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Mild therapeutic hypothermia after cardiac arrest – effect on survival with good neurological outcome outside of randomised controlled trials

A registry-based analysis

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BACKGROUND For nearly 20 years, in international guidelines, mild therapeutic hypothermia (MTH) was an important component of postresuscitation care. However, recent randomised controlled trials have questioned its benefits. At present, international guidelines only recommend actively preventing fever, but there are ongoing discussions about whether the majority of cardiac arrest patients could benefit from MTH treatment.

OBJECTIVE The aim of this study was to compare the outcome of adult patients treated with and without MTH after cardiac arrest.

DESIGN Observational cohort study.

SETTING German Resuscitation Registry covering more than 31 million inhabitants of Germany and Austria.

PATIENTS All adult patients between 2006 and 2022 with out-of-hospital or in-hospital cardiac arrest and comatose on admission.

MAIN OUTCOME MEASURES Primary endpoint: hospital discharge with good neurological outcome [cerebral performance categories (CPC) 1 or 2]. Secondary endpoint: hospital discharge. We used a multivariate binary logistic regression analysis to identify the effects on outcome of all known influencing variables.

RESULTS We analysed 33 933 patients (10 034 treated with MTH, 23 899 without MTH). The multivariate regression model revealed that MTH was an independent predictor of CPC 1/2 survival and of hospital discharge with odds ratio (95% confidence intervals) of 1.60 (1.49 to 1.72), $P < 0.001$ and 1.89 (1.76 to 2.02), $P < 0.001$, respectively.

CONCLUSION Our data indicate the existence of a positive association between MTH and a favourable neurological outcome after cardiac arrest. It therefore seems premature to refrain from giving MTH treatment for the entire spectrum of patients after cardiac arrest. Further prospective studies are needed.

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Introduction

Before 2021, the European Resuscitation Council guidelines recommended mild therapeutic hypothermia (MTH) for all adult patients who did not regain consciousness after out-of-hospital or in-hospital cardiovascular arrest and restoration of spontaneous circulation (ROSC).[1] Furthermore, a target temperature of 32°C to 36°C was recommended. However, the results of the second targeted temperature management (TTM) trial, published in 2021, seemed to call into question the neuroprotective effect of MTH.[2] In this trial, 1850 patients were randomised either to receive MTH with a target temperature of 33°C or for normothermia to be targeted if fever occurred (body temperature ≥37.8°C).

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No significant differences were found in survival or good neurological outcomes between the two temperature regimes. In light of this new evidence, the guidelines now recommend only active fever prevention, claiming that there is insufficient evidence either for or against the use of MTH.[3] However, the transferability of the results of the TTM2 study to everyday clinical practice has been widely questioned, given that, for example, the rate of bystander cardiopulmonary resuscitation (CPR) in this trial was 80%,[2,4–6] which unfortunately does not correspond to the reality in most countries.[7,8]

Moreover, it is not only pathophysiology and the results from animal models that suggest that patients with a longer ischaemia time – and thus a higher risk of post-resuscitation syndrome and hypoxic encephalopathy – may be particularly likely to benefit from MTH.[9–11] Several retrospective human studies and two randomised controlled trials also hint that patients with longer no-flow times (>3 min) or indications that they have suffered more severe neuronal or other organ damage (measured, e.g., using electroencephalography, the Sequential Organ Failure Assessment (SOFA) score or lactate value after ROSC, respectively) may benefit from MTH.[12–18] The goal of this study was therefore to compare neurological outcomes between patients treated with MTH and without MTH after cardiovascular arrest based on data from a large multicentre resuscitation registry.

Materials and methods

German resuscitation registry

This study was designed as an observational cohort study of all out-of-hospital (OHCA) and in-hospital cardiac arrests (IHCA) compiled in the GRR between 2006 and 2022. The GRR is a prospective registry, which is maintained by the German Society of Anaesthesiology and Intensive Care Medicine and covers 30 million residents of Germany and 1.2 million residents of Austria, countries with comparable physician-based out-of-hospital emergency healthcare systems.[19] The GRR's design corresponds to the Utstein style.[20] Data entries from out-of-hospital treatment are carried out by EMS physicians or personnel and have to be cleared by the responsible chief medical officer. Intra-hospital data are entered by the responsible attending physician.

Ethics

Only primarily anonymised data were processed and evaluated. As a result, criteria for research on nonhumans were met and the responsible institutional review board (Landesärztekammer Stuttgart) waived the requirement for a specific ethics vote. The study was approved by the scientific advisory council of the GRR.

