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Clinical paper

Hypothermia in patients with cardiac arrest prior to ECMO-VA: Insight from the HYPO-ECMO trial

Bruno Levy^{a,b,c,*}, Nicolas Girerd^{d,e}, Kevin Duarte^{d,e}, Marie-Lauren Antoine^f, Luca Monzo^{d,e}, Ouattara Alexandre^{g,h}, Delmas Clément^{i,j}, Daniel Brodie^k, Alain Combes^{l,m}, Antoine Kimmoun^{a,b,c}, Guillaume Baudry^{d,e,i}, for the HYPO-ECMO Trial Group, the International ECMO Network ECMONet¹

Abstract

Aim: Venoarterial extracorporeal membrane oxygenation (VA-ECMO) has become a common intervention for patients with cardiogenic shock (CS), often complicated by cardiac arrest (CA). Moderate hypothermia (MH) has shown promise in mitigating ischemia–reperfusion injury following CA. The HYPO-ECMO trial aimed to compare the effect of MH versus normothermia in refractory CS rescued by VA-ECMO. The primary aim of this non-predefined post hoc study was to assess the treatment effect of MH in the subgroup of patients with cardiac arrest (CA) within the HYPO-ECMO trial. Additionally, we will evaluate the prognostic significance of CA in these patients.

Methods: This post hoc analysis utilized data from the randomized HYPO-ECMO trial conducted across 20 French cardiac shock care centers between October 2016 and July 2019. Participants included intubated patients receiving VA-ECMO for CS for less than 6 h, with 334 patients completing the trial. Patients were randomized to early MH (33–34 °C) or normothermia (36–37 °C) for 24 h.

Results: Of the 334 patients, 159 (48%) experienced preceding CA. Mortality in the CA group was 50.9% at 30 days and 59.1% at 180 days, compared to 42.3% and 51.4% in the no-CA group, respectively (adjusted risk difference [RD] at 30 days, 8.1% [−0.8 to 17.1%], $p = 0.074$ and RD at 180 days 7.0% [−3.0 to 16.9%], $p = 0.17$). MH was associated with a significant reduction in primary (RD −13.3% [−16.3 to −0.3%], $p = 0.031$) and secondary outcomes in the CA group only ($p < 0.025$ for all), with a significant interaction between MH and CA status for 180-day mortality [$p = 0.03$].

Conclusions: This post hoc analysis suggests that MH shows potential for reducing mortality and composite endpoints in patients with cardiac arrest and refractory CS treated with VA-ECMO without an increased risk of severe bleeding or infection. Further research is needed to validate these findings and elucidate underlying mechanisms.

Keywords: Extracorporeal Membrane Oxygenation, Shock, cardiogenic, Hypothermia, induced, Cardiac arrest

Introduction

The initiation of venoarterial extracorporeal membrane oxygenation (VA-ECMO) has emerged as an increasingly common intervention in patients with cardiogenic shock (CS), including cardiac arrest refractory to standard therapies.¹

Severe CS, especially in case of associated cardiac arrest, may be associated with ischemia–reperfusion injury. Patients with refractory CS requiring VA-ECMO likely have the most severe ischemia–reperfusion injury.² Moderate hypothermia (MH) may mitigate the

deleterious effects of ischemia–reperfusion.³ The randomized, multi-center, controlled HYPO-ECMO trial was designed to compare the effects of moderate hypothermia (MH) to those of normothermia in CS patients treated with venoarterial extracorporeal membrane oxygenation (VA-ECMO).⁴ Although the results of the primary analysis did not reach statistical significance, MH was associated with a significant 8% absolute risk reduction (−8.3 (−16.3 to −0.3)) in 30-day mortality in patients with CS receiving VA-ECMO.⁴ However, MH was associated with a lower risk of the composite outcome of death, heart transplant, escalation to LVAD implantation and stroke at 30 days. The number of patients with serious adverse reactions (sev-

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¹ The members of the HYPO-ECMO Trial Group and the International ECMO Network are listed in Appendix 1 at the end of the article.

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ere and moderate bleeding, infectious events) was not significantly different between the groups.

In the HYPO-ECMO study, approximately 50% of the patients had cardiac arrest (CA) preceding the ECMO run. CA is a frequent complication in this context, affecting nearly 50–75% of patients, and may represent a strong disease modifier.^{5–7} Patients with refractory CS and CA requiring VA-ECMO are likely to have the most severe ischemia–reperfusion injury⁸ and, consequently, are likely to benefit from hypothermia. In the context of CA, modifications in prognosis may be linked to both severe ischemia–reperfusion injuries and neurological lesions due to brain ischemia⁹ rather than only to extensive cardiac damage.¹⁰ Crucially, moderate hypothermia may have a beneficial effect in these three situations.

However, the prognostic role of CA before VA-ECMO is debated. CA prior to VA-ECMO was associated with a 25% decrease in survival probability among nearly 4000 CS patients between 2003 and 2013 according to the ELSO registry.¹¹ In contrast, in a population of patients with AMI requiring VA-ECMO, the proportion of patients receiving pre-ECMO CA was high (57%) but was not associated with prognosis.⁵ The primary aim of this non-predefined post hoc study was to assess the treatment effect of MH in the subgroup of patients with cardiac arrest (CA) within the HYPO-ECMO trial. Additionally, as a secondary endpoint, we will evaluate the prognostic significance of CA in patients with refractory cardiogenic shock (CS) undergoing treatment with VA-ECMO.

