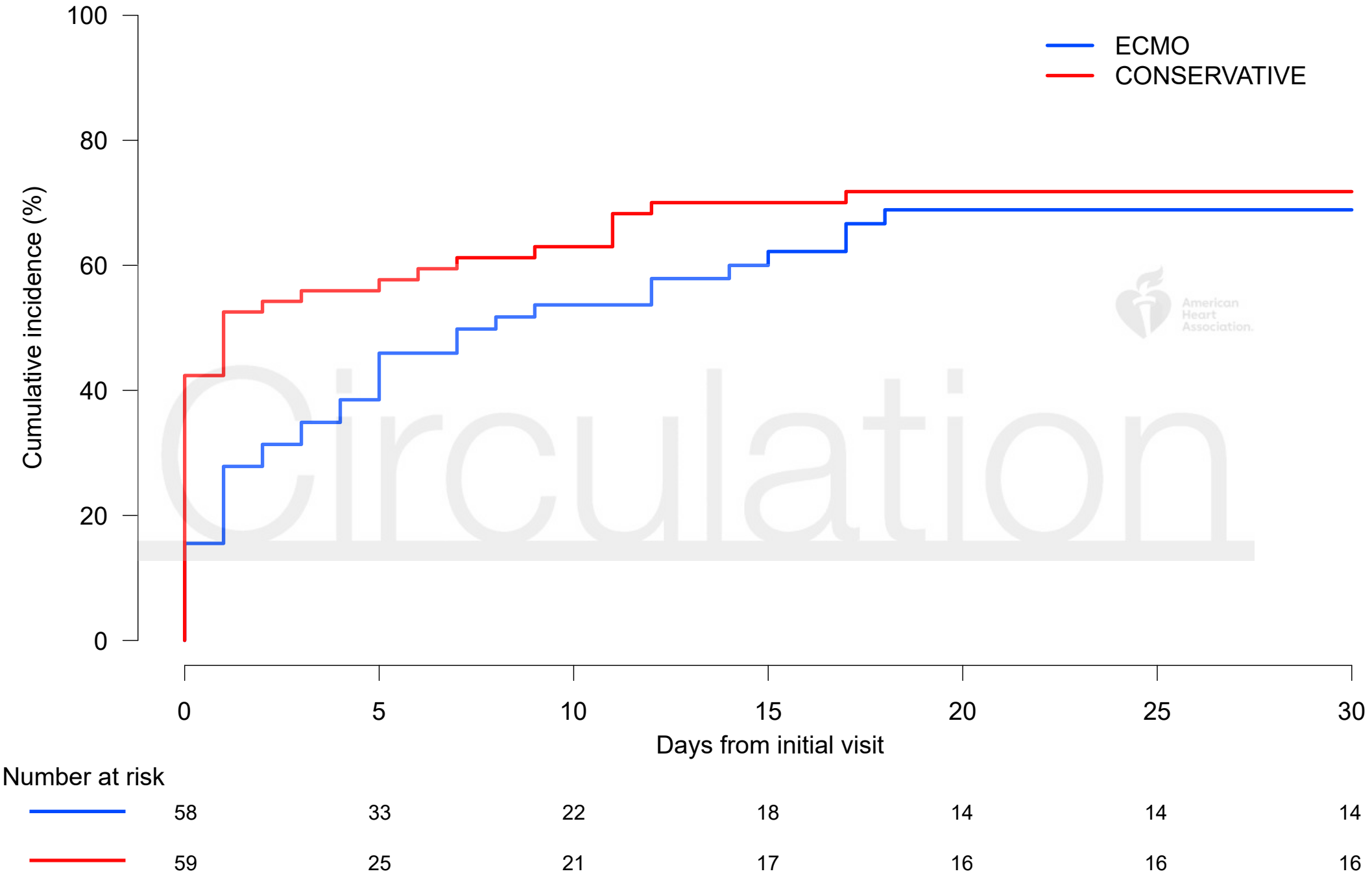

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