Inclusion criteria

The analysis was based on 41 628 anonymous data sets of adult patients who eventually achieved a sustained ROSC after in-hospital and out-of-hospital cardiovascular arrest between 2006 and 2022. Only patient data for cases of OHCA with hospitalisation and subsequent admission to the ICU and cases of IHCA with admission to the ICU were included.

Exclusion criteria

The exclusion criteria were age less than 18 years, non-comatose patients, trauma or bleeding as suspected causes of the arrest, and data sets that were incomplete with regard to cerebral performance category (CPC) status at discharge.

Primary and secondary endpoints

Primary endpoint is discharge with a good neurological outcome, defined as CPC 1 or 2. Secondary endpoint is survival at hospital discharge.

Data processing and statistical analysis

After the inclusion and exclusion criteria were applied, baseline data were derived and the patients were divided into an MTH group (treatment with the local MTH protocol after ROSC) and a non-MTH group (no MTH protocol applied). First, a univariate analysis of the outcome data was performed. Then, the entire cohort was analysed using a multivariate logistic regression model for risk adjustment with regard to the primary and secondary endpoints. Our regression analysis included all available variables that have shown a significant effect on outcome after cardiovascular arrest in previous studies. These are, for the most part, included in the ROSC after cardiac arrest (RACA) score and cardiac arrest survival score (CRASS). Both scores were developed using binary logistic regression analysis to predict survival after CPR. The therapeutic variable of interest was the use of MTH. In addition to the variables already used in other studies on cardiovascular arrest and CPR, we included performance of coronary angiography as a variable in our model, which improved the model quality with an increase in the Nagelkerke R^2 from 0.402 to 0.421. We also added the number of patients per hospital included in our analysis as a regression variable as a surrogate parameter for the caseload of cardiovascular arrest patients treated per hospital (see the discussion for the reasons behind this choice). Patient sex and bystander CPR were not sufficiently powerful to warrant inclusion in our model. This resulted in the following multivariate binary logistic regression model:

(1) age with the reference category '≤60 years' tested against higher age groups (61 to 70, 71 to 80, 81 to 90 and >90 years)[21–26];
(2) initial ECG rhythm with the reference category 'ventricular fibrillation/tachycardia' ("VF/VT") tested against pulseless electrical activity (PEA) or asystole;[21,22,24–27]

(3) presumed aetiology of cardiovascular arrest with the reference category 'cardiac and unknown aetiology' ('cardiac/?') tested against near drowning, hypoxia, others or intracranial pathologies, such as stroke, subarachnoid bleeding (SAB) or intracerebral bleeding (ICB);[22,24–27]
(4) use of mechanical chest compression devices ('mechanical CPR'');[24,28]
(5) categories of epinephrine doses as an established surrogate parameter for the duration of CPR with the reference category 'no epinephrine' ('0 mg') tested against six epinephrine dose groups and a group of unknown epinephrine doses, when epinephrine was given during CPR ('Dose?');[22,24,27]
(6) pre-emergency status (PES) – which is used to classify the medical condition of emergency patients before they enter the acute emergency situation – with significant or severe restriction of daily life and unknown PES ('?/relevant disease') as the reference category, tested against PES without previous disease and PES with only minor previous disease (without significant restriction of daily life);[21,22,24,27]
(7) place of cardiovascular arrest with the reference category 'home/others/unknown' tested against 'nursing home', 'workplace/sports/school', 'physician's office', 'public place' or 'IHCA';[21,22,24,25,27,29]
(8) administration of amiodarone;[24]
(9) admission status with admission in shock (defined as SBP $\leq$90 mmHg) or unknown as reference category ('shock/?') vs. admission with ongoing CPR ('with CPR') or admission with SBP more than 90 mmHg ('RRsyst >90 mmHg')[24]
(10) nonwitnessed cardiovascular arrest as the reference category ('not') tested against cardiovascular arrest witnessed by bystanders, first responders and emergency medical service teams ('EMS/rescue teams');[21,22,24–27]
(11) duration of CPR 5 min or less;[24,30]
(12) duration of no-flow time ('Collapse – CPR') with unknown duration and duration 1 min or less as the reference category ('?/0–1 min') tested against 2 to 9 min of no-flow time and at least 10 min;[24]
(13) performance of a coronary angiography;
(14) number of patients per hospital included in our study with 251 to 500 patients/unknown number as the reference category ('251–500/?') tested against 100 patients or less, 101 to 250 patients, and more than 500 patients.

