Supplementary Appendix

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

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Table of Contents

TRIAL PERSONNEL

CORRESPONDING AUTHOR

Niklas Nielsen, MD, PhD, DEAA, EDIC**,** Department of Anesthesiology and Intensive Care**,** Helsingborg Hospital**,** S Vallgatan 5, 251 87, Helsingborg, Sweden**,** niklas.nielsen@med.lu.se

STEERING GROUP

Niklas Nielsen, Lund University, Helsingborg Hospital, Department of Clinical Sciences Lund, Anesthesiology and Intensive care, Lund, Sweden (Chair and Chief Investigator); **Jan Bělohlávek**, 2nd Department of Medicine, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic (NI); **Clifton Callaway**, Department of Emergency Medicine, University of Pittsburgh, Pittsburgh, PA, USA (NI); **Alain Cariou**, Descaretes University of Paris and Cochin University Hospital, Paris, France (NI); **Tobias Cronberg**, Lund University, Skåne University Hospital Lund, Department of Clinical Sciences, Neurology, Lund, Sweden (Senior Investigator); **Josef Dankiewicz**, Lund University, Skåne University Hospital Lund, Department of Clinical Sciences, Cardiology, Lund, Sweden (Coordinating Investigator); **Glenn Eastwood**, The Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Australia; **David Erlinge**, Lund University, Skåne University Hospital Lund, Department of Clinical Sciences, Cardiology, Lund, Sweden; **Hans Friberg**, Lund University, Skåne University Hospital Malmö, Department of Clinical Sciences, Anesthesia & Intensive care, Lund, Sweden (Senior Investigator); **Jan Hovdenes**, Department of Anesthesiology and Intensive Care, Oslo University Hospital, Rikshospitalet, Oslo, Norway (NI); **Janus Christian Jakobsen**, Copenhagen Trial Unit, Capital Region, Copenhagen, Denmark; Department of Regional Health Research, The Faculty of Health sciences, University of Southern Denmark, Denmark (Trialist); **Michael Joannidis**, Division of Intensive and Emergency Medicine, Department of Internal Medicine, Medical University Innsbruck, Innsbruck, Austria (NI); **Hans Kirkegaard**, Research Center for Emergency Medicine, Department of Clinical Medicine, Aarhus University Hospital and Aarhus University, Aarhus N, Denmark (NI); **Helena Levin**, Lund University, Skåne University Hospital Lund, Department of Clinical Sciences,

Anesthesiology and Intensive care, Lund, Sweden (Clinical Trial Manager); **Gisela Lilja**, Lund University, Skåne University Hospital Lund, Department of Clinical Sciences, Neurology, Lund, Sweden (Follow-up Coordinator); **Matt P. G. Morgan**, Adult Critical Care, University Hospital of Wales, Cardiff, United Kingdom; **Alistair D. Nichol**, University College Dublin- Clinical Research Centre at St Vincent's University Hospital, Dublin, Ireland. **Per Nordberg**, Department of Medicine, Center for Resuscitation Science, Karolinska Institute, Solna, Sweden; **Mauro Oddo**, Neuroscience Critical Care Group, Adult Intensive Care Medicine Service, CHUV-Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland (NI); **Paolo Pelosi**, Anesthesiology and Critical Care, San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy (NI); **Christian Rylander**, Department of Anesthesiology and Intensive Care Medicine, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden (NI); **Manoj Saxena**, Division of Critical Care and Trauma, George Institute for Global Health. Bankstown-Lidcombe Hospital, South Western Sydney Local Health District, Sydney, Australia (NI); **Christian Storm**, Department of Nephrology and Medical Intensive Care, Charité - Universitätsmedizin Berlin, Germany (NI); **Fabio S. Taccone**, Department of Intensive Care, Erasme University Hospital, Université Libre de Bruxelles (ULB), Brussels, Belgium (NI); **Susann Ullén**, Clinical Studies Sweden – Forum South, Skåne University Hospital, Lund, Sweden (Chief Statistician); **Matt P. Wise**, Adult Critical Care, University Hospital of Wales, Cardiff, United Kingdom (NI); **Paul J. Young**, Medical Research Institute of New Zealand, Intensive Care Unit, Wellington Hospital, Wellington, New Zealand (NI).
NI- National Coordinating Investigator

INDEPENDENT DATA MONITORING AND SAFETY COMMITTEE

Kathy Rowan, Intensive Care National Audit & Research Centre, UK (Chair); **David Harrison**, Intensive Care National Audit & Research Centre, UK; **Paul Mouncey**, Intensive Care National Audit & Research Centre, UK; **Manu Shankar-Hari**, Guy's and St Thomas's NHS Foundation Trust, London, UK; **Duncan Young**, Nuffield Department of Clinical Neurosciences, University of Oxford, UK.

STATISTICIANS

Susann Ullén, Clinical Studies Sweden – Forum South, Skåne University Hospital, Lund, Sweden (Chief Statistician); **Theis Lange**, Department of Biostatistics, University of Copenhagen, Copenhagen, Denmark (Independent Statistician); **Karolina Palmér**, Department of Medical Statistics and Epidemiology, Region Skåne, Malmö, Sweden Independent statistician).

COORDINATING ORGANIZATIONS AND TRIAL MANAGEMENT

Region Skåne, Helsingborg Hospital, Helsingborg, Sweden (Sponsor)
Lund University, Lund, Sweden

Core management group: Niklas Nielsen (Chair and Chief Investigator), Josef Dankiewicz (Coordinating Investigator), Tobias Cronberg (Senior Investigator, Neurology), Hans Friberg (Senior Investigator, Intensive Care), Gisela Lilja (Follow-up Coordinator), Helena Levin (Clinical Trial Manager), Janus Christian Jakobsen (Trialist), Susann Ullén (Chief Statistician).

Trial financial management: Helsingborg Hospital: Ulla-Britt Karlsson; Lund University: Simon Heissler.

Australia: The George Institute for Global Health, Sydney (Local Sponsor):
Manoj Saxena, Frances Bass, Naomi Hammond, John Myburgh, Colman Taylor.

France: Clinical Research Unit, Paris Descartes Necker Cochin, Paris (Local Representative): Alain Cariou, Adele Bellino.

TRIAL COORDINATORS AND MONITORS

Australia: The George Institute for Global Health, Sydney: Marwa Abel-all, Ben Finfer, Carolyn Koch, Yang Li, Anne O'Connor, Julia Pilowsky, Tina Schneider, Anna Tippett; Monash University, Melbourne: Bridget Ady, Tessa Broadley, Amanda Brown, Liz Melgaard, Mimi Morgan, Vanessa Singh, Rebecca Symons. **Austria:** Medical University

Innsbruck, Innsbruck: Kathrin Becker. **Belgium:** NVS Consulting, Brussels: Nathalie Van Sante. **Czech Republic:** Aixial, Brno: Vendula Saleova, Silvie Zerzanova. **Denmark**: Lund University, Lund, Sweden: Helena Levin. **France:** Clinical Research Unit, Paris Descartes Necker Cochin, Paris: Samia Sefir-Kribel. **Germany:** Charité Universitätsmedizin, Berlin: Ute Lübeck. **Italy:** Mario Negri Institute for Pharmacological Research, Milan: Martina Carrara. **New Zealand:** Medical Research Institute of New Zealand (MRINZ), Wellington: Kathryn Fernando, Diane Mackle, Leanlove Navarra, Judith Riley. **Norway:** Oslo University Hospital, Oslo: Elin Westerheim; Haukeland University Hospital, Bergen: Marianne Flatebø. **Sweden:** Helsingborg Hospital, Helsingborg: Ameldina Ceric, Zana Haxhija, Lovisa Terling; Skåne University Hospital, Lund: Lena Bossmar, Liz Jergle, Helén Holm Månsson. **Switzerland:** Lausanne University Hospital (CHUV), Lausanne: Samia Abed Maillard, Andreja Vujicic Zagar; Cantonal Hospital St. Gallen, St. Gallen: Christina Jodlauk. **United Kingdom:** University Hospital of Wales, Cardiff: Helen Hill; Niche Science & Technology, Richmond: Jennifer Scrivens; The HRB Irish Critical Care- Clinical Trials Network (ICC-CTN), Dublin, Ireland: Kate Ainscough, Ciara Fahey.

SITES, PRINCIPAL INVESTIGATORS, AND SITE PERSONNEL

Australia:

Austin Hospital, Melbourne: Rinaldo Bellomo (PI), Glenn Eastwood, Leah Peck, Helen Young; **Concord Repatriation General Hospital**, Sydney: Winston Cheung (PI), Rosalba Cross, Michael Hayes, Nitin Jain, Mark Kol, Asim Shah, Atul Wagh, Helen Wong; **John Hunter Hospital**, Newcastle: F. Eduardo Martinez (PI), Gail Brinkerhoff, Dustin Bush; **Liverpool Hospital**, Sydney: Antony Stewart (PI), Anders Aneman, Lien Lombardo, Peter McCanny, James Penketh; **Nepean Hospital,** Sydney: Ian Seppelt (PI), Rebecca Gresham, Julie Lowrey, Kristy Masters, Christina Whitehead; **Princess Alexandra Hospital**, Brisbane: James Walsham (PI), Meg Harward, Josephine Mackay, Jason Meyer, Emma Saylor, Ellen Venz, Krista Wetzig; **Royal North Shore Hospital**, Sydney: Wade Stedman (PI), Angela Ashelford, Frances Bass, Naomi Hammond, Sharon Mar, Julia Pilowsky, Miyuki Tokumitsu, Elizabeth Yarad; **St Vincent's Hospital**, Sydney: Hergen Buscher (PI), Claire Reynolds; **The Alfred Hospital**, Melbourne: Andrew Udy (PI), Stephen Bernard, Aidan Burrell, Jasmin Collins, Dashiell Gantner, Victoria Emma-Leah Martin, Phoebe Mccracken, Vinodh

Nanjayya, Alistair Nichol, Alexander Sacha Richardson, Meredith Young; **The Northern Hospital**, Melbourne: Angaj Ghosh (PI), Simone Said.

Austria:

Medical University Innsbruck, Innsbruck: Michael Joannidis (PI), Ronny Beer, Frank Hartig, Raimund Helbok, Sebastian Klein, Andreas Peer.

Belgium:

Erasme University Hospital, Brussels: Fabio S. Taccone (PI), Jacques Creteur, Dominique Durand; **Ziekenhuis Oost-Limburg**, Genk: Matthias Dupont (PI), Sigrid Christiaens, Carola Claes, Sebastiaan Deckx, Bert Ferdinande, Sanne Lenaerts, Wilifred Mullens, Sarah Stroobants, Evi Theunissen, David Verhaert.