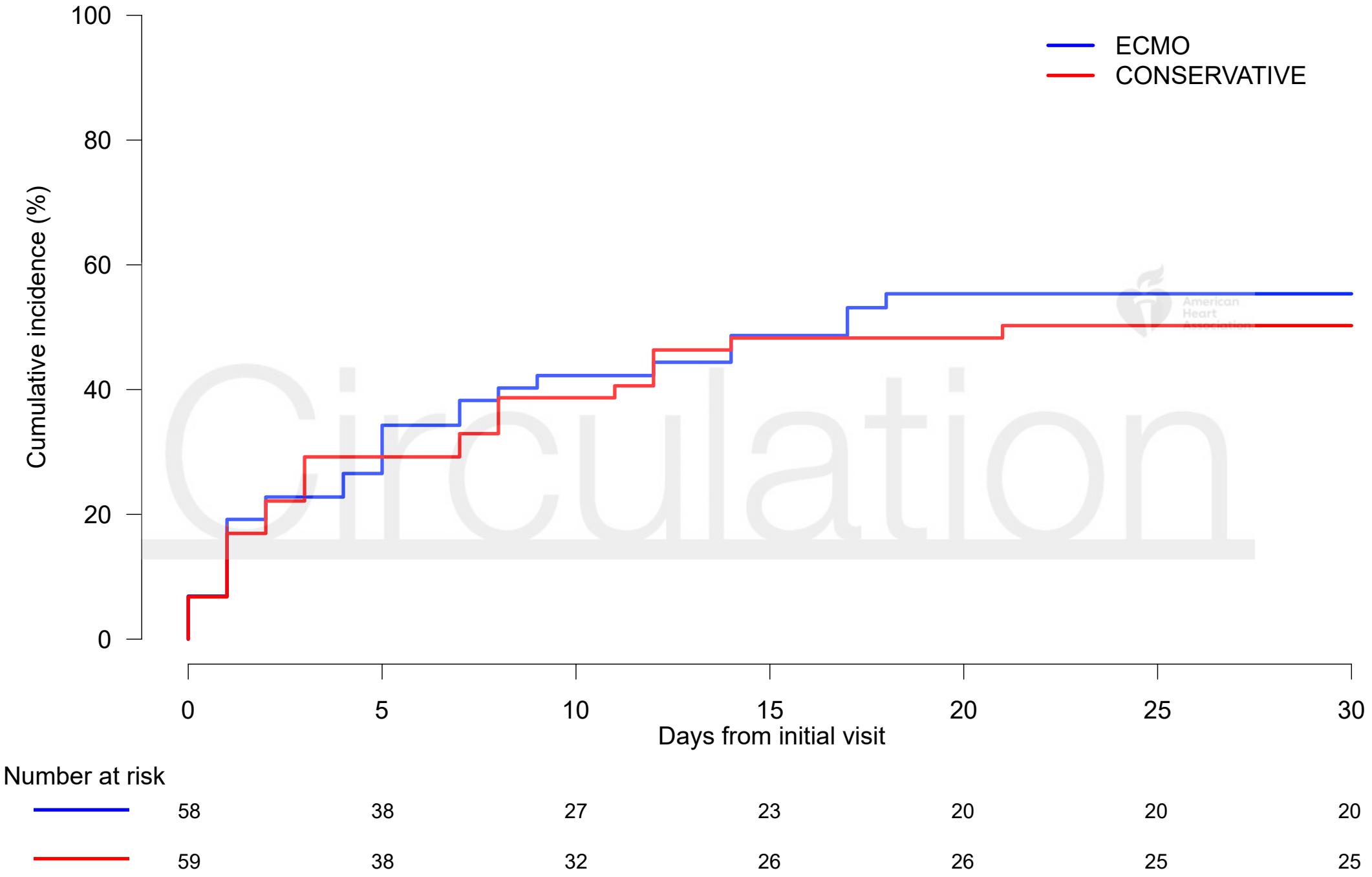

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