Groups were compared using chi-square (χ^2) or the *t*-test as appropriate and *P* value less than 0.05 was considered statistically significant. Values for parametric data were given as means ± standard deviations. Categorical variables were expressed as percentages and as an odds ratio (OR) with a 95% confidence interval (95% CI). As a measure of explained variation in the regression analysis, Nagelkerke R^2 was used. Data were processed using Excel (Version 2312; Microsoft Corporation, Redmond, Washington, USA) and IBM SPSS Statistics (Version 27.0; IBM Corporation, Armonk, New York, USA).

Results

Descriptive statistics

During the period under examination (2006 to 2022), the analysis of the GRR database revealed a total of 41 269 incidents of cardiovascular arrest, including OHCA (29 741) and IHCA (11 528). After application of the inclusion and exclusion criteria outlined above, 33 933 complete data sets (OHCA: 24 987, IHCA: 8946) were subjected to further analysis (Fig. 1). In this group, 10 034 patients were treated with MTH, while 23 899 did not receive MTH.

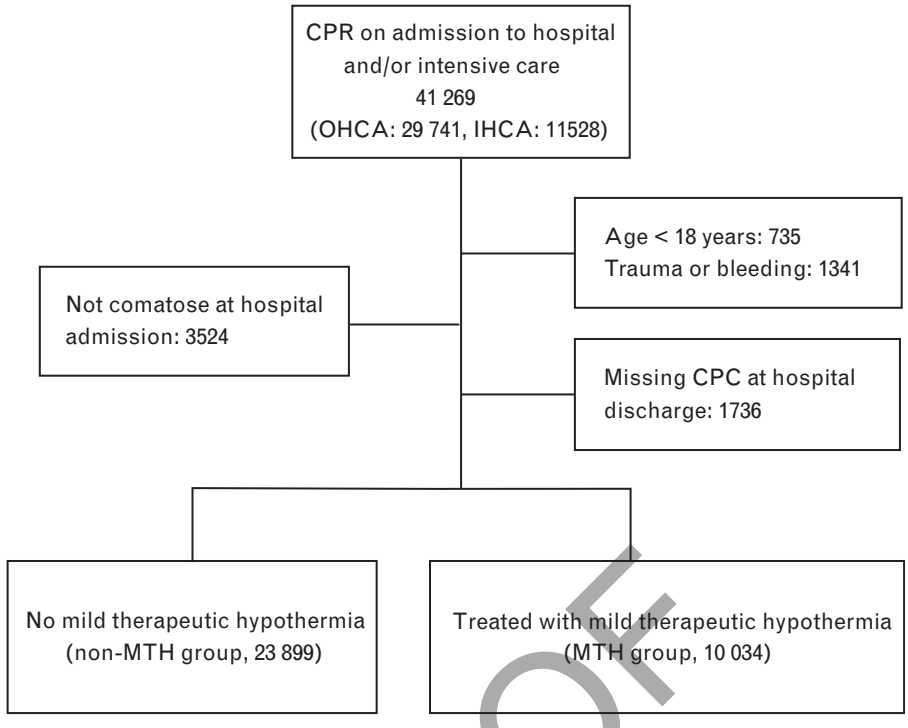
Rates of survival with CPC 1/2 were 33.3% in the MTH group and 14.0% in the non-MTH group ($P < 0.001$), while 30-day survival or hospital discharge rates were 42.3 and 17.3%, respectively ($P < 0.001$). However, the two groups differed significantly in nearly all predictors of outcome (Table 1).

Multivariate regression analysis for risk adjustment

The multivariate logistic regression model applied for the primary endpoint revealed that MTH was an independent predictor of CPC 1/2 survival [OR, 1.60 (1.49 to 1.72), $P < 0.001$, Fig. 2]. The model achieves a value of 0.421 according to Nagelkerke R^2. Further independent predictors for CPC 1/2 in this model were younger age, better PES, witnessed cardiovascular arrest, IHCA, cardiovascular arrest in a doctor's office or in a public place, duration of CPR 5 min or less, SBP more than 90 mmHg on hospital admission, hypoxia as cause of cardiovascular arrest, administration of amiodarone, and ventricular fibrillation (VF) or ventricular tachycardia (VT) as initial rhythm. Performance of a coronary angiography after ROSC was associated with a good neurological outcome with an OR of 2.60 (2.41 to 2.82). A negative correlation with an outcome of CPC 1/2 could be shown for increasing doses of epinephrine, cardiovascular arrest in nursing homes and cardiovascular arrest with intracranial diseases. The use of mechanical chest compression devices, admission with ongoing CPR and the elapse of at least 10 min from collapse to start of CPR were further independent predictors of poor outcome. When we examined the number of patients per hospital, our regression analysis demonstrated that hospitals with 251 to 500 patients treated after cardiovascular arrest and included in our study showed better results than both smaller or larger treatment units (i.e. 1 to 250 or >500 patients).