Czech Republic:

General University Hospital, Prague: Ondřej Šmíd (PI), Marek Flaksa, David Kemlink, Jan Malík, Michal Otáhal, Jan Rulíšek, Michal Šíranec, Zdeněk Stach, Anna Valeriánová, Petra Zavadilova; **University Hospital Hradec Králové,** Hradec Králové: Miroslav Solař (PI), Róber Bánszky, Jana Červená, Renata Černá Pařízková, Libor Šimůnek, Filip Varhaník; **Regional Hospital Liberec,** Liberec: Jiří Karásek (PI), Matěj Strýček.

Denmark:

Aarhus University Hospital, Aarhus: Anders Grejs (PI), Steffen Christensen, Peter Juhl-Olsen, Ida Katrine Thomsen, Lisa Gregersen Østergaard.

France:

Cochin University Hospital (APHP), Paris: Alain Cariou (PI), Albert Cao, Pierre Dupland, Ariane Gavaud, Paul Jaubert, Mathieu Jozwiak, Nathalie Marin, Guillaume Savary; **Lariboisiere University Hospital (APHP)**, Paris: Nicolas Deye (PI), Bruno Megarbane, Pierre Mora, Laetitia Sutterlin; **Centre Hospitalier de Versailles**, Le Chesnay: Stephane Legriel (PI), Hugo Bellut, Alexis Ferre, Guillaume Lacave, Marine Paul; **CHU de Nantes**, Nantes: Jean-Baptiste Lascarrou (PI), Emmanuel Canet, Charlotte Garret, Arnaud Felix Miaihle, Jean Reignier; **Dupuytren Teaching Hospital**, Limoges: Philippe Vignon (PI), Thomas Daix, Arnaud Desachy, Bruno Evrard, Bruno Francois, Anne-Laure Fedou, Marine Goudelin.

Germany:

Charité Universitätsmedizin, Berlin: Christian Storm (PI), Gabriele Kress, Christoph Leithner, Jens Nee, Kaspar Josche Streitberger.

Italy:

San Martino Policlinico Hospital, Genoa: Iole Brunetti (PI), Lorenzo Ball, Denise Battaglini, Giulia Bonatti, Iacopo Firpo, Paolo Frisoni, Arianna Iachi, Simona Maiani, Maura Mandelli, Chiara Robba, Fabio Tarantino; **Civil Hospital, Baggiovara**, Modena: Alberto Barbieri (PI), Elisabetta Bertellini, Enrico Giuliani, Gabriele Melegari; **University of Trieste**, Trieste: Erik Roman-Pognuz (PI), Giorgio Berlot, Umberto Lucangelo, Elisabetta Macchini.

Norway:

Oslo University Hospital, Rikshospitalet, Oslo: Jan Hovdenes (PI), Vibeke Aune, Tomas Drægni, Simon Jacobsen, Søren Pieschke, Åse Rasmussen, Gro Ringstad Akselsen; **St. Olav's University Hospital**, Trondheim: Halvor Langeland (PI), Daniel Bergum, Therese M. Erbe, Pål Klepstad, Helle M. Næss; **Sorlandet Hospital**, Arendal: Roy Bjørkholt Olsen (PI), Lena Eriksen Skjelnes, Marius Holen, Joakim Iver Post; **Haukeland University Hospital**, Bergen: Rune Fanebust (PI), Linda Hårteig Sørensen, Ken Åge Kårstad, Carsten Fredrik Wickman.

New Zealand:

Wellington Regional Hospital, Wellington: Paul Young (PI), Colin Barnes, Ben Barry, Nina Beehre, Dick Dinsdale, Sam Edney, Anna Hunt, Harriet Judd, Charlotte Latimer-Bell, Cassie Lawrence, James Moore, Shaanti Olatunji, Alex Psirides, Chelsea Robinson, Kate Tietjens, Jason Wright; **Christchurch Hospital**, Christchurch: David Knight (PI), Brandon Birker, David Bowie, Tara Burke, David Closey, Rosalind Crombie, Neil Davidson, Seton Henderson, Louise Hitchings, James McKay, Jan Mehrtens, Emmeline Minto, Stacey Morgan, Anna Morris, Jay Ritzemar-Carter, Jessica Roberts, Geoffrey Shaw, Katherine Townend, Kymbalee Vander Heyden.

Sweden:

Sahlgrenska University Hospital, Gothenburg: Christian Rylander (PI), Marita Ahlqvist, Roman Desta Lindgren, Ingrid Eiving, Andreas Lundin, Patrik Martner, Elisabeth Myhrman, Birgitta Ryding; **Skåne University Hospital, Malmö**: Joachim Düring (PI), Mattias Bergström, Mattias Bohm, Ingrid Didriksson, Petrea Frid, Katarina Heimburg, Marina Larsson, Oscar Lundberg, Stefan Olsson Hau, Simon Schmidbauer; **Skåne University Hospital, Lund**: Ola Borgquist (PI), Anne Adolfsson, Anna Bjärnroos, Erik Blennow-Nordström, Irina Dragancea, Thomas Kander, Anna Lybeck, Gustav Mattiasson, Olof Persson, Malin Rundgren, Susann Schrey, Erik Westhall; **Helsingborg Hospital**, Helsingborg: Martin Annborn (PI), Sara Andertun, Florian Ebner, Nerida Gustavsson, Lisa Hassel, Jesper Johnsson, Marie Nelderup, Heléne Petersson, Jörgen Petersson, Frideriki Stafilidou; **Hallands Hospital**, Halmstad: Johan Undén (PI), Frida Antonsson, Git Bergman, Jörgen Gamroth, Maria Meirik, Katarina Rudolfsson, Helena Sandberg, Martin Thorsson**;** **Karlstad Central Hospital**, Karlstad: Kristin Savolainen (PI), Maria Hansbo, Malin Helliksson, Björne Nödtveidt, Johan Sanner, Victoria Sem, Camilla Sund Lindquist; **Södersjukhuset, Karolinska Institute**, Stockholm: Per Nordberg (PI), Akil Awad, Anna-Sofia Börjesson, Malin Hedberg, Mia Henning, Jacob Hollenberg; **Northern Älvsborg County Hospital**, Trollhättan: Per Petersen (PI), Emelia Dahlberg, Johan Forshammar, Veronica Svensson; **Capio S:t Görans Hospital**, Stockholm**:** Michael Wanecek (PI), Håkan Eskilsson; **Skaraborg Hospital**, Skövde: Daniel Rodriguez-Santos (PI), Åsa Appelqvist, Henrietta Jidbratt, Elisabeth Johansson, Lars Kiszakiewicz, Åsa Nilsson, Sinnika Olsson, Anders Paulsson, Urszula Stempel, Andreas Thoren; **Örebro University Hospital**, Örebro: Stefan Persson (PI), Ida Berglund, Eric Bergström, Cathrine Törnqvist, Ingela Östman; **Uppsala University Hospital**, Uppsala: Sten Rubertsson (PI), Ing-Marie Larsson, Elin Söderman, Ewa Wallin, Joanna Wessbergh; **Linköping University Hospital**, Linköping: Thomas Halliday (PI), Filippa Engvall.

Switzerland:

Lausanne University Hospital (CHUV), Lausanne: Mauro Oddo (PI), Nawfel Ben-Hamouda, Adriano Bernini, Pierre-Nicolas Carron, Philippe Eckert, Eva Favre, John-Paul Miroz, Paola Morelli, Olivier Muller, Jan Novi, Andrea Rosseti, Madeleine Schnorf; **Bern University Hospital**, Bern: Matthias Haenggi (PI), Anja Levis, Sandra Nansoz, Marianne Roth & Team, Nicole Söll; **Cantonal Hospital St. Gallen**, St.Gallen: Claudia Schrag (PI), Mensur Alicajic, Philipp Baier, Joel Dütschler, Dominique Flügel, Edith Fässler, Ruth

Gamio-Veis, Marc Güpfert, Yvonne Hilpertshauser, Stefan Hägele-Link, Gian-Reto Kleger, Peter Krähenmann, Maria Elisabeth Mair, Nadja Schai, Christoph Strohmaier, Peter Tangl, Dominik Zieglgänsberger; **University Hospital Zurich**, Zurich: Marco Maggiorini (PI), Gabriele Claus, Gabi Consani-Vogel, Lukas Imbach, Samira Kaiser, Eva-Maria Kleinert, Pedro David Wendel Garcia; **Cardiocentro Ticino**, Lugano: Tiziano Cassina (PI), Pamela Agazzi, Bruno Capelli, Gabriele Casso, Martino Regazzi, Hervé Schlotterbeck, Gabriele Via, Michele Villa.

United Kingdom:

University Hospital of Wales, Cardiff: Matt P. Wise (PI), Jenny Brooks, Eve Cocks, Jade Cole, Jacqueline Curtin, Michelle Davies, Rhys Davies, Stephen Fernandez, Julie Highfield, Helen Hill, Matt P. G. Morgan, Lydia Pennant, Sofia Rose, Emma Thomas, Angharad Williams; **Royal Victoria Hospital**, Belfast: Peter McGuigan (PI), Stephen Haffey, Aisling O'Neill, Kathryn Ward; **Bristol Royal Infirmary**, Bristol: Matthew Thomas (PI), Jeremy Bewley, Anna Chillingworth, Julie Cloake, Libby Cole, Hilary Galvin, Zoe Garland, Lisa Grimmer, Bethany Gumbrill, Lucy Howie, Rebekah Johnson, Chloe Searles, Agnieszka Skorko, Katie Sweet, Victoria Taylor, Denise Webster; **Essex Cardiothoracic Centre,** Basildon: Thomas Keeble (PI), Gill Adams, Rajesh K Aggarwal, Jo-Anne Cartwright, Steven Church, Gerald J Clesham, John R Davies, Kelly Farrell, Reto Gamma, Jane Harding, Rohan Jagathesan, Alamgir Kabir, Paul A Kelly, Lauren Kittridge, Maria Maccaroni, Gracie Maloney, Marco Mion, Naveen Nain, Raghunath Nalgirkar, Gyanesh Namjoshi, Stacey Pepper, Emily Redman, Nicholas M Robinson, Jeremy Sayer, Amanda Solesbury, Kare H Tang, Sali Urovi, Kunal Waghmare, Noel Watson, Teresa Webber; **University Hospitals Birmingham NHS Foundation Trust,** Birmingham: Peter Isherwood (PI), Conor Bentley, Colin Bergin, Ronald Carrera, Amy Clark, Lauren Cooper, Liesl Despy, Natalie Dooley, Karen Ellis, Emma Fellows, Stephanie Goundry, Samantha Harkett, Christopher McGhee, Aoife Neal, Hazel Smith, Catherine Snelson, Elaine Spruce, Tony Whitehouse, Kamal Yakoub; **Royal Berkshire Hospital,** Reading: Andrew Walden (PI), Shauna Bartley, Parminder Bhuie, Matthew Frise, Nicola Jacques, Liza Keating; **Queen Alexandra Hospital**, Portsmouth: David Pogson (PI), Zoe Daly, Steve Rose; **Manchester Royal Infirmary**, Manchester: Jonathan Bannard-Smith (PI), Rachael Quayle; **Royal Bournemouth Hospital**, Bournemouth: Nigel Chee (PI), Nina Barratt, Katie Bowman, Debbie Branney, Elizabeth Howe, Maria Letts, Sally Pitts, Luke Vamplew.