Methods

HYPO-ECMO trial

The HYPO-ECMO study was a randomized, controlled, multicenter trial conducted at 20 French cardiac shock care centers between October 2016 and July 2019. The trial was funded by a national grant (trial registration number NCT02754193). The protocol and main results have already been published.^{12,4} Endotracheally intubated adult patients with CS treated with VA-ECMO were eligible for inclusion during the first 6 h (if possible, within 4 h) after VA-ECMO initiation. MH (temperature maintained at $33\text{ }^{\circ}\text{C} \leq T \leq 34\text{ }^{\circ}\text{C}$) was induced as soon as possible after VA-ECMO implementation, and patients were randomized into groups; MH was maintained for 24 h in the intervention group, followed by progressive rewarming. The main exclusion criteria were under 18 years of age, pregnant, receiving VA-ECMO following cardiac surgery for left ventricular assist device (LVAD) implantation or a heart transplant or combined lung and heart transplant, receiving VA-ECMO due to acute poisoning with cardiotoxic drugs, experiencing uncontrolled bleeding that persisted despite medical intervention (including surgery or medication), required venoarterial ECMO following cardiopulmonary resuscitation (CPR) exceeding 45 min, or out-of-hospital refractory CA.

The trial was authorized by French health authorities (*Agence Nationale de la Sécurité du Médicament et des Produits de Santé*) as well as the appropriate ethics committee (*Comité de Protection des Personnes*) and supported by the International ECMO Network (ECMOnet).

Post-hoc study: Factors associated with refractory CA were pre-specified exclusion criteria for the HYPO-ECMO trial (i.e., out-of-hospital refractory CA requiring ECP, implantation of VA-ECMO under cardiac massage for ≥ 45 min, cerebral deficit with fixed dilated pupils, patient moribund on the day of randomization, and prior irreversible neurological disease).

The outcome definitions were consistent with those used in the HYPO-ECMO trial. The primary outcome was 30-day mortality. The main secondary outcomes included mortality at days 60 and 180, as well as a composite outcome of death, heart transplant, escalation to LVAD implantation and stroke at days 30, 60, and 180. We defined four subgroups based on CA status (yes/no) and study intervention (normothermia versus MH). The Cerebral Performance Category (CPC) was used to classified the neurologic status of cardiac arrest patients. The CPC ranges from 1 to 5 and is commonly dichotomized into “good” (CPC 1–2) versus poor (CPC 3–5).

Statistical analysis

Baseline characteristics are expressed as frequency (percentage) for categorical variables and mean \pm SD or median (IQR) for continuous variables data with normal or skewed distributions, respectively. Baseline characteristics were compared between patients with CA and those without, and between the four subgroups based on CA status and study intervention (normothermia versus moderate hypothermia) using *t*-test or Wilcoxon test as appropriate for continuous variables and the Chi-square test or Fisher’s exact test for categorical variables.

The association of CA with each study endpoint was assessed on an absolute scale, by calculation of risk differences using a binomial generalized estimating equation (GEE) model with an identity link, taking into account intracenter correlation, with and without adjustment on the intervention group.

A subgroup analysis was also performed for the primary outcome using prespecified adjustment variables (age, prior MI, post cardiac surgery, vasopressor dose (patients who have not received vasopressor therapy were coded at a dose of 0 ug/kg/min), lactate and SOFA score at baseline). For each continuous adjustment variable, subgroups were defined by dichotomizing the variable according to the median. Interactions between CA status and the subgroups were assessed by introducing an interaction term within the binomial GEE model adjusted on the intervention group. The adjusted risk differences in each subgroup and the p-values for interaction were assessed using the Wald test. The effect of moderate hypothermia according to CA status was evaluated for each study outcome by calculation of risk differences using a binomial GEE model by adding an interaction term between CA status and study group. Survival probabilities are illustrated using Kaplan-Meier curves and were compared using a log-rank test.

All analyses were performed using R software version 4.1.2 (R Foundation for Statistical Computing).

Results

Patient characteristics

Information on prior CA was available for all 334 patients in the trial (Table 1). Post hoc CA characteristics were available for 137/155 (88%) patients and were extracted from medical records (Table 2). One hundred and fifty-nine (48%) patients experienced CA before VA-ECMO implementation (Table 1). Baseline characteristics at randomization were similar in both groups (Table 1). The intervention (MH) was distributed in a balanced manner across groups. In the subgroup of patients with available data on CA typology (88%), 74% had in-hospital CA and witnessed cardiac arrest occurred in 95% of cases. A VA-ECMO system was implanted during CPR in 38% of patients. The duration of no-flow intervals was less than

Table 1 – Baseline characteristics according to CA status (cardiac arrest vs. no cardiac arrest).

