Supplemental Online Content

Levy B, Girerd N, Amour J, et al; HYPO-ECMO Trial Group and the International ECMO Network (ECMONet). Effect of moderate hypothermia vs normothermia on 30-day mortality in patients with cardiogenic shock receiving venoarterial extracorporeal membrane oxygenation: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2021.24776

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods. Investigators and committees and other information

List of study sites and principal investigators

N° center	Center	Adress	ZIP Code, City, Country	Name	Given name
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2	Hôpitaux Universitaires de Strasbourg. Nouvel Hôpital Civil	1, place de l'hôpital	67091, STRASBOURG, France	MEZIANI	Ferhat
3	Assistance Publique - Hôpitaux de Paris, Hôpitaux Universitaires Pitié Salpêtrière - Charles Foix	47-83 boulevard de l'hôpital	75013, PARIS, France	COMBES	Alain
4	CHU de Bordeaux Centre Médico-Chirurgical Magellan	Avenue de Magellan	33604 PESSAC, France	OUATTARA	Alexandre
5	Hospices Civils de Lyon Hôpital Cardiovasculaire et Pneumologique Louis Pradel	59, boulevard Pinel	69394 LYON, France	FELLAHI	Jean-Luc
6	CH Annecy Genevois, site Annecy	1 Avenue de l'Hôpital,	74370 EPAGNY METZ-TESSY, France	SIRODOT	Michel
7	CHU de Rouen, Hôpital Charles Nicolle	1 Rue De Germont	76100 ROUEN, France	BESNIER	Emmanuel
8	CHU d'Amiens-Picardie	1 Rond-Point du Pr Christian Cabrol	80054 AMIENS, France	DUPONT	Hervé
9	CHU de Nantes, Hôpital G&R Laënnec	Boulevard Professeur Jacques Monod	44800 SAINT-HERBLAIN, France	ROZEC	Bertrand
10	CHU de Rennes, Hôpital Pontchaillou	2 Rue Henri le Guilloux,	35000 RENNES, France	FLECHER	Erwan
11	CHU de Toulouse, Hôpital Rangueil	1 Avenue du Professeur Jean Poulhès	31400 TOULOUSE, France	DELMAS	Clément
12	CHRU de Montpellier , Hôpital Arnaud de Villeneuve	371, avenue Doyen Gaston Giraud	34295 MONTPELLIER, France	COLSON	Pascal
13	Assistance Publique - Hôpitaux de Paris, Hôpital Bichat Claude Bernard	46 Rue Henri Huchard,	75018 PARIS, France	TIMSIT	Jean-François
14	Assistance Publique - Hôpitaux, Hôpitaux Universitaires Pitié Salpêtrière - Charles Foix	47-83 boulevard de l'hôpital	75013, PARIS, France	BOUGLE	Adrien
15	CHU de Grenoble, Hôpital Michallon	Boulevard de la Chantourne,	38700 LA TRONCHE, France	GAIDE-CHEVRONNAY	Lucie
16	CHR de Besançon, Hôpital Jean Minjoz	3 boulevard Fleming	25030 BESANCON, France	CAPELLIER	Gilles

N° center	Center	Adress	ZIP Code, City, Country	Name	Given name
17	Hôpitaux Universitaires de Marseille, Groupe Hospitalier de la Timone	264 Rue Saint-Pierre,	13005 MARSEILLE, France	GUIDON	Catherine
18	Assistance Publique - Hôpitaux de Paris, Hôpital Européen Georges Pompidou	20 Rue Leblanc,	75015 PARIS, France	CHOLLEY	Bernard
19	Hôpitaux Universitaires de Strasbourg. Nouvel Hôpital Civil	1, place de l'hôpital	67091 STRASBOURG, France	MERTES	Paul Michel

Study Monitoring and Independent Data Safety Monitoring (DSMB)

The trial used a Web-based electronic CRF (CleanWeb®, Telemedecine Technology, France and Ennov Clinical 7.5®, Ennov, France).

Data monitoring was performed by the sponsors (CHRU de Nancy, Department of Research and Innovation and each participating national centers).

Furthermore, CHRU de Nancy had full access to all patient charts and checked all data recorded within the electronic CRF.

Data management and statistical analyses were performed by the Centre d'Investigation Clinique plurithématique de Nancy.

An independent data safety monitoring board (DSMB) was set up prior to recruitment of the first patient. The DSMB met after the planned interim analysis.

It was composed of two physicians (Pr Alain CARIOU, AP-HP, Paris and Pr Michel SLAMA, AP-HP, Paris) and one methodologist – biostatistician (Dr Etienne GAYAT, AP-HP, Paris).