When the multivariate logistic regression model was applied to the secondary endpoint of hospital discharge, MTH was once again an independent predictor [OR, 1.89 (1.76 to 2.02); Supplementary Fig. 1, http://links.lww.com/EJA/A963]. This model achieves a value of 0.426 according to Nagelkerke R^2.

Fig. 1 Patient selection from the German Resuscitation Registry.



CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; IHCA, in-hospital cardiac arrest; MTH, mild therapeutic hypothermia; OHCA, out-of-hospital cardiac arrest.

Discussion

In this large cohort, which comprised approximately 34 000 patients suffering from out-of-hospital and in-hospital cardiovascular arrest, our data consistently demonstrate a significant association between MTH and good neurological survival (CPC 1/2) following cardiovascular arrest. Furthermore, the hospital discharge rate was significantly higher in patients treated with MTH, proving the robustness of our results. Thus, our results suggest that MTH has a neuroprotective benefit and support the continued use of MTH in patients with coma following successful CPR. This aligns with the findings a current Cochrane analysis,[31] which compared MTH with fever prevention or no cooling in a data set of 2870 patients and found that participants in the MTH group were more likely to survive with CPC 1/2 [risk ratio: 1.60 (95% CI, 1.15 to 2.23)].

The reasons for the divergences between our results based on a registry analysis and the results from the TTM and the TTM2 trial can only be deduced indirectly, and thus any proposed explanations are speculative. However, one possible explanation is that the significantly different bystander resuscitation rates, 41% in this registry study compared to 80% in the TTM2 trial and 73% in the TTM trial. Hence, the latter two trials had correspondingly short median no-flow times of only one min.[2,32] Unfortunately, the bystander resuscitation rate in the two TTM trials do not correspond to the reality as reported in the resuscitation registers. For example, the bystander resuscitation rate is currently only 40 to 50% in Germany, 37% in Italy and 44% in Switzerland.[8] Substantial damage to the brain occurs after several minutes of ischaemia, and bystander resuscitation is one of the most important predictors of a favourable neurological outcome. We can therefore postulate that the neuroprotective effect of MTH is significantly more pronounced in a population with lower bystander resuscitation rates and longer ischaemia times than in populations with very short ischaemia times.[32] Our finding that MTH may have a neuroprotective effect, especially in systems with lower bystander resuscitation rates, also fits well with the results of other major studies on MTH in recent decades with bystander CPR rates of less than 50%, such as the HACA trial [OR 1.4 (1.08 to 1.81)] and the retrospective cohort study by Testori *et al.* [OR 1.49 (1.14 to 1.93)].[12,18]