| Variable | No cardiac arrest (n = 175) | Cardiac arrest (n = 159) | p-value* |
|--|-------------------------------|------------------------------|----------|
| Intervention group | | | |
| Normothermia | 88 (50.3%) | 78 (49.1%) | 0.82 |
| Moderate hypothermia | 87 (49.7%) | 81 (50.9%) | |
| Demographics | | | |
| Age (years) | 58 ± 12 | 57 ± 12 | 0.33 |
| Sex | | | 0.38 |
| Male | 136 (77.7%) | 117 (73.6%) | |
| Female | 39 (22.3%) | 42 (26.4%) | |
| Body mass index (kg/m ²) ^a | 26.1 ± 4.8 [n = 171] | 27.7 ± 6.1 [n = 152] | 0.009 |
| Cardiovascular history^b | | | |
| Hypertension | 60/172 (34.9%) | 61/154 (39.6%) | 0.38 |
| Ischemic cardiopathy | 39/171 (22.8%) | 33/150 (22.0%) | 0.86 |
| Myocardial infarction | 23/169 (13.6%) | 24/150 (16.0%) | 0.55 |
| Heart failure | 36/170 (21.2%) | 29/151 (19.2%) | 0.66 |
| Valvular cardiopathy | 32/170 (18.8%) | 11/150 (7.3%) | 0.003 |
| Etiologies of cardiogenic shock^c | | | |
| Acute coronary syndrome | 54 (30.9%) | 67 (42.1%) | 0.032 |
| Valvular cardiopathy | 20 (11.4%) | 8 (5.0%) | 0.035 |
| Ischemic cardiomyopathy | 40 (22.9%) | 34 (21.4%) | 0.75 |
| Rhythmic cardiopathy | 20 (11.4%) | 23 (14.5%) | 0.41 |
| Post-cardiac surgery | 32 (18.3%) | 18 (11.3%) | 0.075 |
| Acute myocarditis | 13 (7.4%) | 18 (11.3%) | 0.22 |
| Unlabeled dilated cardiomyopathy | 20 (11.4%) | 6 (3.8%) | 0.009 |
| Pulmonary embolism | 6 (3.4%) | 11 (6.9%) | 0.15 |
| Tako-Tsubo | 6 (3.4%) | 5 (3.1%) | 0.88 |
| Echocardiogram and laboratory results | | | |
| LVEF before VA-ECMO implantation (%) | 20 (15 – 30) [n = 124] | 20 (15 – 35) [n = 89] | 0.35 |
| pH ^d | 7.35 ± 0.13 [n = 169] | 7.29 ± 0.17 [n = 156] | 0.0003 |
| Arterial lactate level, median (IQR), mmol/L ^e | 3.9 (2.2 – 7.1) [n = 167] | 5.9 (3.3 – 9.8) [n = 151] | 0.0004 |
| Sequential organ failure assessment score, median (IQR) ^f | 10 (7 – 12) [n = 144] | 11 (8 – 13) [n = 118] | 0.17 |
| Creatinine (μmol/L) | 137 (101 – 195) [n = 170] | 126 (93 – 173) [n = 150] | 0.22 |
| Total bilirubin (umol/L) | 17.0 (10.1 – 31.8) [n = 140] | 12.1 (8.0 – 20.0) [n = 126] | 0.0007 |
| Medications | | | |
| Vasopressor use | 152/172 (88.4%) | 117/153 (76.5%) | 0.005 |
| Vasopressor dose (μg/kg/min) | 0.48 (0.14 – 1.30) [n = 167] | 0.27 (0.01 – 0.84) [n = 144] | 0.003 |
| Norepinephrine use | 140/172 (81.4%) | 106/153 (69.3%) | 0.011 |
| Norepinephrine dose (μg/kg/min) ^g | 0.58 (0.22 – 1.49) [n = 136] | 0.40 (0.18 – 1.04) [n = 99] | 0.14 |
| Epinephrine use | 47/172 (27.3%) | 34/153 (22.2%) | 0.29 |
| Epinephrine dose (μg/kg/min) ^g | 0.30 (0.20 – 0.72) [n = 45] | 0.20 (0.10 – 0.60) [n = 29] | 0.27 |
| Dobutamine use | 120/172 (69.8%) | 82/153 (53.6%) | 0.003 |
| Dobutamine dose (μg/kg/min) ^g | 6.00 (4.83 – 10.00) [n = 117] | 8.00 (4.59 – 11.00) [n = 76] | 0.46 |
| Epinephrine during CPR (%) | | 75/106 (70.8%) | |
| Coronarography after stabilization of patients (%) | | 75/106 (70.8%) | |

Values are mean ± SD or median (Q1 – Q3) for continuous variables, n (%) for categorical variables.

*p-value from t-test or Wilcoxon test for continuous variables, Chi-square test or Fisher's exact test for categorical variables.

Abbreviations: CA, cardiac arrest; ECMO, extracorporeal membrane oxygenation; LVEF, left ventricular ejection fraction. SI units conversion factor: to convert lactate to mg/dL, divide by 0.111.

^aCalculated as weight in kilograms divided by height in meters squared.

^bDetermined by the clinician in charge of the patient and based on chart review.

^cMay have 1 or more cardiogenic shock etiologies.

^dNormal range is 7.35–7.45.

^eA normal level is less than 2 mmol/L.

165 1 min, and the median duration of low-flow was 17 (9–33) minutes. A
166 shockable rhythm was present in 51.8% of patients.

167 The etiology of CS was more frequently characterized as acute
168 coronary syndrome (ACS) in patients who experienced CA than in
169 patients who did not (42.1% vs. 30.9%, $p = 0.043$). CA patients
170 had a lower pH ($p = 0.0003$) and higher lactate ($p = 0.0004$) and total

171 bilirubin ($p = 0.0007$) levels. In contrast, at baseline, CA patients
172 were less often treated with dobutamine ($p = 0.004$) or nore-
173 pinephrine ($p = 0.016$) than were patients without CA, but the fre-
174 quency of epinephrine treatment did not differ among CA patients
175 and those without a CA history. The SOFA score, left ventricular
176 ejection fraction, and creatinine level at baseline were not signifi-

Table 2 – Cardiac arrest characteristics.

