Standardized EEG interpretation accurately predicts prognosis after cardiac arrest

Westhall, Erik; Rossetti, Andrea O; van Rootselaar, Anne-Fleur; Wesenberg Kjaer, Troels; Horn, Janneke; Ullén, Susann; Friberg, Hans; Nielsen, Niklas; Rosén, Ingmar; Åneman, Anders; Erlinge, David; Gasche, Yvan; Hassager, Christian; Hovdenes, Jan; Kjaergaard, Jesper; Kuiper, Michael; Pellis, Tommaso; Stammet, Pascal; Wanscher, Michael; Wetterslev, Jørn; Wise, Matt P; Cronberg, Tobias

Standardized EEG interpretation accurately predicts prognosis after cardiac arrest

Erik Westhall, MD

Andrea O. Rossetti, MD, PhD

Anne-Fleur van Rootselaar, MD, PhD

Troels Wesenberg Kjaer, MD, PhD

Janneke Horn, MD, PhD

Susann Ullén, PhD

Hans Friberg, MD, PhD

Niklas Nielsen, MD, PhD

Ingmar Rosén, MD, PhD

Anders Åneman, MD, PhD

David Erlinge, MD, PhD

Yvan Gasche, MD, PhD

Christian Hassager, MD, DMSci

Jan Hovdenes, MD, PhD

Jesper Kjaergaard, MD, DMSci

Michael Kuiper, MD, PhD

Tommaso Pellis, MD

Pascal Stammet, MD

Michael Wanscher, MD, PhD

Jørn Wetterslev, MD, PhD

Matt P. Wise, MD, DPhil

Tobias Cronberg, MD, PhD

On behalf of the TTM-trial investigators

Correspondence to
Dr. Westhall:
erik.westhall@med.lu.se

ABSTRACT

Objective: To identify reliable predictors of outcome in comatose patients after cardiac arrest using a single routine EEG and standardized interpretation according to the terminology proposed by the American Clinical Neurophysiology Society.

Methods: In this cohort study, 4 EEG specialists, blinded to outcome, evaluated prospectively recorded EEGs in the Target Temperature Management trial (TTM trial) that randomized patients to 33°C vs 36°C. Routine EEG was performed in patients still comatose after rewarming. EEGs were classified into highly malignant (suppression, suppression with periodic discharges, burst-suppression), malignant (periodic or rhythmic patterns, pathological or nonreactive background), and benign EEG (absence of malignant features). Poor outcome was defined as best Cerebral Performance Category score 3–5 until 180 days.

Results: Eight TTM sites randomized 202 patients. EEGs were recorded in 103 patients at a median 77 hours after cardiac arrest; 37% had a highly malignant EEG and all had a poor outcome (specificity 100%, sensitivity 50%). Any malignant EEG feature had a low specificity to predict poor prognosis (48%) but if 2 malignant EEG features were present specificity increased to 96% ($p < 0.001$). Specificity and sensitivity were not significantly affected by targeted temperature or sedation. A benign EEG was found in 1% of the patients with a poor outcome.

Conclusions: Highly malignant EEG after rewarming reliably predicted poor outcome in half of patients without false predictions. An isolated finding of a single malignant feature did not predict poor outcome whereas a benign EEG was highly predictive of a good outcome. *Neurology*® 2016;86:1482–1490

GLOSSARY

ACNS = American Clinical Neurophysiology Society; **CPC** = Cerebral Performance Category scale; **CI** = confidence intervals; **SSEP** = somatosensory evoked potentials; **TTM** = Target Temperature Management; **WLST** = withdrawal of life-sustaining therapy.

Out-of-hospital cardiac arrest is common[1] and most patients remain unconscious after restoration of spontaneous circulation. Approximately half of these patients will die during the hospital stay, the majority from hypoxic-ischemic brain injury.[2]

Intensive care is usually continued until a prediction of poor outcome is made, based on clinical neurologic examination, commonly combined with other prognostic tools.[3,4] EEG is the most widely used prognostic tool to support a clinical examination and is accessible in most hospitals[5]; it is recommended for both prognostication and ruling out subclinical seizures.[6,7]

There is no high-level evidence for predicting poor prognosis using EEG and meta-analysis of available data is confounded by the wide variety of classification systems used.[8–10] Other drawbacks of EEG include interrater variability[11,12] and the confounding effects of ongoing or residual sedation.

The American Clinical Neurophysiology Society (ACNS) has proposed a standardized critical care EEG terminology[13] to facilitate multicenter studies and maximize interrater reliability. We used this recently revised terminology to evaluate prospectively recorded EEGs in the Target Temperature Management (TTM) trial, which randomized 950 patients to 33°C vs 36°C controlled temperature after cardiac arrest and reported no differences in mortality or neurocognitive function.[14,15]

Using the ACNS terminology, we defined highly malignant EEG patterns[16] and found substantial interrater and intrarater agreement.[11] The main objective of this study was to evaluate whether the proposed highly malignant EEG patterns reliably predict a poor neurologic outcome for patients who remain in a coma after cardiac arrest. Moreover, we explored the prognostic performance of malignant and benign EEG patterns.[16]

METHODS The TTM trial randomized 950 adult comatose patients resuscitated after out-of-hospital cardiac arrest of presumed cardiac cause from November 2010 to January 2013.