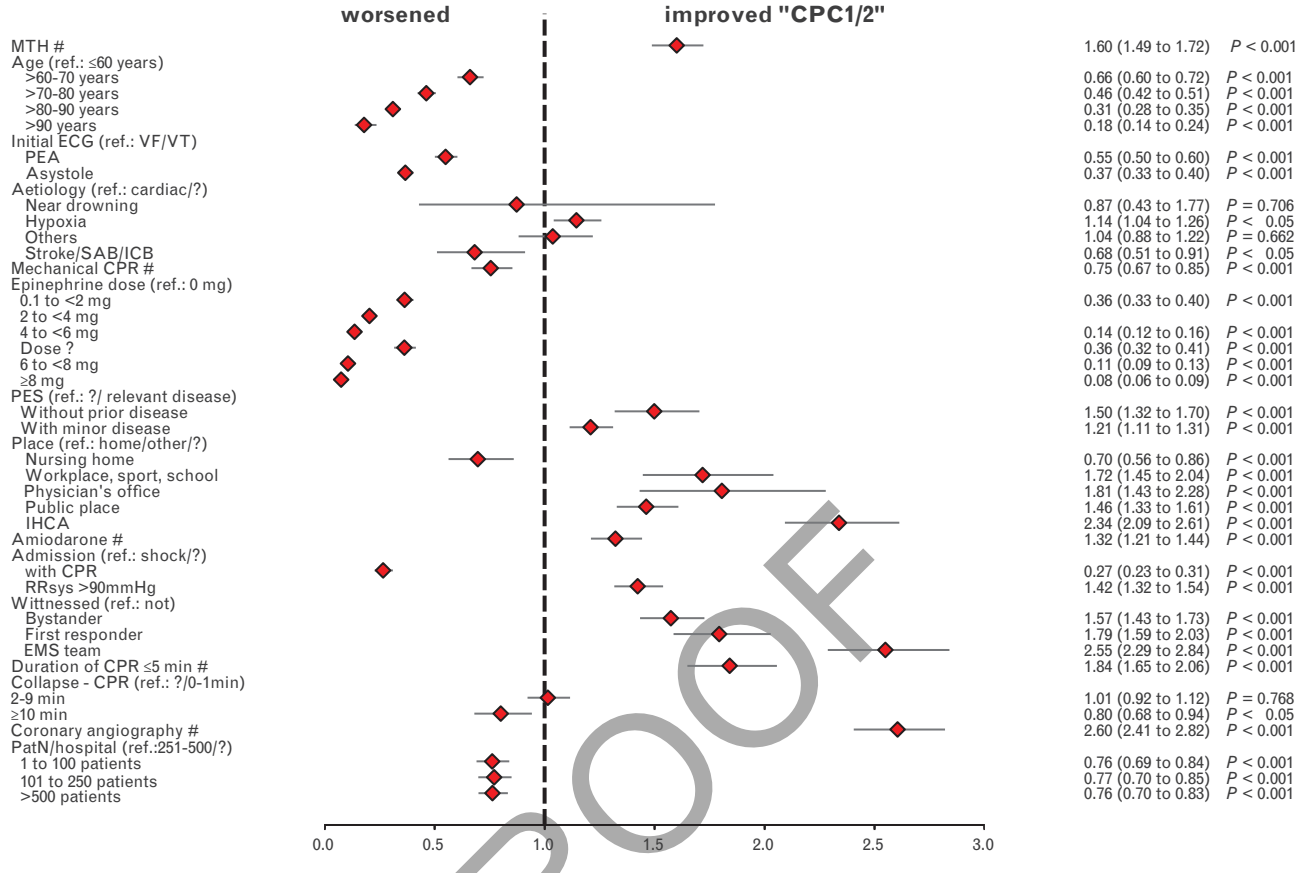
An individual meta-analysis of patient data from the TTM and TTM2 trials also provides strong evidence that patients who do not undergo bystander resuscitation are more likely to benefit from MTH [OR 0.88 (0.79 to 0.99) for poor functional outcome after 6 months]. In contrast, after bystander CPR, the outcome was comparable between patients treated with MTH compared to normothermia [OR 1.07 (0.98 to 1.16)].[33] The results of two other studies point in the same direction. In the first

Table 1 Group comparison of patients treated with MTH versus non-MTH: Univariate analysis of patient characteristics, therapeutic measure and outcome