| | CA (n = 159) |
|--|---------------------|
| In-hospital CA (%) | 102/137 (74.5%) |
| Out-of-hospital CA (%) | 35/137 (25.5%) |
| Witnessed CA | 130/137 (94.9%) |
| Emergency department CA (%) | 12/137 (8.8%) |
| Catheter laboratory CA (%) | 22/137 (16.1%) |
| Operating room or intensive care unit CA (%) | 68/137 (49.6%) |
| ECMO implantation during CPR (%) | 52/137 (38.0%) |
| Shockable rhythm (%) | 71/137 (51.8%) |
| No-flow duration, min | 1 (0–1) [n = 137] |
| Low-flow duration, min | 17 (9–33) [n = 137] |
| Epinephrine during CPR (%) | 109/137 (79.6%) |
| Coronary angiography after patient stabilization (%) | 119/137 (86.9%) |

Abbreviations: CA, cardiac arrest; ECMO, extracorporeal membrane oxygenation. SI units conversion factor: to convert lactate to mg/dL, divide by 0.111.

^aCalculated as weight in kilograms divided by height in meters squared.

^bDetermined by the clinician in charge of the patient and based on chart review.

^cMay have 1 or more CS etiologies.

^dNormal range is 7.35 to 7.45.

^eA normal level is less than 2 mmol/L.

^fMortality prediction score based on the degree of dysfunction in 6 organ systems. Scores range from 0 to 24. The score was determined by the clinicians in charge of the patients during the trial.

^gOnly considered in patients with available data.

177 cantly different across groups ($p > 0.1$). Importantly, all survivors
178 patients who experienced a cardiac arrest were in Cerebral Perform-
179 ance Scale 1–2 (no or moderate cerebral disability) one month
180 after inclusion.

181 **Potential beneficial effects of moderate hypothermia**

182 Effect of moderate hypothermia (vs. normothermia) according to CA
183 status is presented in Fig. 1 and Table 3. MH was associated with a
184 significant reduction in mortality at 7 days (RD –12.4%, CI 95%

185 [–21.4 to –3.3%], $p = 0.008$), 30 days (RD –13.3%, CI 95%
186 [–16.3 to –0.3%], $p = 0.031$), 60 days (RD –14.8%, CI 95%
187 [–27.6 to –2.0%], $p = 0.024$), and 180 days (RD –15.0%, CI 95%
188 [–27.6 to –2.3%], $p = 0.020$) in the CA group only. The interaction
189 between CA status and MH benefit increased over time and became
190 significant at 180 days (p for interaction = 0.031).

191 Similarly, MH was associated with a significant reduction in the
192 composite endpoint of death, cardiac transplant, escalation to LVAD
193 or stroke at days 30, 60 and 180 ($p < 0.025$ for all) in the CA group

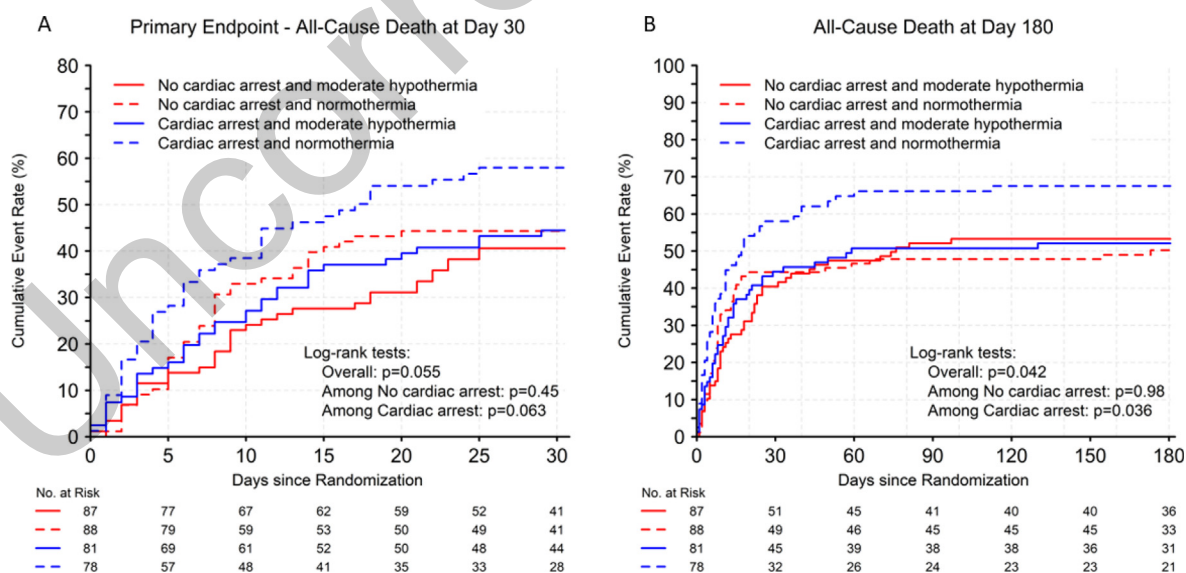


Fig. 1 – Kaplan-Meier curves for all-cause mortality at days 30 (A) and 180 (B) according to CA status and study group. All-cause mortality according to cardiac arrest (CA) status and study group illustrated using Kaplan-Meier curves on day 30 (A) and day 180 (B). Differences between survival curves were analyzed using the log-rank test. Moderate hypothermia (MH) was associated with a trend toward a reduction in mortality at 30 days (log-rank test $p = 0.063$), which became significant at 180 days (log-rank test $p = 0.036$) in only the CA group (no-CA group: log-rank test $p = 0.45$ on day 30 and $p = 0.98$ on day 180).