They reviewed the interim analyses (blinded to allocation of groups) and decided on the termination of the study.

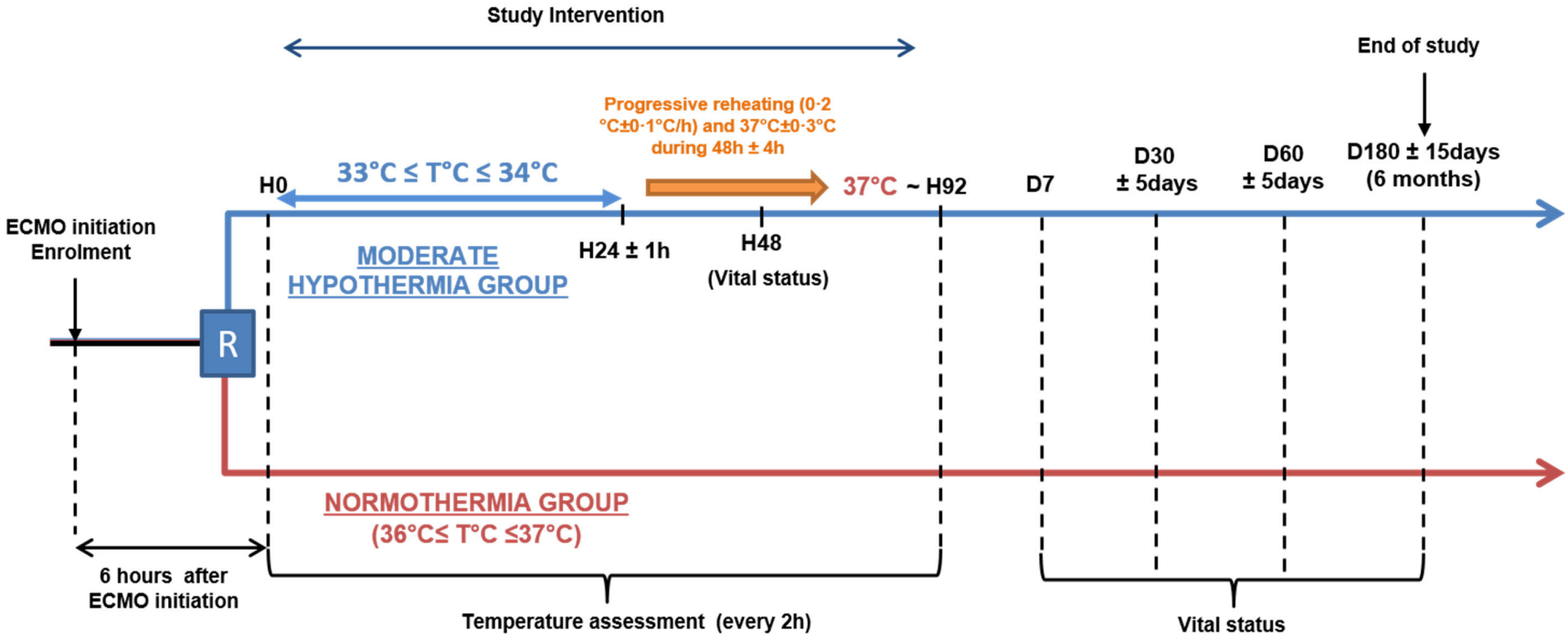
Study protocol amendments

There were 7 amendments to the study protocol (see Appendix Protocol). They were approved by investigators, the study methodologist – statistician, the sponsor (CHRU de Nancy), the Comité de Protection des Personnes (CPP, French institutional review board) and the Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM, French Health Authorities).