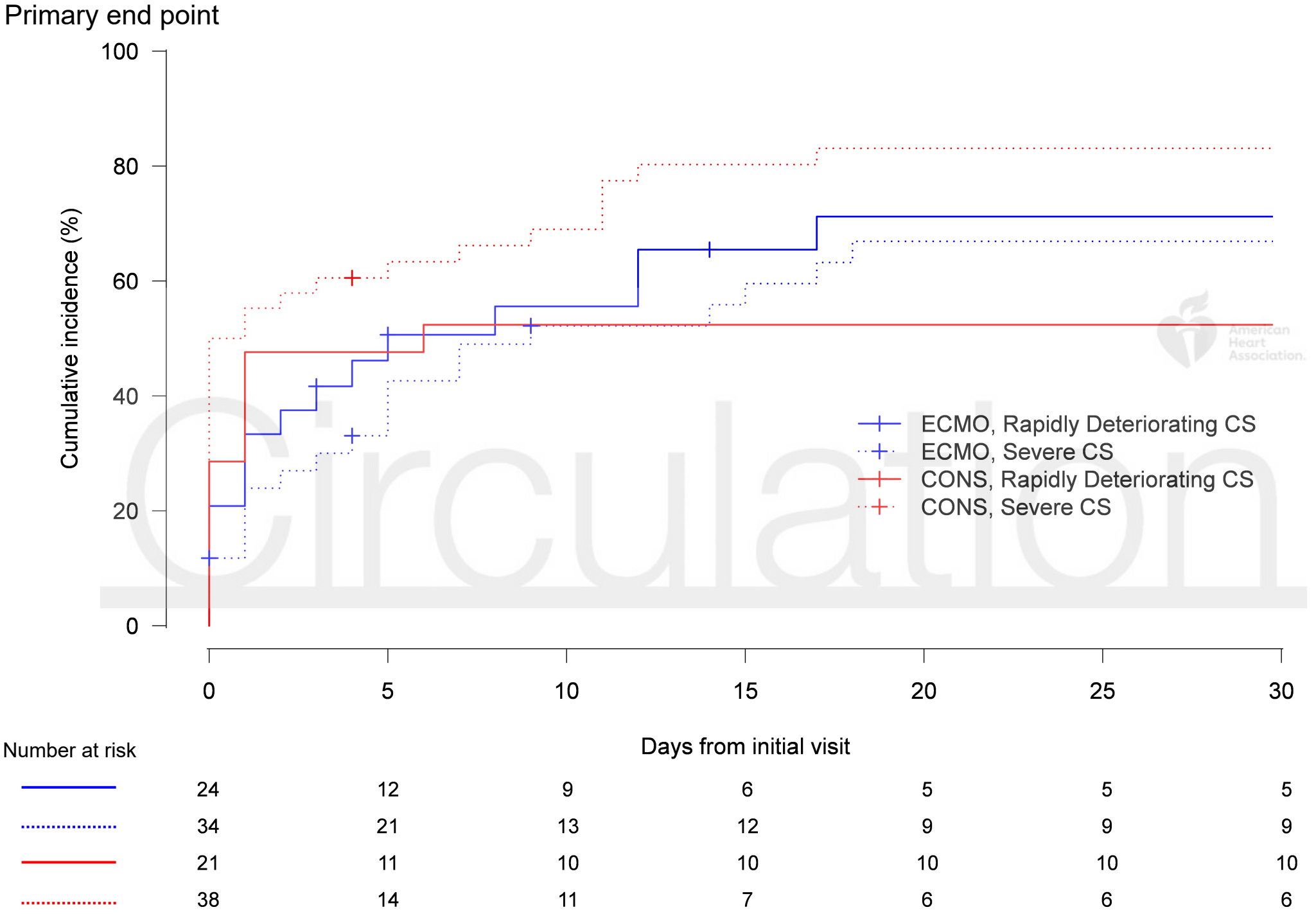

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