USA:

University of Pittsburgh, Pittsburgh PA: Clifton W. Callaway (PI), Sara Difiore Sprouse, Ankur A. Doshi; **Mayo Clinic**, Rochester MN: Jennifer Fugate (PI), Amy M. Headlee, Eelco F.M.Wijdicks.

PI – Principal Investigator

RELATED ORGANIZATIONS

Copenhagen Trial Unit, Copenhagen, Denmark; Clinical Studies Sweden – Forum South, Skåne University Hospital, Lund, Sweden; The George Institute for Global Health, Sydney, Australia; Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Australia; Medical Research Institute of New Zealand - (MRINZ), Wellington, New Zealand; Clinical Research Unit, Paris Descartes Necker Cochin, Paris, France; Scandinavian Critical Care Trials Group (SCCTG); The HRB Irish Critical Care- Clinical Trials Network (ICC-CTN); The ANZICS Clinical Trials Group (CTG); Spiral Software, Wellington, New Zealand; Allianz Global Corporate & Specialty SE, Copenhagen, Denmark; IBBL (Integrated BioBank of Luxembourg), Dudelange, Luxembourg.

SUPPLEMENTARY METHODS

INVESTIGATOR RESPONSIBILITIES

The trial steering group designed the trial. Site investigators vouch for the data recorded at each hospital. Data analysis was performed independently by two statisticians (Susann Ullén and Theis Lange). A final statistical report was written after consensus was achieved. The steering group vouches for the accuracy and completeness of the data and analysis and for the adherence of this report to the trial protocol and the statistical analysis plan.
The initial version of the manuscript was drafted by the first and last authors, developed and approved by all authors. The funders had no role in the analysis of the data, in the preparation or approval of the manuscript, or in the decision to submit the manuscript for publication.

DATA COLLECTION AND VERIFICATION.

Data for the primary outcome measure were obtained from national- or hospital registries, or from contacting patients, relatives, and general practitioners. Assessment of functional outcome at the six-month follow-up was made at a face-to-face follow-up, a visit of a trial investigator at the patients' residence or by telephone contact with patients, relatives, or general practitioners. Source data verification was performed according to monitoring plan which was not available to the investigators. Date of birth, time of return of spontaneous circulation, temperature data, unexpected serious adverse events (if reported) and the primary outcome were verified for all participants. Pre-hospital characteristics, admission motor score, lactate levels, neuroprognostication, time of ICU-discharge and time of hospital discharge were verified for the first two participants at each site and in 20% of subsequent participants.

INCLUSION AND EXCLUSION CRITERA

Inclusion criteria

- Out-of-hospital cardiac arrest of a presumed cardiac or unknown cause
- Sustained Return of spontaneous circulation (ROSC) - defined as 20 minutes with signs of circulation without the need for chest compressions.
- Unconsciousness defined as not being able to obey verbal commands (FOUR-score motor response of <4) and no verbal response to pain after sustained ROSC.
- Eligible for intensive care without restrictions or limitations
- Inclusion within 180 minutes of ROSC

Exclusion criteria

- Unwitnessed cardiac arrest with an initial rhythm of asystole
- Temperature on admission <30°C.
- On Extracorporeal Membrane Oxygenation prior to ROSC
- Obvious or suspected pregnancy
- Intracranial bleeding
- Severe chronic obstructive pulmonary disorder (COPD) with long-term home oxygen therapy

SEDATION

All participants were sedated for 40 hours. There was no mandated protocol for sedation, but short-acting drugs or volatile anaesthesia was recommended. Sedation was titrated to a Richmond Agitation-Sedation Scale (RASS) of minus 4 (No response to voice, but any movement to physical stimulation.)[1] Drugs and doses are described in table S5 and S6.

SHIVERING

Shivering was assessed according to the Bedside Shivering Assessment Scale (BSAS).[2] The treatment goal for shivering was to maintain a BSAS score of 0 or 1 (Table S1). To ensure adequate control of shivering the following was recommended.

1) Adherence to local protocols for management of shivering and administration of acetaminophen for all patients.
2) Increased sedation with propofol/dexmedetomidine and/or opiate. If the participant was hemodynamically unstable midazolam could be used instead of propofol.
3) Administration of a neuromuscular blocking agent.

The Bedside Shivering Assessment Scale (BSAS)

Score	Severity	Description
0	None	No shivering
1	Mild	Shivering localized to neck/thorax, may be seen only as artifact on ECG or felt by palpation
2	Moderate	Intermittent involvement of the upper extremities ±thorax
3	Severe	Generalized shivering or sustained upper/lower extremity shivering

DEFINITION OF ADVERSE EVENTS

Adverse events were recorded during the ICU stay. Pneumonia was defined as purulent tracheal secretions, a radiographic infiltrate and a decreased P/F ratio (PaO2/FiO2 <32 kPa or < 240 mmHg), a pragmatic adaption of the
Clinical Pulmonary Infection Score (CPIS)[3] Sepsis was defined according to the 3rd international consensus definitions for sepsis and septic shock.[4] Bleeding was defined as moderate or severe bleeding, according to the GUSTO criteria[5] (Bleeding requiring transfusion, intracerebral haemorrhage, or bleeding resulting in substantial hemodynamic compromise requiring treatment). Device related skin complications were defined as blistering or skin necrosis. Arrhythmias were recorded if they resulted haemodynamic compromise, required pacing or CPR.

DETAILS OF THE INTERVENTION

The intervention period of 40 hours commenced at the time of randomization. Core body temperature was measured using a temperature probe in the bladder. If urinary output was low, or if a bladder probe was unavailable, an esophageal or intravascular probe was used for temperature monitoring.

In the hypothermia group, all participants received a feedback-controlled device (either a surface cooling device or an intravascular cooling device). The goal was to reach a temperature of 33°C as soon as possible. Adjunctive cooling methods such as ice-packs, intra-nasal or esophageal cooling devices, and infusion of cold (4°C) fluids (maximal volume: 30ml/kg) were allowed. When participants' body temperature reached 33°C this temperature was maintained until 28 hours after randomization. Rewarming then commenced at 1/3°C per hour.

In the normothermia group the treatment goal was to avoid a temperature ≥37.8°C through the use of exposure, lowering of the ambient temperature and treatment with anti-pyretics. If a temperature of ≥37.8°C was recorded a device for temperature management was applied and a target temperature set at 37.5°C. A device could be applied prophylactically, but cooling was not initiated before a temperature of 37.8°C was recorded.

Active warming was only allowed for participants with a temperature below 33°C.

After 40 hours, those participants who remained comatose were kept normothermic (36.5 – 37.7°C) until 72h after randomization. If needed a temperature management device could be initiated after 40 hours.

NEUROLOGICAL PROGNOSTICATION

Prognostication was performed in all participants still in the ICU at 96 hours after randomisation. The prognostication was performed at approximately 96h after randomization. The physician performing the prognostication was not involved in patient care and was blinded for group allocation, but not for relevant clinical data. The result of the prognostic assessment was categorised as “YES” or “NO”, based on the answer to the question “Does this patient fulfil the TTM2-trial criteria for a likely poor neurological outcome?”. The assessment of neurological prognosis did not include making any recommendation regarding withdrawal of life-sustaining therapy (WLST). Efforts were made to sufficiently delay prognostication to ensure that any lingering effects of sedative agents would not affect the assessment. Prognostication was based on two mandatory (clinical examination and electroencephalogram (EEG)), and four optional modalities (Brain CT, Brain MRI, Neuron specific enolase (NSE), somatosensory evoked potentials (SSEP)).

TTM2 criteria for a likely poor neurological prognosis

In the TTM2 trial the prognosis was considered *likely poor* if criteria A, B and C were all fulfilled.

A. Confounding factors such as severe metabolic derangement and lingering sedation has been ruled out.

B. The patient has no response or a stereotypic extensor response to bilateral central and peripheral painful stimulation at ≥ 96 hours after randomization.

C. At least two of the below mentioned signs of a poor prognosis are present:

C.1. Bilateral absence of pupillary and corneal reflexes at 96h after cardiac arrest or later

C.2. A prospectively documented early (within 48 hours) status myoclonus (continuous and generalized myoclonus persisting for at least 30 min).

C.3. A highly malignant EEG-pattern according to the TTM2 definition without reactivity to sound and painful stimulation.[6]

C.4. CT brain with signs of global ischemic injury, such as: generalized edema with reduced grey/white matter differentiation and sulcal effacement or MRI-brain with signs of global diffuse, or bilateral multifocal ischemic lesions.

C.5. Serial serum-NSE samples consistently higher than locally established levels associated with a poor outcome

C.6. Bilaterally Absent cortical SSEP N20-responses more than 48 hours after randomization.

WITHDRAWAL OF LIFE-SUSTAINING THERAPIES (WLST)

According to the trial protocol all participants were treated actively until 96 hours after randomization unless further treatment was considered unethical due to irreversible organ failure, a documented comorbidity or other reasons. The assumption of a poor neurological prognosis alone was not sufficient to employ withdrawal of active intensive care prior to 96 hours after randomisation. After prognostication was performed, WLST due to a presumed poor prognosis was allowed if the TTM2-trial criteria for a likely poor neurological outcome were fulfilled. Participants who had an unclear prognosis at 96h were re-examined daily and active treatment could be withdrawn if neurological function did not improve. However, supporting therapies could also be continued regardless of the neurological assessment of prognosis, at the discretion of the treating physician.

CHANGES FROM THE STATISTICAL ANALYSIS PLAN

Estimation of sample size

As the total number of recruiting sites and recruitment speed were unknown when the trial protocol was written sample size estimation did not take clustering of patients within sites into account. The power analysis was therefore based on a chi2-test. It is possible that we thus slightly underestimated the required sample size.