Randomization

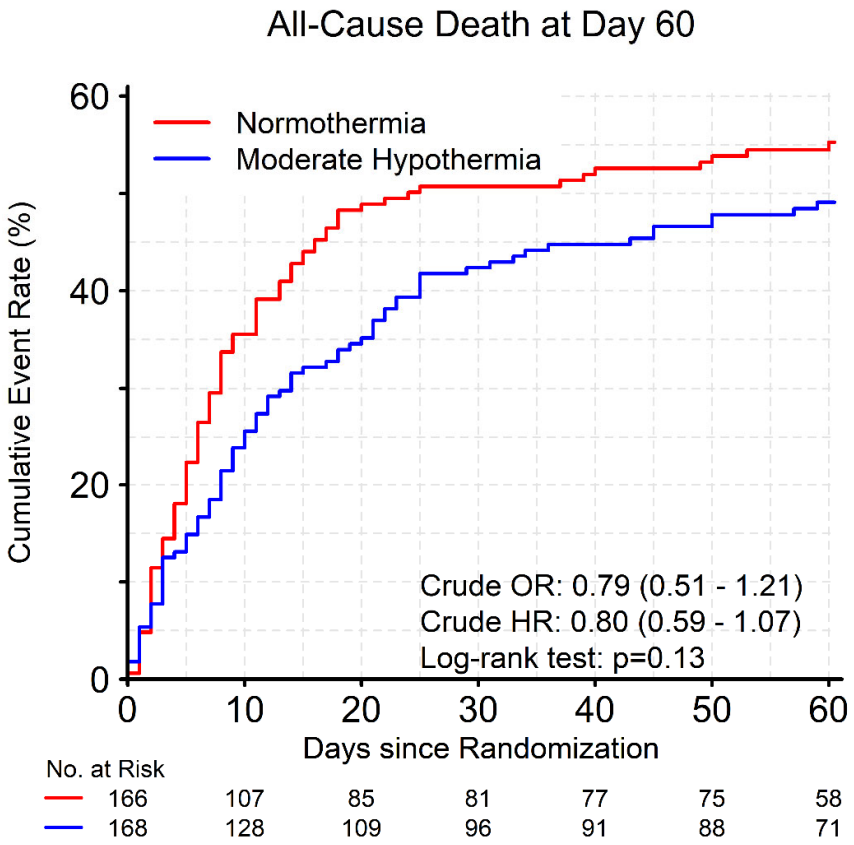
Randomization was performed through a secured server using a predefined randomization list stratified on the centers and using blocks (alternative block of 2 and 4). The randomization list was created by the data-manager in charge of the trial and verified by another analysis-scientist. These professionals had no interactions with the investigators and investigators were not aware of block sizes and stratification as these details were not mentioned (on purpose) in the study protocol.

eFigure 1. HYPO-ECMO study: treatment protocol and follow up

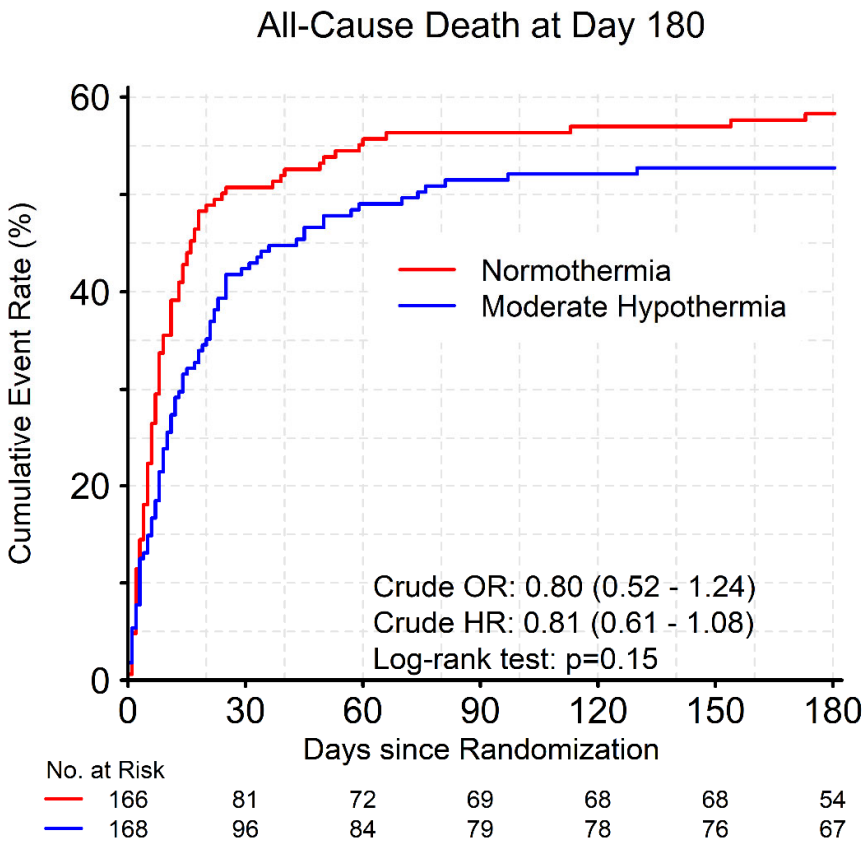


Abbreviation: H stands for hour and D for days.

eFigure 2. Kaplan Meier survival estimates during the 60 of VA-ECMO patients treated with moderate hypothermia or normothermia