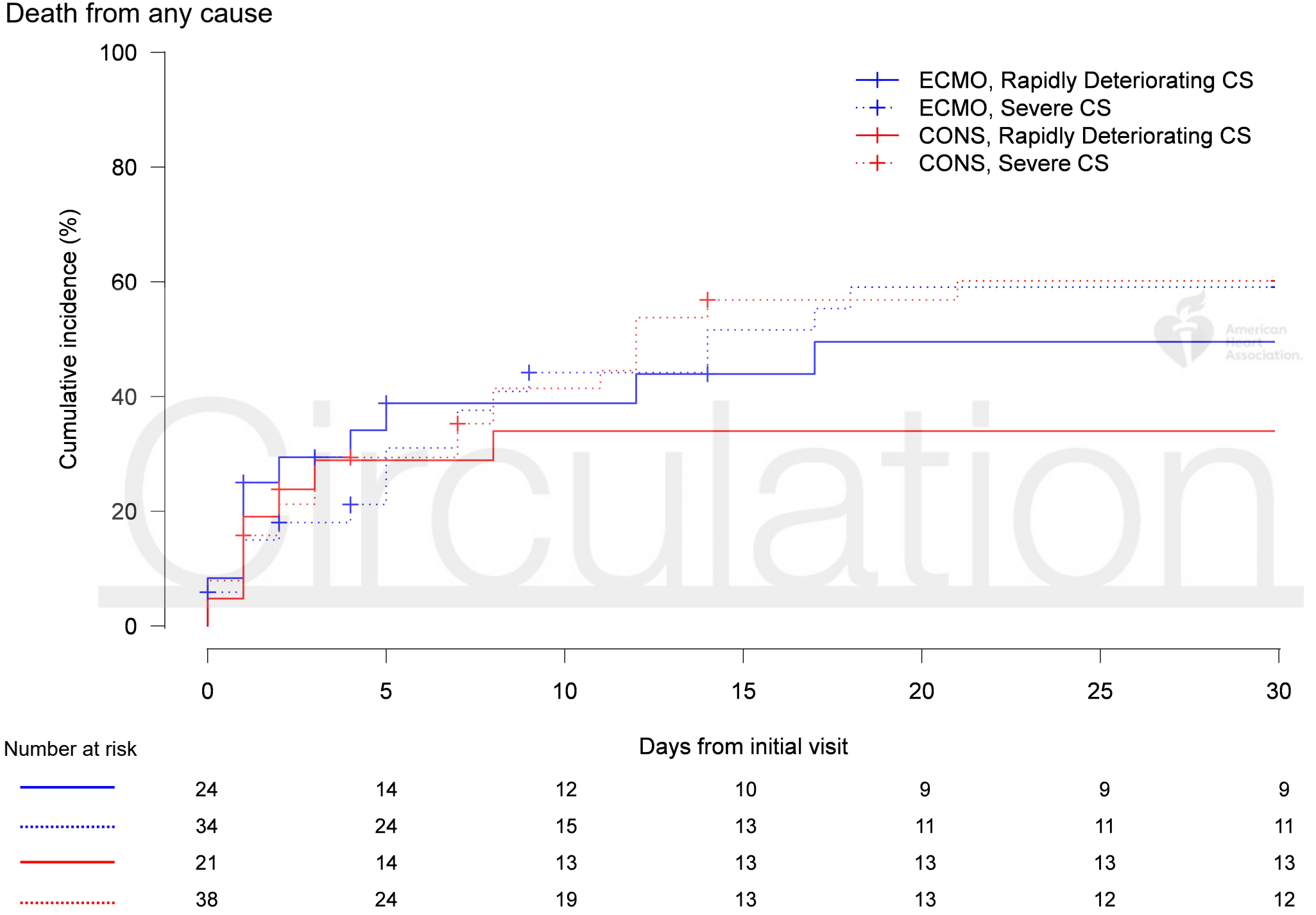

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