Assessment of functional outcome:

The trial protocol and statistical analysis plan stated that the secondary outcome functional outcome would be assessed by comparing the proportion of participants with a mRS score of 0-3 vs 4-6.[7,8] This assessment required a mRS score from a structured assessment. The Covid-19 pandemic resulted in a decline in formal follow-up visits and structured mRS-assessments.

Participants missing a structured assessment are more likely to have a severe disability. To minimize this bias, and to avoid missing data we used an additional approach which included all available data related to disability to perform a simplified overall rating of functional outcome. Functional outcome was classified as "good" if the participant was independent in basic activities of daily life. Functional outcome was classified as "poor" if the participant was dependent on other for basic activities of daily life and could not attend to their own bodily needs. This dichotomization corresponds to the dichotomized mRS-scale although it does not provide any detailed information on neurologic recovery and remaining disability. Participants with a structured assessment of mRS and a score of 0-3 were also classified as having a "good" functional outcome. Participants with a structured assessment of mRS and a score of 4-6 were classified as having a "poor" functional outcome.

In the manuscript we therefore present two outcomes assessing functional outcome:

1. **mRS 0-3 vs. mRS 4-6**, which only includes participants with a structured mRS-assessment, and which was specified in the protocol and statistical analysis plan.
2. **"Good" vs. "Poor" functional outcome,** which includes (1) *and* all participants in whom an assessment of independence/dependence in basic activities of daily life (able to attend own bodily needs) could be made. This outcome was not specified in the protocol and statistical analysis plan.

Statistical tests and data presentation:

The statistical analysis plan stated that the primary outcome and the secondary outcome poor functional outcome were to be assessed using a log-link mixed model, with site as a random effect and possible co-enrollment as a fixed effect. These models did not converge. Instead, a logit link mixed model was used. Population-level (marginal) risk ratios were calculated using G-computation. Bootstrapping was used to calculate 95% confidence intervals.

The secondary outcome "numbers of days alive outside hospital" was to be presented with means/median and 95% confidence interval/inter-quartile range. Due to the skewed distribution of this variable only histograms are presented.

All regression analyses were to be adjusted for site and potential co-enrollment in the Targeted hypercapnia versus Targeted Normocapnia after Out-of-hospital Cardiac Arrest-trial (NCT03114033). This was not feasible when assessing "days alive outside hospital", in survival analysis using Cox regression and when assessing adverse events. These analyses were therefore only adjusted for potential co-enrollment, and not for site. Due to very few events, the adverse event "Device-related skin complications" was analyzed without any adjustments.

The details of the statistical analysis process are available in the statistical report.

During the course of manuscript preparation adverse events were included in Table 2 and the secondary outcomes "number of days alive outside hospital", "health-related quality of life" and "time-to-death" were moved. In Table 1 the summary measure for lactate was changed from mean to median to allow an easier comparison with earlier trials.

SUPPLEMENTARY FIGURES

Figure S1. CONSORT FLOW CHART

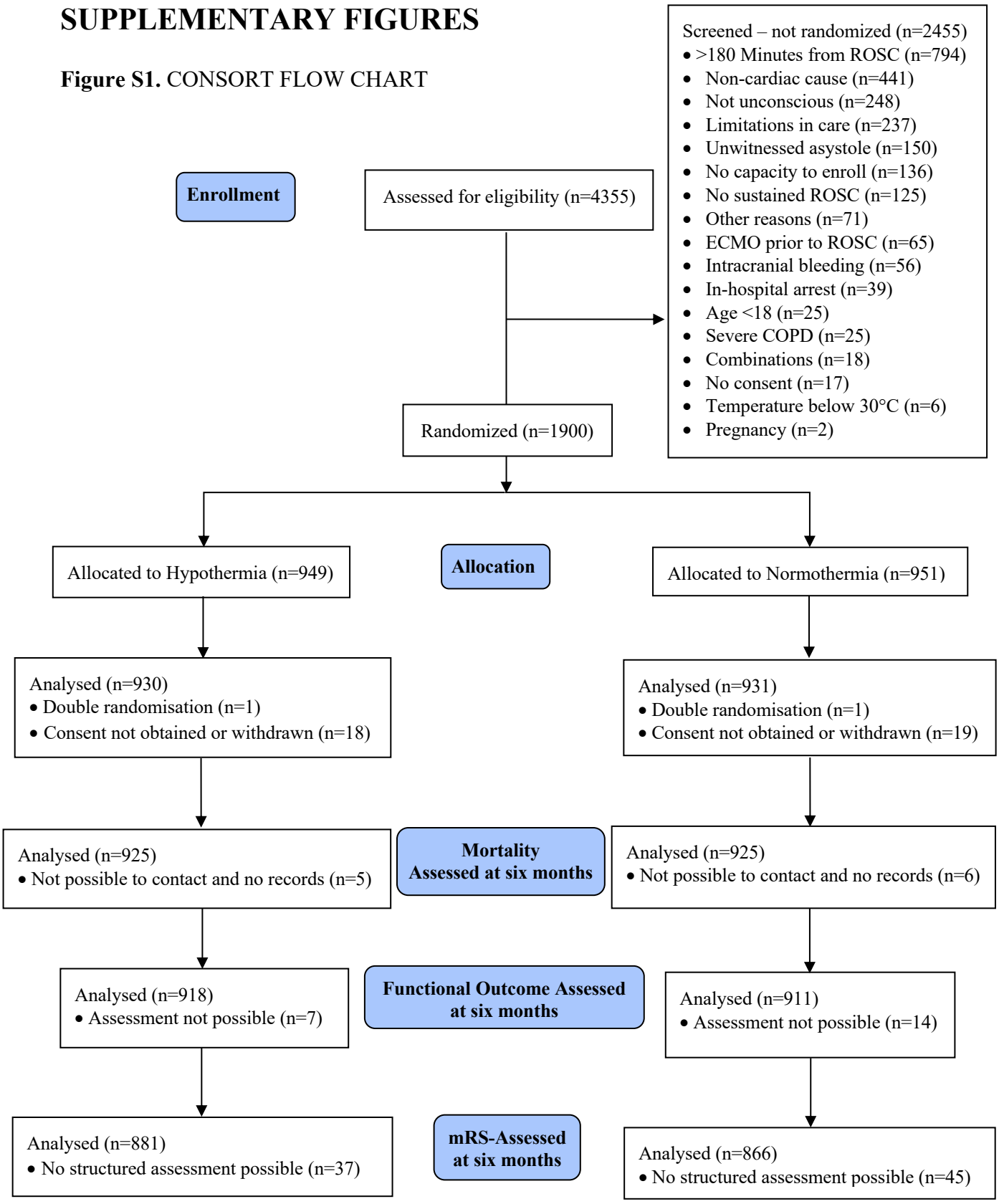
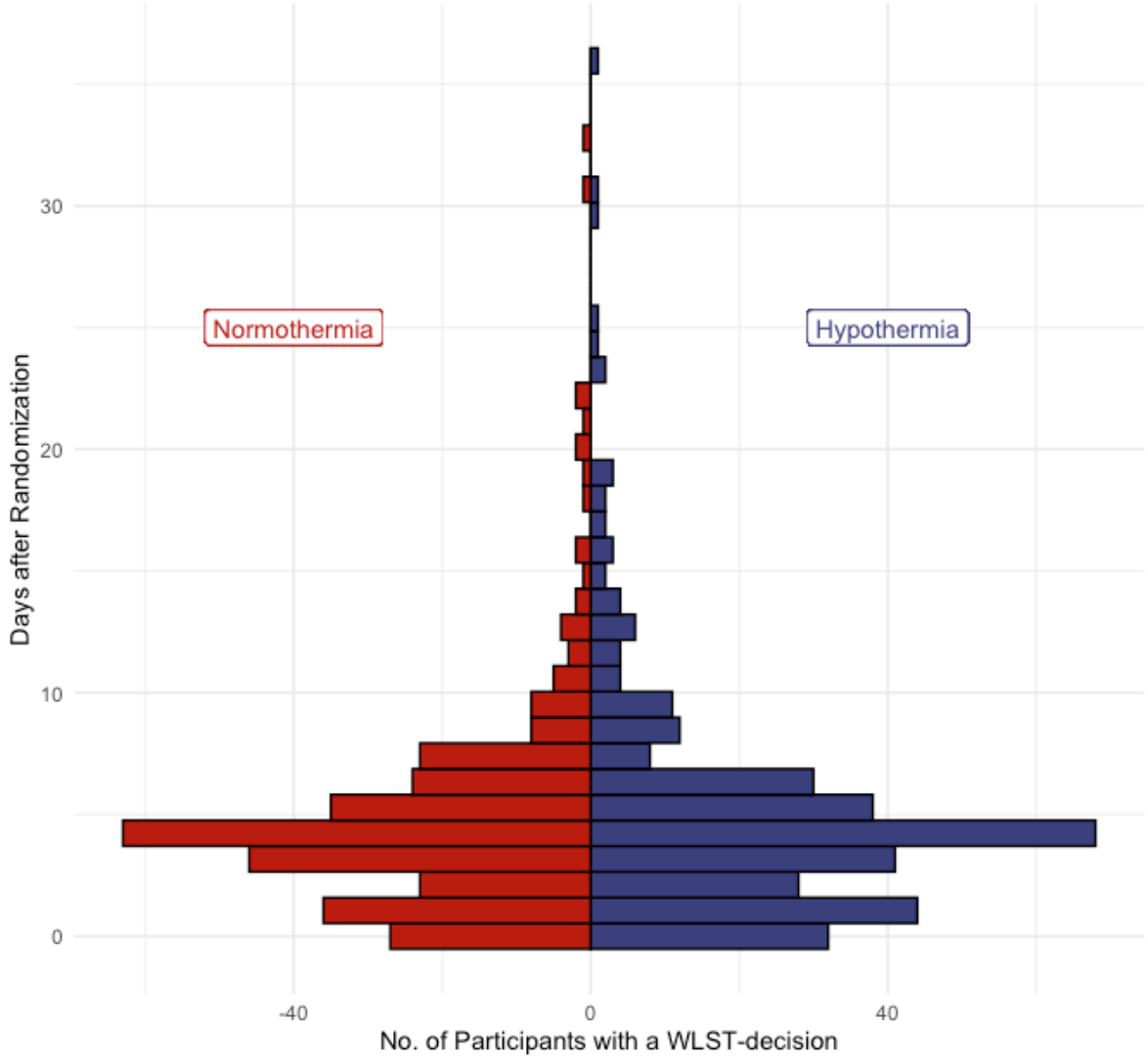
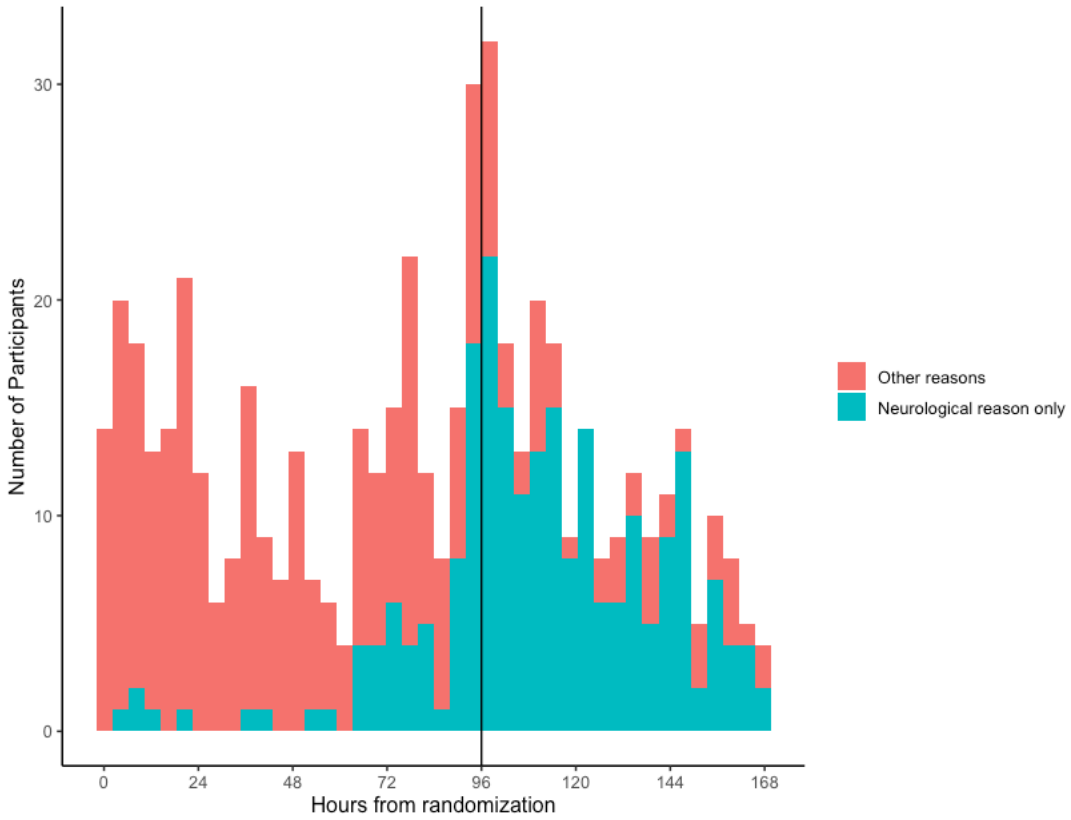