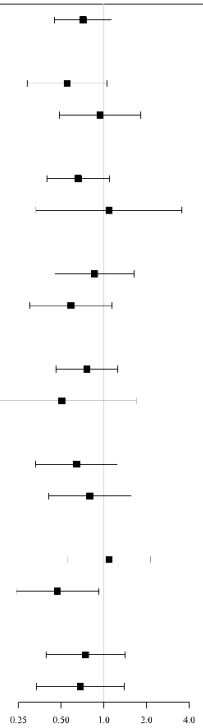


eFigure 3. Kaplan Meier survival estimates during the 180 days of VA-ECMO patients treated with moderate hypothermia or normothermia



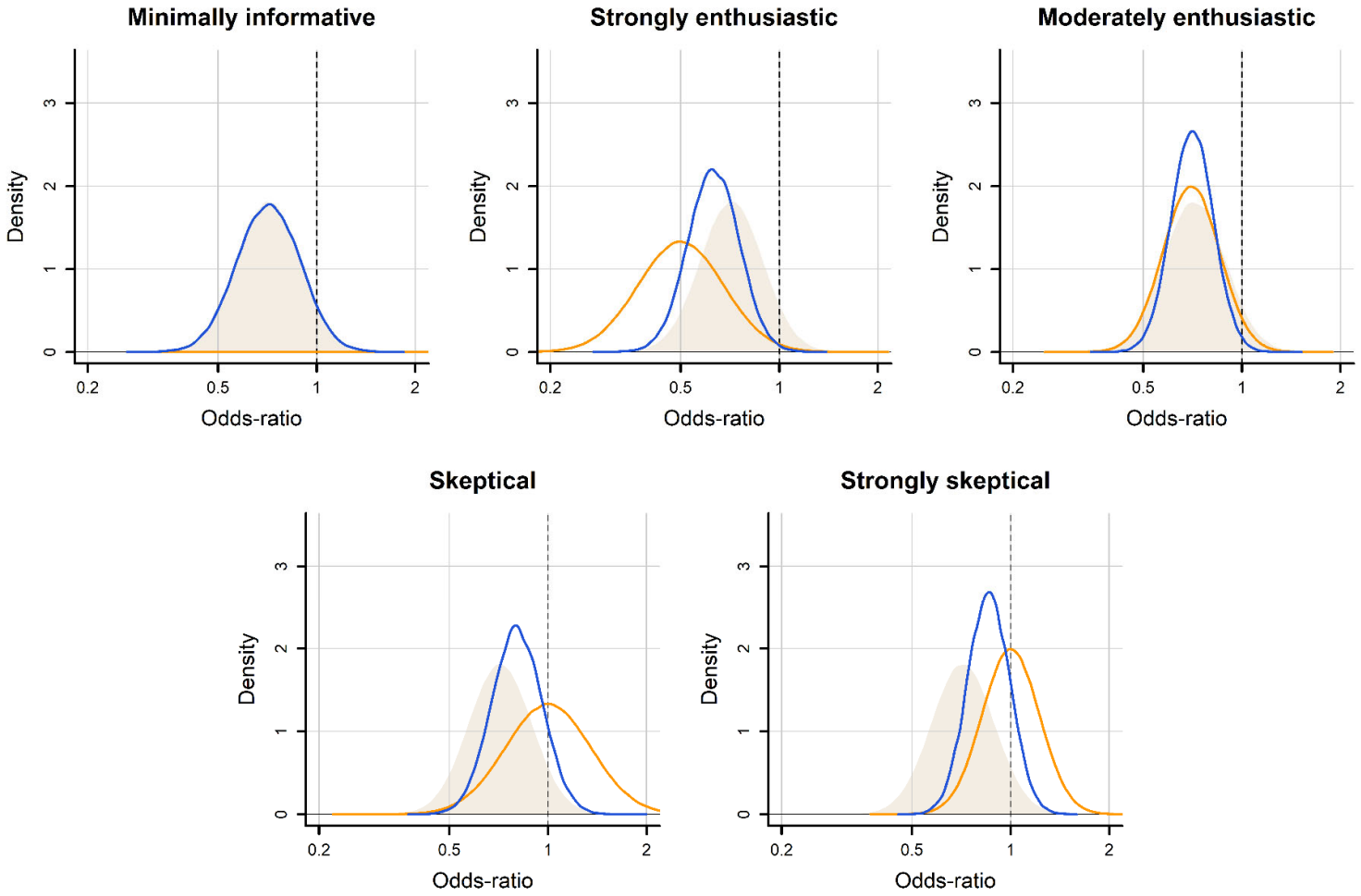
eFigure 4. Primary endpoint - subgroup analysis and interaction terms (forest plot)