Table 3 – Effect of moderate hypothermia (vs. normothermia) according to CA status on binary endpoints according to risk differences.

| | Moderate hypothermia (n = 168) | Normothermia (n = 166) | Unadjusted | | |
|---|--------------------------------|------------------------|-----------------------|---------|---------------------|
| | N events/N (%) | | RD (CI 95%) | p-value | Interaction p-value |
| Primary endpoint of All-cause mortality at 30 days | | | | | |
| Overall | 71/168 (42.3%) | 84/166 (50.6%) | –8.3 (–16.3 to –0.3) | 0.041 | |
| No cardiac arrest | 35/87 (40.2%) | 39/88 (44.3%) | –4.0 (–16.7 to 8.8) | 0.54 | 0.34 |
| Cardiac arrest | 36/81 (44.4%) | 45/78 (57.7%) | –13.3 (–25.4 to –1.2) | 0.031 | |
| Secondary endpoints | | | | | |
| All-cause mortality at 2 days | | | | | |
| Overall | 10/168 (6.0%) | 11/166 (6.6%) | –0.7 (–5.3 to 3.9) | 0.77 | |
| No cardiac arrest | 4/87 (4.6%) | 2/88 (2.3%) | 2.3 (–2.5 to 7.2) | 0.35 | 0.23 |
| Cardiac arrest | 6/81 (7.4%) | 9/78 (11.5%) | –4.1 (–12.5 to 4.2) | 0.33 | |
| All-cause mortality at 7 days | | | | | |
| Overall | 29/168 (17.3%) | 46/166 (27.7%) | –10.4 (–16.6 to –4.3) | 0.0009 | 0.72 |
| No cardiac arrest | 12/87 (13.8%) | 20/88 (22.7%) | –8.9 (–21.5 to 3.6) | 0.16 | |
| Cardiac arrest | 17/81 (21.0%) | 26/78 (33.3%) | –12.4 (–21.4 to –3.3) | 0.008 | |
| All-cause mortality at 60 days | | | | | |
| Overall | 82/168 (48.8%) | 91/166 (54.8%) | –6.0 (–16.7 to 4.6) | 0.27 | |
| No cardiac arrest | 41/87 (47.1%) | 40/88 (45.5%) | 1.7 (–11.9 to 15.4) | 0.80 | 0.068 |
| Cardiac arrest | 41/81 (50.6%) | 51/78 (65.4%) | –14.8 (–27.6 to –2.0) | 0.024 | |
| All-cause mortality at 180 days | | | | | |
| Overall | 88/168 (52.4%) | 96/166 (57.8%) | –5.5 (–17.5 to 6.5) | 0.37 | |
| No cardiac arrest | 46/87 (52.9%) | 44/88 (50.0%) | 3.0 (–12.0 to 17.9) | 0.70 | 0.031 |
| Cardiac arrest | 42/81 (51.9%) | 52/78 (66.7%) | –15.0 (–27.6 to –2.3) | 0.020 | |
| Composite endpoint at day 30 | | | | | |
| Overall | 92/168 (54.8%) | 112/166 (67.5%) | –12.7 (–22.3 to –3.2) | 0.009 | |
| No cardiac arrest | 50/87 (57.5%) | 58/88 (65.9%) | –8.4 (–19.1 to 2.3) | 0.12 | 0.23 |
| Cardiac arrest | 42/81 (51.9%) | 54/78 (69.2%) | –17.5 (–30.5 to –4.4) | 0.009 | |
| Composite endpoint at day 60 | | | | | |
| Overall | 102/168 (60.7%) | 117/166 (70.5%) | –9.8 (–20.9 to 1.3) | 0.083 | |
| No cardiac arrest | 55/87 (63.2%) | 60/88 (68.2%) | –4.8 (–17.2 to 7.5) | 0.44 | 0.12 |
| Cardiac arrest | 47/81 (58.0%) | 57/78 (73.1%) | –15.3 (–28.2 to –2.4) | 0.020 | |
| Composite endpoint at day 180 | | | | | |
| Overall | 106/168 (63.1%) | 121/166 (72.9%) | –9.8 (–21.9 to 2.3) | 0.11 | |
| No cardiac arrest | 58/87 (66.7%) | 63/88 (71.6%) | –5.0 (–20.4 to 10.5) | 0.53 | 0.20 |
| Cardiac arrest | 48/81 (59.3%) | 58/78 (74.4%) | –15.1 (–28.0 to –2.3) | 0.021 | |

(continued on next page)

Table 3 (continued)

| | Moderate hypothermia (n = 168) | Normothermia (n = 166) | Unadjusted | | |
|--|--------------------------------|------------------------|-----------------------|---------|---------------------|
| | N events/N (%) | | RD (CI 95%) | p-value | Interaction p-value |
| Renal replacement therapy during the study | | | | | |
| Overall | 61/165 (37.0%) | 77/164 (47.0%) | -9.4 (-20.9 to 2.1) | 0.11 | |
| No cardiac arrest | 34/86 (39.5%) | 41/87 (47.1%) | -7.8 (-28.4 to 12.9) | 0.46 | 0.86 |
| Cardiac arrest | 27/79 (34.2%) | 36/77 (46.8%) | -11.0 (-34.0 to 12.0) | 0.35 | |

Effect of moderate hypothermia is reported (reference = normothermia).

The RDs (unadjusted or adjusted) are expressed as percentages and were calculated using a binomial generalized estimating equation (GEE) model with identity link that accounted for intracenter correlation.

194 only, although the interaction did not reach statistical significance (p
195 for interaction > 0.10).