Figure S2. Days from randomization to decision to withdrawal of life-sustaining therapies



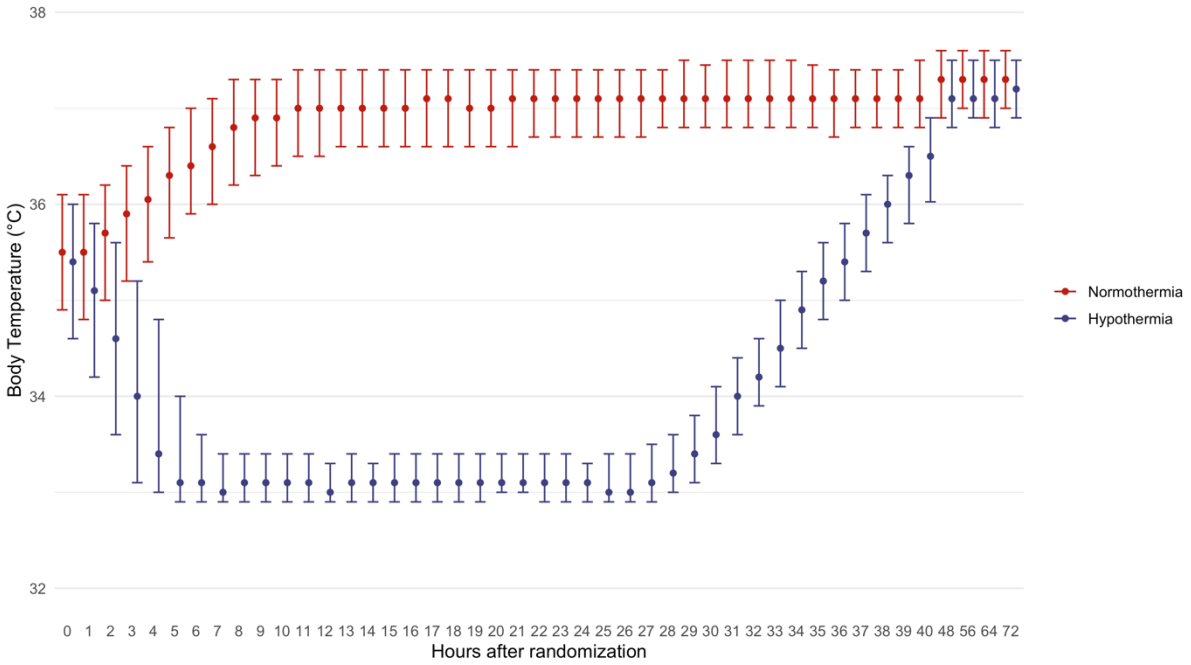
Histogram depicting the number of participants for whom a decision to withdraw life-sustaining therapies (WLST) was made and the time of the decision. A WLST-decision was made on day 127 for one participant in the normothermia group, not visible in the figure.

Figure S3. Withdrawal of life-sustaining therapies, by reason.



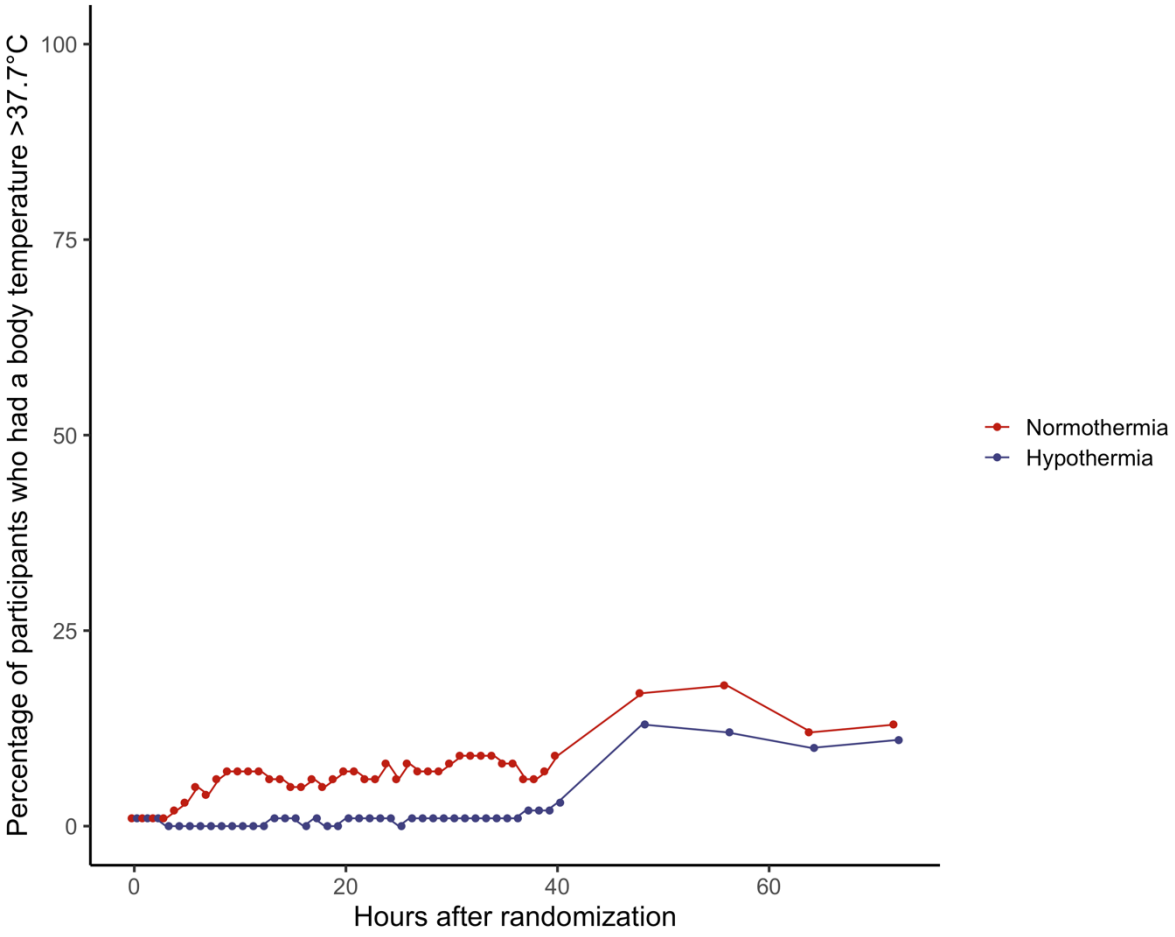
Reason and timing of WLST during the first 7 days after randomization. WLST: Withdrawal of life-sustaining therapies. The vertical black line denotes the time point from which protocolized neuroprognostication was allowed.

Figure S4. Body temperature from randomization to hour 72.