	All patients $n = 33\,933$	MTH $n = 10\,034$	Non-MTH $n = 23\,899$	P	OR (95% CI)
Outcome data					
ROSC rate	29 208 (86.1)	9572 (95.4)	19 636 (82.2)	< 0.001	4.50 (4.07 to 4.97)
Hospital admission with ROSC	26 333 (77.6)	9177 (91.5)	17 156 (71.8)	< 0.001	4.21 (3.90 to 4.54)
Hospital discharge	8007 (23.6)	4089 (40.8)	3918 (16.4)	< 0.001	3.51 (3.33 to 3.70)
Hospital discharge with CPC 1/2	6698 (19.7)	3343 (33.3)	3355 (14.0)	< 0.001	3.06 (2.89 to 3.23)
Hospital discharge with CPC 3/4	1313 (3.9)	748 (7.5)	565 (2.4)	< 0.001	3.33 (2.97 to 3.72)
Patient characteristics and prehospital therapeutic measures					
Age [years]	68.9 ± 14.5	65.9 ± 14.1	70.2 ± 14.4	< 0.001	
Age groups ≤ 60 years	8708 (25.7)	3240 (32.3)	5469 (22.9)	< 0.001	1.61 (1.53 to 1.69)
60 to ≤ 70 years	7434 (21.9)	2441 (24.3)	4993 (20.9)	< 0.001	1.22 (1.15 to 1.29)
70 to ≤ 80 years	9426 (27.8)	2690 (26.8)	6736 (28.2)	< 0.01	0.93 (0.89 to 0.98)
80 to ≤ 90 years	7204 (21.2)	1548 (15.4)	5656 (23.7)	< 0.001	0.59 (0.55 to 0.63)
> 90 years	1162 (3.4)	116 (1.2)	1046 (4.4)	< 0.001	0.26 (0.21 to 0.31)
First rhythm VF/VT/?	11 402 (33.6)	4890 (48.7)	6512 (27.2)	< 0.001	2.54 (2.42 to 2.66)
First rhythm PEA	9758 (28.8)	2069 (20.6)	7689 (32.2)	< 0.001	0.55 (0.52 to 0.58)
First rhythm asystole	12 773 (37.6)	3075 (30.6)	9698 (40.6)	< 0.001	0.65 (0.62 to 0.68)
Cause: Cardiac/?	25 194 (74.2)	7955 (79.3)	17 239 (72.1)	< 0.001	1.48 (1.40 to 1.56)
Near drowning	148 (0.4)	31 (0.3)	117 (0.5)	< 0.05	0.63 (0.42 to 0.94)
Hypoxia	6537 (19.3)	1606 (16.0)	4931 (20.6)	< 0.001	0.73 (0.69 to 0.78)
Stroke/ICB/SAB	531 (1.6)	85 (0.8)	446 (1.9)	< 0.001	0.45 (0.36 to 0.57)
PES (?/ relevant disease)	23 882 (70.4)	6172 (61.5)	17 710 (74.1)	< 0.001	0.56 (0.53 to 0.59)
Without prior disease	2406 (7.1)	993 (9.9)	1413 (5.9)	< 0.001	1.75 (1.61 to 1.90)
With minor disease	7645 (22.5)	2869 (28.6)	4776 (20.0)	< 0.001	1.60 (1.52 to 1.69)
Place (home/other/?)	16 223 (47.8)	5317 (53.0)	10 906 (45.6)	< 0.001	1.34 (1.28 to 1.41)
Nursing home	1830 (5.4)	337 (3.4)	1493 (6.2)	< 0.001	0.52 (0.46 to 0.59)
Workplace, sport, school	1101 (3.2)	527 (5.3)	574 (2.4)	< 0.001	2.25 (2.00 to 2.54)
Physician's office	574 (1.7)	188 (1.9)	386 (1.6)	0.092	1.16 (0.98 to 1.39)
Public place	5259 (15.5)	1935 (19.3)	3324 (13.9)	< 0.001	1.48 (1.39 to 1.57)
IHCA	8946 (26.4)	1730 (17.2)	7216 (30.2)	< 0.001	0.48 (0.45 to 0.51)
Witnessed: Bystander	14 041 (41.4)	5364 (53.5)	8677 (36.3)	< 0.001	2.01 (1.92 to 2.11)
First responder	4972 (14.7)	949 (9.5)	4023 (16.8)	< 0.001	0.52 (0.48 to 0.56)