196 **CA was associated with a trend toward increased 30-day** 197 **mortality**

198 Results on the primary and secondary outcomes according to risk
199 difference models are presented in Table 4. Overall, 81/159 patients
200 (50.9%) in the CA group had died compared to 74/175 patients
201 (42.3%) in the no-CA group at 30 days. CA was associated with a
202 trend toward increased 30-day mortality (adjusted risk difference
203 (RD), 8.1%, CI 95% [-0.8 to 17.1%], $p = 0.074$; adjusted OR 1.31,
204 CI 95% [0.82 to 2.11], $p = 0.26$) illustrated by the Kaplan-Meier

205 curves (Log-rank test $p = 0.082$) (Fig. 2). The results were consistent
206 across all subgroups with no significant interaction, except for lac-
207 tate > 4.8 which was associated with an increased 30-day mortality
208 (RD 19.7%, CI 95% [6.9 to 32.5%], p for interaction = 0.002) (figure
209 online supplement).

210 Discussion

211 The main findings of our study are as follows: 1) in VA-ECMO-treated
212 CS patients managed according to current protocols, almost half of
213 the patients experienced CA either before or during ECMO implanta-

Table 4 – Effect of cardiac arrest (vs. no cardiac arrest) on binary endpoints according to risk differences.

| | No cardiac arrest (n = 175) | Cardiac arrest (n = 159) | Unadjusted | | Adjusted for study group | |
|--|-----------------------------|--------------------------|---------------------|---------|--------------------------|---------|
| | N events/N (%) | | RD (CI 95%) | p-value | RD (CI 95%) | p-value |
| Primary endpoint | | | | | | |
| All-cause mortality at 30 days | 74/175 (42.3%) | 81/159 (50.9%) | 8.1 (-1.6 to 17.8) | 0.10 | 8.1 (-0.8 to 17.1) | 0.074 |
| Secondary endpoints | | | | | | |
| <u>All-cause mortality</u> | | | | | | |
| All-cause mortality at 2 days | 6/175 (3.4%) | 15/159 (9.4%) | 6.0 (1.5 to 10.5) | 0.009 | 6.1 (1.7 to 10.5) | 0.006 |
| All-cause mortality at 7 days | 32/175 (18.3%) | 43/159 (27.0%) | 8.7 (1.1 to 16.3) | 0.026 | 8.6 (1.2 to 16.0) | 0.023 |
| All-cause mortality at 60 days | 81/175 (46.3%) | 92/159 (57.9%) | 10.8 (-0.5 to 22.1) | 0.062 | 10.9 (0.1 to 21.8) | 0.048 |
| All-cause mortality at 180 days | 90/175 (51.4%) | 94/159 (59.1%) | 6.8 (-3.7 to 17.2) | 0.20 | 7.0 (-3.0 to 16.9) | 0.17 |
| <u>Composite endpoint</u> | | | | | | |
| Composite endpoint at day 30 | 108/175 (61.7%) | 96/159 (60.4%) | -0.6 (-10.1 to 8.9) | 0.90 | -0.3 (-9.1 to 8.6) | 0.95 |
| Composite endpoint at day 60 | 115/175 (65.7%) | 104/159 (65.4%) | 1.0 (-9.0 to 10.9) | 0.85 | 1.3 (-8.2 to 10.8) | 0.79 |
| Composite endpoint at day 180 | 121/175 (69.1%) | 106/159 (66.7%) | -2.0 (-11.9 to 7.8) | 0.68 | -1.6 (-10.9 to 7.8) | 0.74 |
| Renal replacement therapy during the study | 75/173 (43.4%) | 63/156 (40.4%) | -4.9 (-15.4 to 5.5) | 0.36 | -4.9 (-14.9 to 5.1) | 0.34 |

Effect of cardiac arrest is reported (reference = no cardiac arrest).

The RDs (unadjusted or adjusted) are expressed as percentages and were calculated using a binomial generalized estimating equation (GEE) model with identity link that accounted for intracenter correlation.

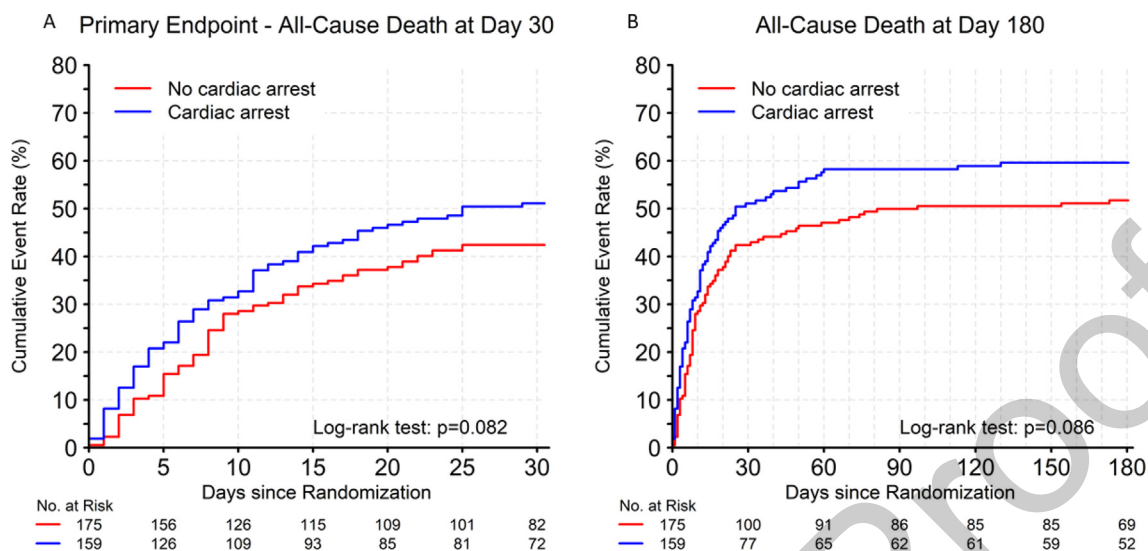


Fig. 2 – Kaplan-Meier curves for all-cause mortality at days 30 (A) and 180 (B) Kaplan-Meier curves for all-cause mortality according to cardiac arrest status at days 30 (A) and 180 (B).