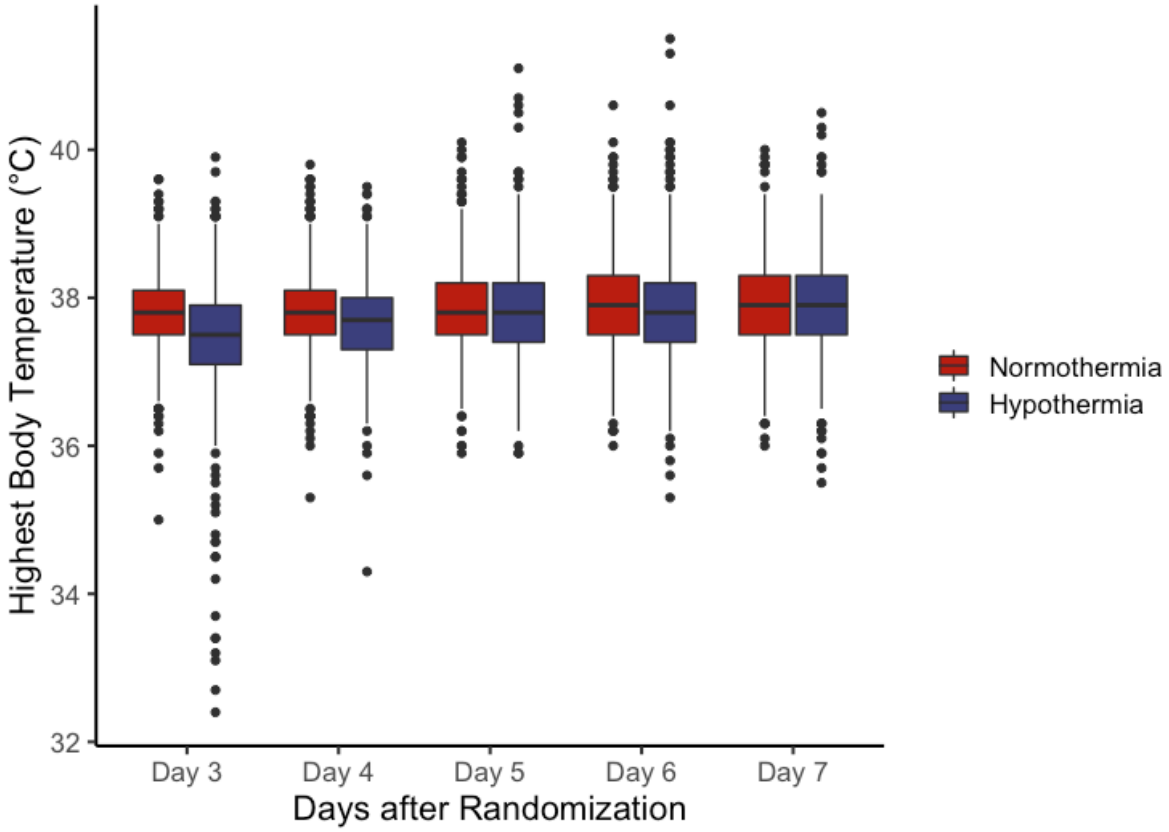
Body temperature curves in the hypothermia and normothermia groups for the patients in whom bladder temperature was recorded. The median number of temperature recordings was 41 in both the hypothermia and normothermia group, out of 44 possible recordings. The temperature curves display the medians, and I-bars indicate the inter-quartile range.

Figure S5. Percentage of participants who were febrile per hour



The figure depicts the percentage of participants who had a recorded body temperature above 37.7°C at each time point (0-72 hours after randomization, bladder measurement). The denominator is the total number of participants with a bladder measurement at each time point.

Figure S6. Highest body temperatures between day 3 and day 7.



Boxplot of highest body temperature from day 3 to day 7 after randomization in participants who remained in the intensive care unit. The black lines represent median values. Boxes represent inter-quartile range (IQR), whiskers cover values within 1.5 IQR of the 25th and 75th percentile respectively. Dots are outliers.

Figure S7. Shivering on day 1.

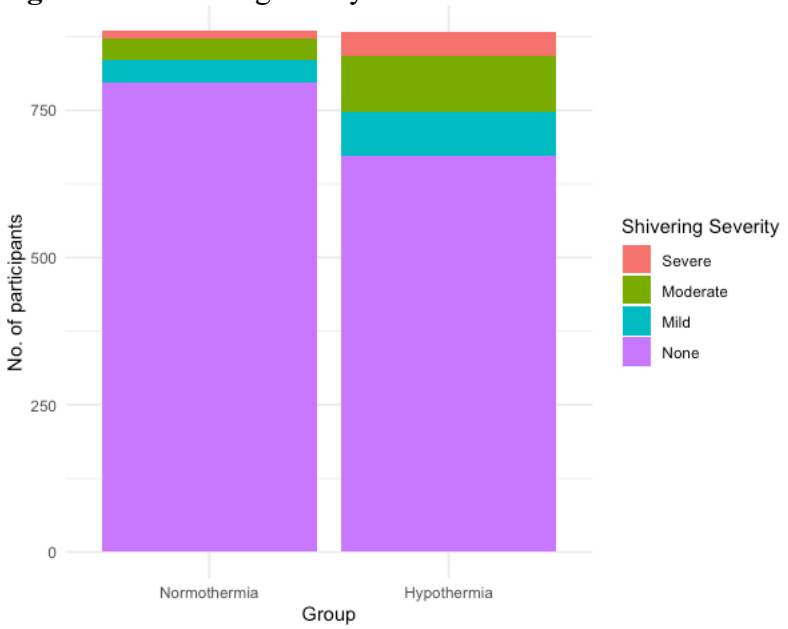


Figure S8. Modified Rankin Score (mRS) at six-month follow-up.

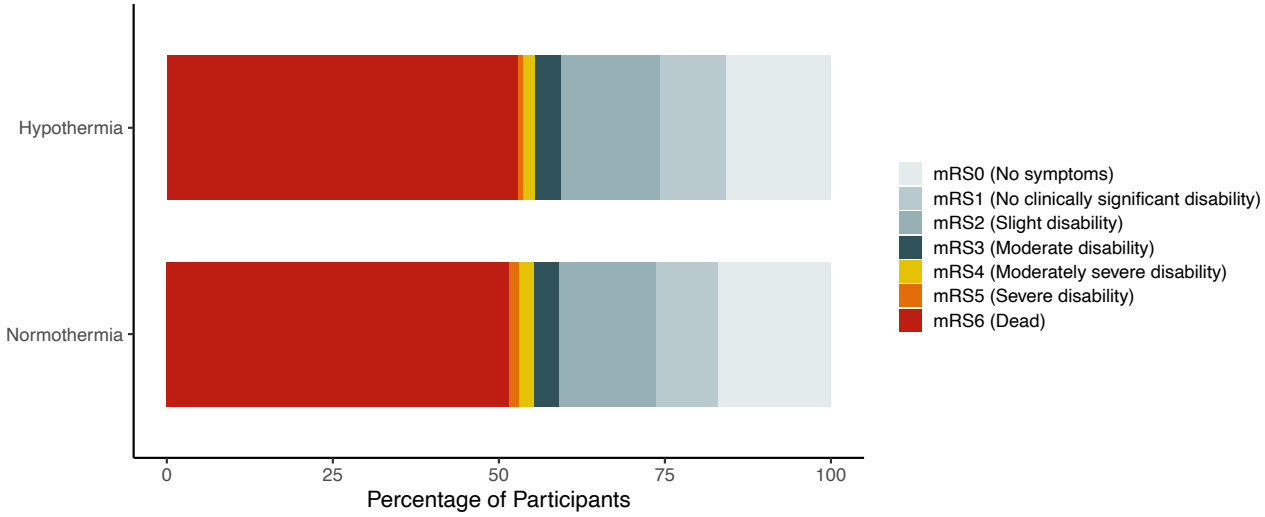
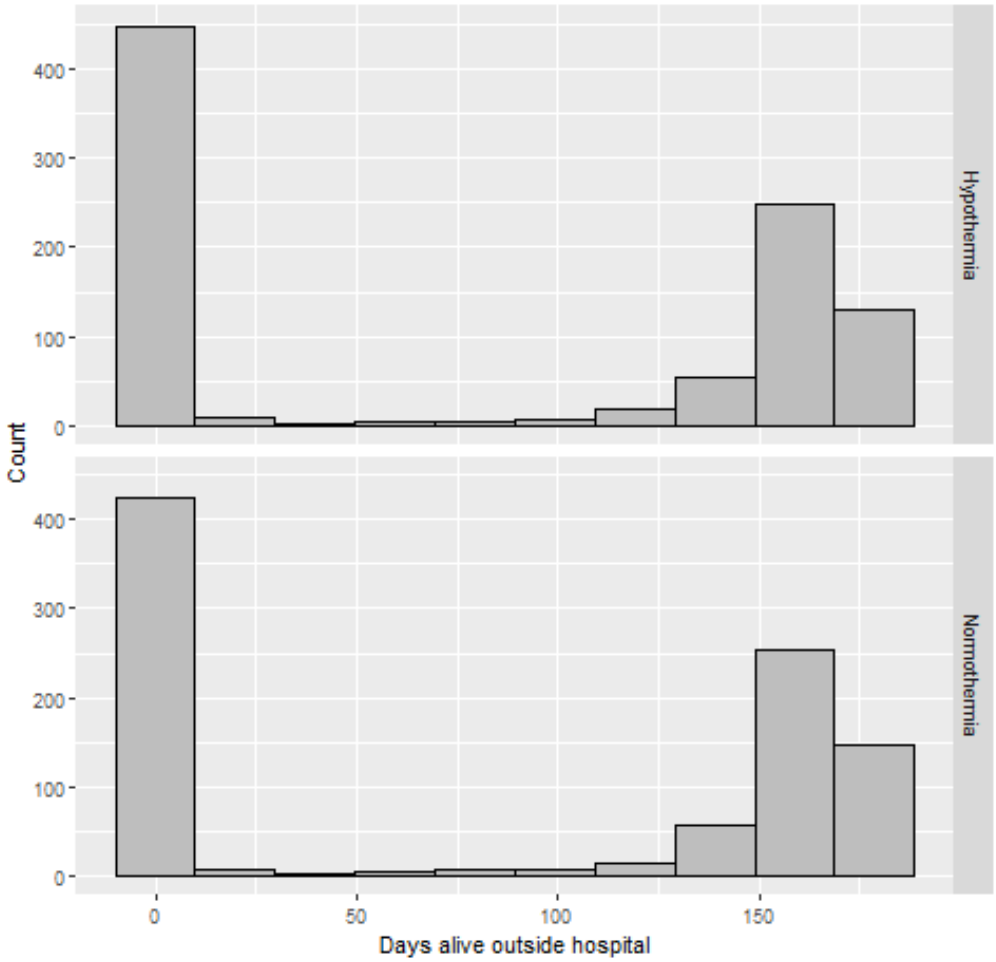


Figure S9. Distribution of days alive outside hospital after the first hospitalization within 180 days



Due to the distribution of the data, we present the results in a histogram instead of summarizing measures. The figures are based on the 1850 patients with data on mortality. Only complete case analysis was performed. Follow-up was performed at 6 months after randomization, but actual dates differed several weeks for logistical reasons.