EMS team	5712 (16.8)	1169 (11.7)	4543 (19.0)	< 0.001	0.56 (0.52 to 0.60)
Response time [min]	6.36 ± 3.66	6.40 ± 3.64	6.35 ± 3.67	0.316	
No-flow time: collapse to CPR [min]	4.02 ± 5.49	4.56 ± 5.50	3.76 ± 5.47	< 0.001	
Duration of CPR [min]	19.27 ± 14.36	19.19 ± 14.10	19.31 ± 14.49	0.543	
Duration of CPR ≤ 5 min	2230 (6.6)	659 (6.6)	1571 (6.6)	0.984	1.00 (0.91 to 1.10)
Bystander CPR	9689 (34.3)	3652 (41.2)	6037 (31.2)	< 0.001	1.55 (1.47 to 1.63)
First responder CPR	7232 (25.6)	1521 (17.2)	5711 (29.5)	< 0.001	0.49 (0.46 to 0.53)
Telephone CPR	4611 (16.3)	1841 (20.8)	2770 (14.3)	< 0.001	1.57 (1.47 to 1.68)
Epinephrine	27 606 (81.4)	8035 (80.1)	19571 (81.9)	< 0.001	0.89 (0.84 to 0.94)
Amiodarone	8282 (24.4)	3340 (33.3)	4942 (20.7)	< 0.001	1.91 (1.82 to 2.02)
Lysis	1713 (5.0)	385 (3.8)	1328 (5.6)	< 0.001	0.68 (0.60 to 0.76)
Defibrillation	15 137 (44.6)	5989 (59.7)	9148 (38.3)	< 0.001	2.39 (2.28 to 2.50)
Non-EMS defibrillation	973 (2.9)	387 (3.9)	586 (2.5)	< 0.001	1.60 (1.40 to 1.82)
ETI	28 468 (83.9)	8558 (85.3)	19 910 (83.3)	< 0.001	1.16 (1.09 to 1.24)
SGA only	3180 (9.4)	1077 (10.7)	2103 (8.8)	< 0.001	1.25 (1.15 to 1.35)
IV	26 108 (76.9)	8527 (85.0)	17 581 (73.6)	< 0.001	2.03 (1.91 to 2.16)
IO	4105 (12.1)	1152 (11.5)	2953 (12.4)	< 0.05	0.92 (0.86 to 0.99)
Feedback system	5343 (15.7)	1814 (18.1)	3529 (14.8)	< 0.001	1.27 (1.20 to 1.36)
Mechanical CPR	5728 (16.9)	1320 (13.2)	4408 (18.4)	< 0.001	0.67 (0.63 to 0.72)
Hospital admission					
HAd with shock / ?	7966 (23.5)	2275 (22.7)	5691 (23.8)	< 0.05	0.94 (0.89 to 0.99)
HAd with CPR	7600 (22.4)	857 (8.5)	6743 (28.2)	< 0.001	0.24 (0.22 to 0.26)
HAd with RRsys > 90 mmHg	18 367 (54.1)	6902 (68.8)	11 465 (48.0)	< 0.001	2.39 (2.28 to 2.51)
Glasgow Coma Score at admission	3.1 ± 0.5	3.1 ± 0.5	3.1 ± 0.5	< 0.05	0.48 (0.01 to 1.96)
Hospital treatment					
MTH	10 034 (29.6)	10 034 (100.0)	0 (0.0)		
CORO	10 753 (31.7)	6075 (60.5)	4678 (19.6)	< 0.001	6.30 (5.99 to 6.64)
Secondary Complication (sepsis, cerebral ischemia, ICB, severe bleeding, acute renal failure, aspiration, pneumonia, others)	4606 (13.6)	2406 (24.0)	2200 (9.2)	< 0.001	3.11 (2.92 to 3.31)
Treated patients per hospital (?)	1757 (5.2)	564 (5.6)	1193 (5.0)	< 0.05	1.13 (1.02 to 1.26)
1 to 100	7547 (22.2)	1907 (19.0)	5640 (23.6)	< 0.001	0.76 (0.72 to 0.81)
101 to 250	7420 (21.9)	1787 (17.8)	5633 (23.6)	< 0.001	0.70 (0.66 to 0.75)
251 to 500	7177 (21.2)	2447 (24.4)	4730 (19.8)	< 0.001	1.31 (1.24 to 1.38)
> 500	10 032 (29.6)	3329 (33.2)	6703 (28.0)	< 0.001	1.27 (1.21 to 1.34)