tion and 2) the influence of MH on both survival and overall outcomes was notably pronounced in patients with a history of CA, demonstrating significant benefits in terms of the 180-day mortality rate indicating that additional studies focusing on cardiac arrest patients could be beneficial to corroborate this finding.

CA incidence and VA-ECMO

In the present study, one hundred and fifty-nine (48%) patients experienced CA before VA-ECMO implementation. Up to 40% of patients with severe CS and half of those with AMI-CS have a history of CA.^{6,11} In our study of VA-ECMO treated CS patients with various etiologies, we observed a higher incidence of ACS and a lower incidence of unlabeled dilated cardiomyopathy as etiology of CS in patients experiencing CA. The CULPRIT-SHOCK trial revealed a slightly higher incidence of VA-ECMO implantation in the CA group than in the control group.³

Prognostic value of pre-ECMO CA

The occurrence of CA prior to VA-ECMO was associated with a 25% reduction in survival probability among nearly 4000 CS patients recorded in the ELSO registry from 2003 to 2013.¹¹ In this post-hoc analysis, CA was associated with a trend towards increased mortality at day 30 in all subgroups, except for patients with elevated baseline lactate levels. In this specific subgroup, CA patients exhibited a 20% statistically significant increased risk of 30-day mortality, with a notable interaction between CA and lactate levels. Patients with persistently high blood lactate levels constitute a particularly high-risk population.¹³

Effect of MH in patients with CA

In comatose patients not supported with VA-ECMO after out-of-hospital CA (OHCA), targeted hypothermia did not lead to a lower incidence of death at 6 months than targeted normothermia.^{14,15} Our results suggest that an overall reduction in 30-day mortality is associated with MH therapy, which was primarily driven by its effect in patients with CA. Similarly, the benefits of MH on the composite outcome of death, heart transplantation, escalation to LVAD implantation, or stroke were evident in patients who had experienced CA.

The TTM 2 trial and a recent meta-analysis¹⁶ found that in patients with coma after out-of-hospital cardiac arrest, targeted hypothermia did not lead to a lower incidence of death by 6 months than targeted normothermia. The distinct effect of MH in the HYPO-ECMO trial compared to studies focusing on OHCA may be attributed to various factors, the most notable of which are the potential of MH to mitigate the deleterious effects of ischemia-reperfusion.^{17–19} Other potential reasons for the discrepant findings include the following: i) The HYPO-ECMO trial excluded moribund patients and those with a priori suspicion of poor neurological prognosis, resulting in a population with potentially good neurological prognosis as assessed by CPC one month after inclusion. ii) ACS was the predominant etiology of CS in patients in the CA group, and there was a trend toward a reduction in mortality with the use of MH in CS patients with CA complicating AMI although this point was recently challenged⁷; we cannot exclude the possibility that the results are partly associated with the potential benefits of hypothermia in AMI.^{20,3} iii) MH in OHCA is linked to an elevated risk of malignant arrhythmia, a risk that might have been prevented or stabilized by VA-ECMO in our trial.¹⁵ iv) The number of witnessed arrests was the same in the HYPO-ECMO trial and the TTM2 trial; the main difference was that in the present study, witnesses were highly specialized in resuscitation in the in-hospital setting. v) The time taken to achieve hypothermia was longer in the TTM2 trial¹⁵ than in the HYPO-ECMO trial (8 versus 2 h; this difference is important, as animal experiments have consistently demonstrated improved outcomes when cooling is initiated promptly after injury.⁴

Implications for clinical practice

The findings from the current trial are likely to change clinical practices. First, our findings indicate that CA in CS in patients rescued by VA-ECMO was not associated with a catastrophic prognosis. While the current cohort includes a portion of patients who underwent ECPR for intra-hospital cardiac arrest, the majority of patients were not in cardiac arrest during cannulation. Second, our results suggest that MH reduces all-cause mortality and a composite endpoint encompassing death, heart transplant, escalation to LVAD implantation, and stroke in patients with preceding CA. Therefore,

given that the implementation of hypothermia was feasible, safe and not associated with an increased risk of severe bleeding or infection, there may be a role for therapeutic hypothermia in this population.