SUPPLEMENTARY TABLES

Table S1. Length of stay and mechanical ventilation

	Hypothermia	Normothermia
Days from randomization to hospital discharge (median (IQR))	9.4 (4.0–17.0)	9.8 (5.0–17.4)
- *Survivors*	15.4 (10.4–25.4)	14.6 (9.7–23.6)
- *Died in hospital*	4.0 (2.0–7.0)	5.0 (2.0–8.0)
Days from randomization to ICU-discharge (median (IQR))	4.9 (3.0-8.3)	4.8 (2.9-8.0)
- *Survivors*	5.9 (3.9–9.6)	5.4 (3.2–8.9)
- *Died in the ICU*	3.8 (1.2–5.8)	3.9 (1.4–6.2)
Days from randomization to extubation or death (n=1759) (median (IQR))	3.7 (1.9–6.0)	3.2 (1.8–5.7)
- *Survivors*	3.8 (2.0–6.4)	2.9 (1.9–5.5)

IQR: Inter-quartile range

Table S2. Cardiac procedures

Procedure performed	**Hypothermia**	**Normothermia**
Coronary angiogram	721/929 (78%)	720/929 (78%)
- within 2 hours of randomization	652/721 (90%)	629/720 (87%)
Percutaneous coronary intervention	351/929 (38%)	375/929 (38%)
Coronary artery bypass grafting	12/929 (1%)	17/929 (2%)
Implantable cardiac defibrillator	149/929 (16%)	152/929 (16%)

Table S3. Neuromuscular blocking agents used up until 72 hours after randomization.

DRUG	HYPOTHERMIA	NORMOTHERMIA
ATRACURIUM	156 (17%)	120 (13%)
CISATRACURIUM	164 (18%)	100 (11%)
ROCURONIUM	286 (31%)	207 (22%)
VECURONIUM	7 (1%)	11 (1%)
OTHER NMBA	47 (5%)	36 (4%)
ANY NMBA	614 (66%)	418 (45%)

N=1858, data not available for three participants. NMBA: Neuromuscular blocking agent

Table S4. Noradrenaline, sedatives and analgesics until 72 hours after randomization

	HYPOTHERMIA		NORMOTHERMIA	
DRUG	**Participants who received drug**	**Median cumulative dose if given (IQR)**	**Participants who received drug**	**Median cumulative dose if given (IQR)**
NORADRENALINE	824/914 (90%)	24 mg (10-52 mg)	793/914 (85%)	22 mg (9-48 mg)
PROPOFOL	791/914 (85%)	8768 mg (3683-13365 mg)	819/915 (88%)	7744 mg (3183-12595 mg)
MIDAZOLAM	364/915 (39%)	117 mg (16-309 mg)	346/916 (37%)	125 mg (16-283mg)
REMIFENTANIL	326/915 (35%)	21 mg (6-39 mg)	317/915 (34%)	22 mg (8-41mg)
FENTANYL	495/914 (53%)	5 mg (2-8 mg)	477/916 (51%)	4mg (2-8 mg)
DEXMEDETOMIDINE	66/915 (7%)	1 mg (0.4-2 mg)	78/916 (8%)	1 mg (0.6-2 mg)
ACETAMINOPHEN	540/915 (58%)	4875 mg (2000-8000 mg)	661/916 (71%)	6000 mg (3000-10000 mg)
OXYCODONE	50/915 (5%)	12 mg (6-37 mg)	63/917 (7%)	12 mg (5-27 mg)
MORPHINE	98/915 (11%)	20 mg (10-130 mg)	124/916 (13%)	20 mg (10-75 mg)

Drugs administered during the first 72h hours following randomization. Number and percentage of participants who received the drug. Median cumulative dose during the first 72hours is presented for the subset of participants in whom the drug was given. IQR: Inter-Quartile Range.

Table S5. Prognosis and prognostic modalities used.

PROGNOSTICATION VARIABLES		
	HYPOTHERMIA	NORMOTHERMIA
PROGNOSTICATION PERFORMED	441 (47.4)	442 (47.6)
POOR PROGNOSIS LIKELY	131 (29.5)	133 (29.6)
EEG PERFORMED	484 (52.1)	445 (47.9)
CT PERFORMED	625 (67.3)	622 (67.0)
MRI PERFORMED	80 (8.6)	86 (9.3)
SSEP PERFORMED	159 (17.1)	165 (17.8)
NSE ANALYSED	510 (54.9)	508 (54.7)
HOURS TO PROGNOSTICATION	129.00 [110.00-137]	118.00 [110.00-138]

Prognostication of patients who were fully awake and still in the ICU at 96h was not performed in some cases, which was not considered a protocol deviation. In total 37% of all participants where awake at 96h and 20% had died. In 17 cases (<1%) prognostication was not performed due to transfer to a non-study ICU. EEG denotes electroencephalogram; CT computed tompography, MRI, magnetic resonance imaging; SSEP somatosensory evoked potentials; NSE neuron specific enolase

Table S6. Number and proportion of participants in the intention to treat analysis who were co-enrolled in the TAME-trial.

	Total (n=1861)	Hypothermia (n=930)	Normothermia (n=931)
Not co-enrolled	1494 (80%)	748 (80%)	745 (80%)
Co-enrolled TAME group A	182 (10%)	89 (10%)	93 (10%)
Co-enrolled TAME group B	185 (10%)	93 (10%)	92 (10%)

Table S7. Reasons for rewarming in the hypothermia group.

	No. of participants (% of total rewarmed)
Hemodynamic compromise	17 (32%)
Bradycardia	12 (23%)
Ventricular Fibrillation or Ventricular Tachycardia	6 (11%)
Intracranial hemorrhage	5 (9%)
Bleeding	3 (6%)
Brain death diagnosis	2 (4%)
Cardiac surgery	2 (4%)
ECMO	2 (4%)
Compartment syndrome	1 (2%)
Tachyarrhythmia	1 (2%)
Skin complications	1 (2%)
Unclear reasons	1 (2%)

ECMO denotes extracorporeal membrane oxygenation

Table S8. Shivering by group, day 1 to 3 after randomization.

	Day 1		Day 2		Day 3	
	Hypothermia	**Normothermia**	**Hypothermia**	**Normothermia**	**Hypothermia**	**Normothermia**
None	673 (76%)	798 (90%)	618 (73%)	720 (83%)	606 (76%)	650 (82%)
Mild	75 (8%)	37 (4%)	93 (11%)	59 (7%)	74 (9%)	49 (6%)
Moderate	95 (11%)	36 (4%)	103 (12%)	58 (7%)	77 (10%)	60 (8%)
Severe	40 (5%)	13 (1%)	33 (4%)	27 (3%)	36 (4%)	34 (4%)

Shivering according to the Bedside shivering assessment scale (BSAS).

Table S9. Health-related quality of life at six months.

EQ-VAS	**Hypothermia**	**Normothermia**	**Mean difference (95% CI)**
All participants*	Median score: 0 (IQR: 0 – 80)	Median score: 0 (IQR: 0 – 80)	
Participants alive at six months	Mean score: 74 (SD: 20)	Mean score: 75 (SD: 20)	-0.8 points (-3.6 to +2.0 points)

EQ-VAS denotes the EuroQol groups visual analogue scale for assessment of health-related quality of life, as part of the EQ5D-5L questionnaire. CI denotes confidence interval, IQR inter quartile range, SD standard deviation. Scores range from 0 – "The worst health you can imagine" to 100 – "The best health you can imagine". In participants alive, data on EQ-VAS was missing in 139 participants (54 and 85 participants respectively in the hypothermia and normothermia groups). In a best-case scenario for hypothermia (and worst for normothermia) mean difference was +37 (95% CI 35 to 39) and worst-case for hypothermia (and best for normothermia) -37 (95% CI -39 to -36).[8] There was no significant interaction between group allocation and allocation in the TAME-trial ($P_{interaction}$=0.67). *In the analysis of all participants a value of 0 was given to those participants who were dead at six months.

Table S10. Best-worst and worst-best case analysis of missing data in the intention-to-treat population.

Outcome	Missing (n)	Relative risk (95% confidence interval)	
		Alive/Good outcome assumed for all participants with missing data in the hypothermia group. & Death/Poor outcome assumed for all participants with missing data in the normothermia group.	Death/Poor outcome assumed for all participants with missing data in the hypothermia group. & Alive/Good outcome assumed for all participants with missing data in the normothermia group
Mortality at 6 months	11	1.03 (0.94 -1.13)	1.06 (0.96-1.16)
Binary functional outcome at 6 months*	32	0.97 (0.89-1.05)	1.03 (0.95-1.12)

mRS denotes modified Rankin Score

*We did not perform best-worst and worst-best case analysis for the outcome measure of structured mRS 4-6 at 6 months since the addition of the binary functional outcome replaces this analysis.

Table S11a. Unadjusted analyses in the intention-to-treat population.

	Relative risk	95% confidence interval
Mortality at 6 months	1.04	0.95-1.14
mRS 4-6 at 6 months	1.00	0.92-1.09
Binary functional outcome at 6 months	1.00	0.92-1.08

mRS denotes modified Rankin Score

Table S11b. Unadjusted analyses in 1494 participants of the intention-to-treat population where the 367 patients co-enrolled in the TAME-trial were excluded.

	Relative risk	95% confidence interval
Mortality at 6 months	1.04	0.94-1.16
mRS 4-6 at 6 months	1.02	0.93-1.12
Binary functional outcome at 6 months	1.01	0.92-1.10

mRS denotes modified Rankin Score

Table S12. Interaction analyses between trial group allocation and co-enrollment/allocation in the two groups of the TAME-trial for the outcomes

Outcome	P for interaction (overall)
All cause mortality at 6 months	0.94
mRS 4-6 at 6 months	0.58
Poor functional outcome at six months	0.75
Time to event (survival)	0.93
EQ-5D-VAS for participants alive at follow up	0.67

EQ-VAS denotes the EuroQol groups visual analogue scale for assessment of health-related quality of life, as part of the EQ5D-5L questionnaire, mRS modified Rankin Score. No P-value for interaction was calculated for the outcome Days alive outside hospital.

PARTICIPATING HOSPITALS

Table S13. Participating hospitals and number of randomizations.