Data are mean ± SD, number (%) and odds ratio (95% confidence interval). CI, confidence interval; CORO, coronary angiography; CPC, cerebral performance category; CPR, cardio-pulmonary resuscitation; EMS, emergency medical services; ETI, endotracheal intubation; HAd, hospital admission; ICB, intracerebral bleeding; IHCA, in-hospital cardiac arrest; IO, intra-osseous; IV, intravenous; MTH, mild therapeutic hypothermia; non-MTH, not treated with mild therapeutic hypothermia; OR, odds ratio; PEA, pulseless electrical activity; PES, pre-emergency status; ROSC, returns of spontaneous circulation; RRsys, systolic blood pressure; SAB, subarachnoid bleeding; SGA, supraglottic device.

Fig. 2 Forest plot of the odds ratio with 95% confidence interval of the multivariate binary logistic regression analysis with the endpoint 'CPC 1/2 at discharge'.



($n = 33\,933$; MTH $n = 10\,034$; non-MTH $n = 23\,899$, Nagelkerke $R^2 = 0.421$); on the right side of the image, the odds ratio (95% confidence interval) and *P* value of the regression analysis are listed. #, reference all others; ?, expression unknown; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; ECG, electrocardiogram; EMS, emergency medical service; ICB, intracerebral bleeding; IHCA, in-hospital cardiac arrest; MTH, mild therapeutic hypothermia; PatN/hospital, number of cardiac arrest patients treated per hospital during the study period; PEA, pulseless electrical activity; PES, pre-emergency status; ref., reference category; RRsys, systolic blood pressure; SAB, subarachnoidal bleeding; VF, ventricular fibrillation; VT, venticular tachycardia.

study, 1111 patients from the Japanese resuscitation register were divided into three risk groups according to risk factors for hypoxic encephalopathy (e.g. initial rhythm, witnessed cardiovascular arrest, duration of resuscitation).[16] The temperature regimes chosen were either 33°C to 34°C or 35°C to 36°C. Only patients at medium risk benefited from the lower hypothermia, whereas no difference was observed in patients who were either considered to be at low risk or expected to suffer high harm. Another study, which classified the patients according to the severity of the suspected damage based on the findings of the electroencephalography, points in the same direction.[15] Patients with a reduced pattern of damage usually had a good neurological outcome after six months, irrespective of the selected target temperature. In contrast, patients with moderate encephalopathy who had been treated with a target temperature of 33°C showed a good neurological outcome significantly more frequently compared to study patients in the 36°C group.

After the publication of the TTM trial in 2013, many centres changed TTM from 32°C to 34°C to 36°C.[34,35] This resulted in significantly more patients developing fever within 24 h of arriving in the ICU.[36] A meta-analysis of retrospective data revealed worse neurological outcomes when patients received a 36°C TTM as compared to a 33°C.[37] It is possible that this effect will be even more pronounced with TTM2 and the complete renunciation of hypothermia treatment.

Furthermore, we ought to take into account that, in the context of participation in highly controlled international multicentre studies of MTH, there is likely to be significantly greater vigilance regarding temperature control in study patients than is possible in everyday clinical practice, wherein study conditions are not in place. Moreover, truly consistent fever avoidance (via physical external cooling measures) imposes a continuous workload on nurses that is higher than in machine-guided controlled

MTH (e.g. via an intravascular cooling catheter). This is especially true in view of the fact that in the TTM2 trial 46% of patients ultimately required device-assisted temperature control.

The proportion of patients who were not cooled according to the GRR survey is surprisingly high (69%). This is certainly due not only to a lack of compliance with international guidelines, but above all to the fact that the research situation in relation to MTH has changed several times in recent years. The non-MTH group therefore presumably also includes patients with asystole or PEA who were often not cooled before the HYPERION study[38] was published, patients with IHCA (from the period when the guidelines only recommended low-level cooling for these patients) or, since the publication of TTM2,[2] patients who were only treated according to a normothermia protocol.

Limitations

This retrospective registry analysis can only reveal associations; the ultimate cause of the effect remains unknown. In addition, in a registry study, the possibility of data entry errors and missing data cannot be completely ruled out. However, in developing our model, we followed the systematic approach used in other large registry studies and validated scores for prognosis assessment after severe trauma or OHCA.[24,39–41] Moreover, in our multivariate logistic regression analysis, we considered all known and measurable variables that have been shown to influence outcome after cardiovascular arrest and that could improve our model quality.

We also followed the same approach as earlier registry studies with regard to the handling of missing data: if the percentage of missing values in one variable was low (<10%) and the rate of survival with CPC 1/2 was nearly average, we included those cases in the reference category. Thus, it is not possible for missing values to introduce bias into our regression model. In the case of the variable 'epinephrine dosage', the percentage of missing values reached 7.5%, but since the rate of CPC 1/2 was lower than in the group without epinephrine administration, a separate category was created. The quality of our regression model can be rated as moderate, which corresponds to the quality of similar registry studies on OHCA and CPR.[21,24,39,41]

One bias that we could only take into account indirectly concerns the fact that treatment took place in a university hospital or specialised cardiac arrest centre. It could be argued that, in such centres, treatment bundles (which include, e.g., haemodynamic management and early coronary angiography, in addition to temperature management) are more likely to have been established and to be followed, thus improving the outcome. In order to adjust for this bias insofar as possible, we added the caseload of cardiovascular arrest patients per hospital included in our study to our regression model.

Conclusion

Our data from the GRR show a positive association between MTH and favourable neurological outcome after cardiovascular arrest. It therefore seems premature to refrain from applying MTH to the entire spectrum of patients after CPR. Further prospective studies are needed.

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