289 **Limitations**

290 This study has several limitations. Our study was a post-hoc analysis, that bears significant limitations, including the risk of selection bias, an increased risk of type I errors, a lack of control for confounding variables, and the absence of external validation. Nevertheless, despite these limitations, the current findings are biologically plausible. The HYPO-ECMO trial was not designed to assess differences in 30-day mortality according to CA. CA was not prespecified as a randomization stratum for intervention allocation; however, due to the high prevalence of CA (nearly 50%), the proportion of patients treated with MH or normothermia was well balanced. The information on prognostic modifiers, such as the initial location of CA, shockable rhythm, and no-flow or low-flow durations, was not available for the entire population. Nevertheless, complete information were obtained in 86% of cardiac arrest patients. The present results should be interpreted according to the HYPO-ECMO exclusion criteria since 74% of the arrests occurred in the hospital, and patients with prolonged CA or out-of-hospital refractory arrest, were excluded from the study. The last patient was enrolled in late 2019. However, there have been no significant modifications to the recommendations for either cardiac arrest or ECMO management since then. Finally, neuroprognostication in CA patients was not protocolized, but it was recommended that treatment of these patients adhere to the latest guidelines. Importantly, all survivors who experienced CA were classified as CPC 1–2 (no or moderate cerebral disability) one month after inclusion.

315 **Conclusions**

316 This post hoc analysis suggests that in patients with cardiogenic shock and supported by VA-ECMO, moderate hypothermia appears to be associated with a potential reduction in mortality and the composite endpoint in the cardiac arrest group. Our results carry two primary implications for clinical practice and knowledge dissemination. Firstly, VA-ECMO may be considered in cardiogenic shock complicated by cardiac arrest. Secondly, in this distinct population, the favorable effects of hypothermia are likely. Therefore, additional research is needed to validate these findings and delve into the potential mechanisms behind these associations.

326 **Disclosures**

327 Pr. Levy reported receiving personal fees from Abiomed, Gettlinge, 328 Baxter, Novartis, Sanofi, Amomed, and Orion, outside the submitted 329 work.

330 Pr. Girerd reported receiving personal fees from Novartis, Bayer, 331 AstraZeneca, Lilly, Boehringer, and Vifor, outside the submitted 332 work.

333 Dr. Duarte reported no conflicts of interest regarding this work.

334 Dr. Marie-Lauren Antoine reported no conflicts of interest regarding 335 this work.

336 Mrs. Victoire Huyhn reported no conflicts of interest regarding this 337 work.

338 Dr. Monzo reported receiving personal fees from AstraZeneca 339 and Vifor, outside the submitted work.

Dr. Ouattara reported receiving personal fees from Abiomed, 340 Nordic Pharma, LFB, VifOR Pharma, Orion Pharma, ISEP, Masimo, 341 and Medtronic. 342

Dr. Delmas reported receiving personal fees from Abiomed and 343 Abbott Laboratories. 344

Pr. Brodie reports receiving research support from and consults 345 for LivaNova. He has been on the medical advisory boards for 346 Abiomed, Xenios, Medtronic, Inspira and Cellenkos. He is the 347 President-elect of the Extracorporeal Life Support Organization 348 (ELSO) and the Chair of the Executive Committee of the International 349 ECMO Network (ECMONet), and he writes for UpToDate. 350

Pr. Combes reported receiving personal fees from Gettlinge, Baxter, 351 and Fresenius-Xenios, outside the submitted work. 352

Pr. Kimmoun reported no conflicts of interest regarding this work. 353

Dr. Baudry reported receiving personal fees from Abbott, Astra- 354 Zeneca, and Boehringer, outside the submitted work. 355

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363 **Bruno Levy:** Writing – review & editing, Writing – original draft, Val- 364 idation, Project administration, Investigation, Funding acquisition, 365 Conceptualization. **Nicolas Girerd:** Writing – review & editing, Writing 366 – original draft, Validation, Software, Methodology, Formal analysis, 367 Data curation. **Kevin Duarte:** Validation, Software, 368 Methodology, Formal analysis, Data curation. **Marie-Lauren** 369 **Antoine:** Writing – original draft, Validation, Methodology, Conceptual- 370 ization. **Luca Monzo:** Writing – original draft, Visualization, Formal 371 analysis. **Ouattara Alexandre:** Writing – original draft, Supervision, 372 Investigation. **Delmas Clément:** Writing – original draft, Validation, 373 Methodology, Investigation. **Daniel Brodie:** Writing – original draft, 374 Investigation, Conceptualization. **Alain Combes:** Writing – original 375 draft, Methodology, Investigation, Funding acquisition, Conceptual- 376 ization. **Antoine Kimmoun:** Writing – original draft, Validation, 377 Methodology, Investigation. **Guillaume Baudry:** Writing – original 378 draft, Validation, Software, Methodology, Formal analysis. 379

Declaration of competing interest

380 The authors declare the following financial interests/personal 381 relationships which may be considered as potential competing inter- 382 ests: Pr. Levy reported receiving personal fees from Abiomed, Get- 383 tlinge, Baxter, Novartis, Sanofi, Amomed, and Orion, outside the 384 submitted work. Pr. Girerd reported receiving personal fees from 385 Novartis, Bayer, AstraZeneca, Lilly, Boehringer, and Vifor, outside 386 the submitted work. Dr. Duarte reported no conflicts of interest 387 regarding this work. Dr. Marie-Lauren Antoine reported no conflicts 388 of interest regarding this work. Mrs. Victoire Huyhn reported no con- 389 flicts of interest regarding this work. Dr. Monzo reported receiving 390 personal fees from AstraZeneca and Vifor, outside the submitted 391 work. Dr. Ouattara reported receiving personal fees from Abiomed, 392 Nordic Pharma, LFB, VifOR Pharma, Orion Pharma, ISEP, Masimo, 393 and Medtronic. Dr. Delmas reported receiving personal fees from 394

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403 Pr. Kimmoun reported no conflicts of interest regarding this work. Dr.
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406 Appendix A. Supplementary material

407 Supplementary data to this article can be found online at <https://doi.org/10.1016/j.resuscitation.2024.110235>.

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