Country	Hospital	No . Randomized
Sweden	Sahlgrenska University Hospital, Gothenburg	78
Sweden	Skåne University Hospital Malmö	76
Sweden	Skåne University Hospital Lund	46
Sweden	Helsingborg Hospital	37
Sweden	Halland Hospital, Halmstad	34
Sweden	South General Hospital, Stockholm	33
Sweden	Norra Älvsborg Hospital - Trollhättan	27
Sweden	Centralsjukhuset, Karlstad	26
Sweden	Skaraborg Hospital, Skövde	19
Sweden	Akademiska University Hospital, Uppsala	14
Sweden	Linköping University Hospital	13
Sweden	Örebro University Hospital	6
Sweden	Capio-St.Göran Hospital	5
UK	Bristol Royal Infirmary	152
UK	The Essex Cardiac Centre	75
UK	University Hospital of Wales, Cardiff	54
UK	Royal Victoria Hospital, Belfast	30
UK	Manchester Royal Infirmary	25
UK	Queen Alexandra Hospital - Portsmouth	23
UK	Royal Bournemouth Hospital	22
UK	Birmingham University Hospital	11
UK	Royal Berkshire Hospital	11
Switzerland	Bern University Hospital	78
Switzerland	Cantonal Hospital St. Gallen	65
Switzerland	Zurich University Hospital	64
Switzerland	Lausanne University Hospital	44
Switzerland	Instituto Cardiocentro Ticino, Lugano	28
France	Cochin University Hospital, Paris	56
France	University Hospital Center, Limoges	28
France	University Hospital Center Lariboisière, Paris	25
France	University Hospital Center, Nantes	24
France	Versailles Hospital, Versailles	17
Czech Republic	Prague General University Hospital	74
Czech Republic	Hradec Kralove University Hospital	48
Czech Republic	Liberec Hospital	10

Norway	Oslo University Hospital	57
Norway	Sørlandet Hospital Arendal	30
Norway	St. Olav's University Hospital	25
Norway	Haukeland University Hospital, Bergen	18
Australia	Royal North Shore Hospital, Sydney	18
Australia	Liverpool Hospital, Sydney	16
Australia	Princess Alexandra Hospital, Brisbane	16
Australia	Northern Hospital, Epping	15
Australia	Austin Hospital, Melbourne	14
Australia	Nepean Hospital, Sydney	12
Australia	The Alfred, Melbourne	12
Australia	St Vincent's Hospital, Sydney	5
Australia	John Hunter Hospital, Newcastle	3
Australia	Concord Repatriation General Hospital	1
Denmark	Aarhus University Hospital	83
New Zealand	Wellington Regional Hospital	40
New Zealand	Christchurch Hospital	25
Italy	San Martino Policlinico Hospital, University of Genoa	34
Italy	Modena NOCSAE University Hospital	11
Italy	Trieste University Hospital	8
Germany	Charité University Hospital	45
Belgium	Erasme University Hospital, Brussles	22
Belgium	Ziekenhuis Oost-Limburg	3
Austria	Innsbruck University Hospital	5
USA	Mayo Clinic, Rochester, MN	2
USA	University of Pittsburgh, Medical Center, PA	2

PROTOCOL DEVIATIONS AND ADVERSE EVENTS

PROTOCOL DEVIATIONS

Protocol deviations reports were assessed by the trial management committee. In total there were 130 protocol deviations in 126 participants (63 in the hypothermia group and 63 in the normothermia group). A total of 8 participants were randomized despite not fulfilling the eligibility criteria. Of these 3 were randomized despite being awake, 2 were enrolled following a clear non-cardiac cause of arrest, 2 were in-hospital arrests and one participant had not had a cardiac arrest. The intervention was not started in 10 participants due to cerebral hemorrhage (9 participants) or brain death (1 participant). In 7 participants the trial interventions were stopped before six hours and palliative care was started. There were 3 protocol deviations due to major deviations in temperature management, in one case cooling was delayed approximately 10 hours due to confusion about whether the participant was randomized or not, one participant was cooled to 35°C despite being randomized to normothermia, and in one participant in the hypothermia group the cooling device was wrongly set at 36°C for 10 hours. Early awakening (before 40 hours) occurred in 29 cases. An EEG was missed in 11 cases and there were other deviations from the protocol for neuroprognostication in 62 participants.

Randomization despite known ineligibility, intervention not started (cerebral bleed or brain death), intervention stopped early for palliative care, and early awakening were not considered per-protocol. In total 57 participants had a protocol deviation in one of these categories.

UNEXPECTED ADVERSE EVENTS

Adverse events that were considered unexpected were reported in the eCRF by investigators. In total there were 47 events reported in 42 participants (30 in the hypothermia group and 12 in the normothermia group). The reported events are described in Table S11. All reports were assessed by the trial management committee and an external physician. In four cases the reported event was considered unexpected and possibly related to the intervention.

One participant in the normothermia group had regained consciousness and complained of pain in the lower leg. A deep venous thrombosis was suspected, and an ultrasound was requested. Before the scan was performed the intravascular cooling device was removed. Following removal, the participant had a cardiac arrest (with initial pulseless electric activity (PEA)). The participant was successfully resuscitated but deteriorated and died due to hemodynamic failure after 24 hours. A bedside echocardiogram showed a dilated right ventricle. A pulmonary embolism from a device-related clot with was considered the probable cause. A second participant in the normothermia group had woken up in the ICU and then developed chest pain. A CT-scan showed two small pulmonary emboli. A device-related clot was considered a possible cause and the device was left in-situ whilst anticoagulation was started. The device was later removed, and the participant was discharged without further complications. In the hypothermia group one participant was cooled to a temperature of 30.8°C and subsequently developed bradycardia and worsening hemodynamics. The participant was rewarmed but did not improve and died due to hemodynamic failure. The investigators considered the worsening hemodynamics as probably related to overshooting the temperature target. In a second participant in the hypothermia group a clot was visualized in the inferior vena cava during an

echocardiographic assessment. Anticoagulation was started and the clot resolved. In this case the investigators considered the clot possibly related to the intravenous cooling device.

Table S14. All events reported as potential unexpected serious adverse events.

	Group	uSAE Category	Description	Meets critera for uSAE
1	Normothermia	Limb complication	Leg ischemia, treated by PTCA	No
2	Normothermia	Limb complication	Leg ischemia, no intervention possible	No
3	Normothermia	Tamponade	Cardiac tamponade, pacing wire perforation. Managed in OR	No
4	Normothermia	Bleeding	Splenic bleeding. Managed in the OR	No
5	Normothermia	Bleeding	Bleeding from femoral artery (PCI) requiring transfusion	No
6	Normothermia	Bleeding	Severe liver bleeding after CPR, managed in OR	No
7	Normothermia	Sepsis	Ventilator associated pneumonia and sepsis	No
8	Normothermia	Bradycardia	Temporary pacemaker needed	No
9	Normothermia	Bleeding	Major bleeding. Thoracostomy performed	No
10	Normothermia	Stroke	Major stroke after intervention	No
11	Normothermia	Other	Intravenous catheter not working resulting in inadequate sedation	No
12	Normothermia	Venous Thromboembolism	Cardiac arrest after removal of intravascular cooling device. Suspected PE	Yes
13	Normothermia	Venous Thromboembolism	Minor pulmonary embolism in patient with intravascular cooling device	Yes
14	Hypothermia	Hemodynamics	Overcooling, below 31 with severe hemodynamic instability, bradycardia and subsequent death	Yes
15	Hypothermia	Arrhythmia	Bradycardia, requiring adrenalin	No
16	Hypothermia	Arrhythmia	PEA-arrest, due to LVOT-obstruction	No
17	Hypothermia	Pneumothorax	Tension pneumothorax resulting in death	No
18	Hypothermia	Bleeding	Bleeding from femoral artery (PCI), stenting required	No
19	Hypothermia	Arrhythmia	Ventricular arrhythmia, needed CPR	No
20	Hypothermia	Arrhythmia	Hemodynamic instability and VT	No
21	Hypothermia	Bowel ischemia	Bowel ischemia resuting in death	No
22	Hypothermia	Arrhythmia	VT during rewarming (faster than according to protocol), resolved spontaneously	No
23	Hypothermia	Bradycardia	Bradycardia requiring atropine	No
24	Hypothermia	Vascular	Carotid/Jugular fistula as a result of ECCO2-cannulation - stented	No
25	Hypothermia	Vascular	Compartment syndrome needing decompression after ECCO2	No
26	Hypothermia	Tracheal injury	Tracheal injury during intubation	No
27	Hypothermia	Arrhythmia	Re-arrest, WPW syndrome, CPR required	No
28	Hypothermia	Bleeding	Liver bleeding after CPR - rewarming and transfusion	No
29	Hypothermia	Bleeding	Bleeding treated with FFP	No
30	Hypothermia	Coagulopathy	On warfarin with worsening coagulopathy during cooling. No bleeding. Rewarmed.	No
31	Hypothermia	Hypercapnia	Hypercapnia, transported for ECMO	No
32	Hypothermia	Bleeding	Minior intracranial bleed	No
33	Hypothermia	Cervical injury	Cervical fracture with complete medullar injury, resulting in death	No
34	Hypothermia	Bleeding	Massive bleeding during PCI, resulting in death	No
35	Hypothermia	Bleeding	Intracranial bleed, hematoma evacuated in the OR	No
36	Hypothermia	Bleeding	Liver bleeding, coiled by IR. Subsequent liver abscess	No
37	Hypothermia	Bleeding	Hemothorax, drained. Lung suture needed	No
38	Hypothermia	Bleeding	Major bleeding and shock due to rib fractures, intervention discontinued	No
39	Hypothermia	Vascular	Aortic dissection during surgery resulting in death	No
40	Hypothermia	Hemodynamics	Hemodynamic instability and low heart rate, rewarmed	No
41	Hypothermia	Sepsis	Septic shock	No
42	Hypothermia	Bleeding	Liver bleeding after CPR - treated medically	No
43	Hypothermia	Arrhythmia	New VF arrest, CPR performed	No
44	Hypothermia	Bradycardia	Bradycardia with ventricular bigeminy	No
45	Hypothermia	Bradycardia	Bradycardia treated with isoprenaline, intervention discontinued	No
46	Hypothermia	Arrhythmia	New VT-arrest, CPR performed, ROSC 1 min	No
47	Hypothermia	Venous Thromboembolism	Clot seen in IVC. Intravascular device used	Yes

STATEMENT ON DATA SHARING

Deidentified individual participant data collected during the TTM2-trial (and the data dictionary) will be shared beginning two years after article publication with no end date. These data will be available to researchers who provide a methodologically sound proposal for the purposes of achieving specific aims outlined in that proposal. Proposals should be directed to the corresponding author via email: niklas.nielsen@med.lu.se and will be reviewed by the TTM2-trial steering group. Requests to access data to undertake hypothesis-driven research will not be unreasonably withheld. To gain access, data requesters will need to sign a data access agreement and to confirm that data will only be used for the agreed purpose for which access was granted.

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