Subgroup	Moderate Hypothermia	Normothermia	Adjusted Odds Ratio (CI 95%)	P Value for Interaction	Risk Difference (CI 95%)
Overall effect	71/168	84/166	0.71 (0.45 - 1.13)		-8.3 (-16.3 to -0.3)
Age				0.26	
≤60 years	32/94	38/82	0.55 (0.29 - 1.06)		-12.7 (-23.4 to -2.0)
>60 years	39/74	46/84	0.94 (0.48 - 1.82)		-0.9 (-16.7 to 14.9)
Previous MI				0.45	
No	57/139	72/141	0.66 (0.40 - 1.10)		-10.4 (-18.2 to -2.7)
Yes	14/29	12/25	1.09 (0.33 - 3.56)		2.5 (-27.9 to 32.9)
Cardiac arrest during hospitalization				0.42	
No	35/87	39/88	0.86 (0.45 - 1.64)		-4.0 (-16.7 to 8.8)
Yes	36/81	45/78	0.59 (0.30 - 1.14)		-13.3 (-25.4 to -1.2)
Post cardiac surgery				0.55	
No	62/145	70/139	0.76 (0.46 - 1.25)		-7.6 (-15.9 to 0.6)
Yes	9/23	14/27	0.51 (0.15 - 1.69)		-12.1 (-30.2 to 6.1)
Vasopresssor dose				0.66	
<0.4 µg/kg/min	33/88	38/81	0.64 (0.33 - 1.24)		-9.7 (-28.4 to 9.0)
≥0.4 µg/kg/min	38/80	46/85	0.80 (0.41 - 1.56)		-6.2 (-23.8 to 11.4)
Lactate				0.09	
≤4.8 mmol/L	34/85	32/82	1.09 (0.56 - 2.13)		0.4 (-12.6 to 13.3)
>4.8 mmol/L	37/83	52/84	0.47 (0.24 - 0.92)		-16.7 (-33.2 to -0.3)
SOFA score				0.86	
≤10	34/91	41/94	0.74 (0.39 - 1.41)		-5.4 (-20.2 to 9.5)
>10	37/77	43/72	0.68 (0.33 - 1.39)		-12.9 (-27.9 to 2.2)



The primary endpoint was mortality at 30 days. Each subgroup variable was evaluated at baseline. For each continuous variable (age, vasopressor dose, lactate and SOFA score), subgroups were defined by dichotomizing the variable according to the median observed in the study population. Adjusted odds-ratios were calculated using logistic model after Multiple Imputation by Chained Equations (see Supplementary Appendix for more details). An interaction test was performed for each binary endpoint using the Wald test for the cross-product of intervention group and binary endpoint in adjusted logistic model. Risk difference with confidence interval adjusted for center was calculated using binomial GEE model with identity link. CI denotes confidence interval.

eFigure 5. Bayesian analysis: posterior probability distributions for OR for the benefit of moderate hypothermia on mortality at day 30



OR: odds-ratio. Orange lines indicate the reference prior. The shaded areas indicate the effect (OR) of moderate hypothermia observed in the

trial. Blue lines indicate posterior probability distribution. The vertical dashed line indicates where OR = 1 to provide a visual reference point. Reference prior is combined with the effect of moderate hypothermia observed in the trial to compute the posterior probability for the effect of moderate hypothermia. Variation in the posterior distribution arises from variation in the prior. This approach assess the influence of prior enthusiasm or skepticism for moderate hypothermia on the interpretation of the trial's results.

eTable. Characteristics of reference prior probability distributions representing prior beliefs about mortality benefit from moderate hypothermia and probability of treatment effects estimated by Bayesian analysis according to varying prior beliefs

Prior belief	Assumed median OR	Assumed SD of logarithm OR	Posterior median OR (95% credible interval)	Posterior probability that true OR is < specified threshold, %					
				OR < 1	OR < 0.9	OR < 0.8	OR < 0.7	OR < 0.6	OR < 0.5
Minimally informative	1	10	0.71 (0.46 - 1.09)	94	85	70	47	22	6
Strongly enthusiastic	0.50	0.30	0.63 (0.44 - 0.89)	100	98	91	72	40	10
Moderately enthusiastic	0.70	0.20	0.71 (0.53 - 0.94)	99	95	80	48	14	1
Skeptical	1	0.30	0.80 (0.57 - 1.14)	89	74	49	22	5	0
Strongly skeptical	1	0.20	0.86 (0.64 - 1.15)	85	63	32	9	1	0

Abbreviations: OR, odds-ratio; SD, standard deviation.