Standard protocol approvals, registrations, and patient consents. The trial protocol[17] was approved by the ethics committees in the participating countries and registered at ClinicalTrials.gov (NCT01020916). Consent was obtained from a legal surrogate and from each patient regaining mental capacity.

Sedation was mandatory during temperature management and tapered at normothermia if not needed for intensive care reasons or treatment of status epilepticus.[17]

A routine EEG was performed during office hours 12–36 hours after rewarming in patients who were still comatose, typically corresponding to 48–72 hours after the cardiac arrest or later if this period coincided with a weekend. The detailed rationale of the present EEG study, including the prespecified hypotheses, was published previously.[16] All 36 intensive care units in Europe and Australia participating in the TTM trial performed routine EEGs.

For this EEG study, we included all patients from sites that had an EEG system allowing EEG data export including notations on reactivity testing. Patients who awoke or died before the recommended time point of EEG were excluded. Sedation, antiepileptic medication, and level of consciousness were documented prospectively.[14,17]

At 72 hours after rewarming, a physician blinded to target temperature, but not to the local EEG report, performed a neurologic evaluation and recommended continuation or withdrawal of life-sustaining therapy (WLST).[17–19] Persisting deep coma (Glasgow Coma Scale: motor 1–2) was a criterion of poor prognosis and allowed WLST if combined with either bilateral loss of somatosensory evoked potentials (SSEP) N20 responses or treatment-refractory status epilepticus.[17] Treatment refractory was defined as unresponsive to propofol, midazolam, or thiopental in combination with at least 1 IV antiepileptic substance for at least 24 hours. In addition, a clinical finding of early status myoclonus, regardless of EEG correlate, in combination with bilateral loss of N20 potentials after rewarming was a criterion of poor prognosis. In patients not fulfilling these criteria, continued active intensive care was protocolized and patients reevaluated daily. The details and rationale of the prognostication algorithm and how WLST was implemented in the trial was published.[14,17–19]

EEGs were retrieved as electronic data format files to a central EEG database and analyzed using the ACNS standardized terminology,[13] independently by 4 EEG specialists (Sweden: E.W., Denmark: T.W.K., The Netherlands: A.-F.v.R., and Switzerland: A.O.R.). The EEG specialists were blinded to all clinical data including outcome and reported EEG findings through a Web-based electronic case report form structured to assure complete data. The EEGs were full-length (>20 minutes) and at least 16 EEG channels were used. Based on the findings regarding periodic or rhythmic patterns, background pattern, and reactivity, the EEGs were classified according to the prespecified hypotheses into the following categories:

1. Highly malignant EEG (figure 1)
   - Suppressed background without discharges
   - Suppressed background with continuous periodic discharges
   - Burst-suppression background with or without discharges
2. Malignant EEG
   - Malignant periodic or rhythmic patterns (abundant periodic discharges; abundant rhythmic polyspike-/spike-/sharp-and-wave; unequivocal electrographic seizure)
   - Malignant background (discontinuous background; low-voltage background; reversed anterior-posterior gradient)
   - Unreactive EEG (absence of background reactivity or only stimulus-induced discharges)
3. Benign EEG (absence of all malignant features stated above)

Surviving patients attended a follow-up 180 days after their cardiac arrest by a blinded assessor.[14] Outcome was dichotomized according to the Cerebral Performance Category scale (CPC).[20] Good neurologic outcome was defined as CPC 1–2 (no or moderate disability) at follow-up or at any time during the hospital stay. Poor outcome was defined as best achieved CPC of 3–5 (severely disabled, comatose, or deceased).

Prognostic ability (specificity, sensitivity) was calculated for the highly malignant patterns (primary hypothesis) and the other prespecified patterns (secondary hypotheses) and is presented as the mode value for the 4 interpreters, i.e., the pattern that 2 or more interpreters have reported, with 95% confidence intervals (CI). If 2 interpreters reported 1 pattern and the other 2 interpreters reported another, the most malignant pattern was assigned.

For comparisons among temperature groups, sedation, and EEG patterns, we applied generalized linear mixed models including interpretations from all 4 EEG specialists.

Statistical analysis was performed using R, version 3.0.2.

RESULTS Eight study sites randomized 202 patients to targeted temperature management at 33°C (n = 103) or 36°C (n = 99). A routine EEG was recorded at a median 77 hours (interquartile range 53–102) after cardiac arrest in 103 patients still comatose after rewarming.

Exclusion and inclusion in the present study is described in figure 2. In 99 of the 202 randomized patients, 69 of whom awoke and 22 died before the recommended time point of prognostication, EEGs were not performed.
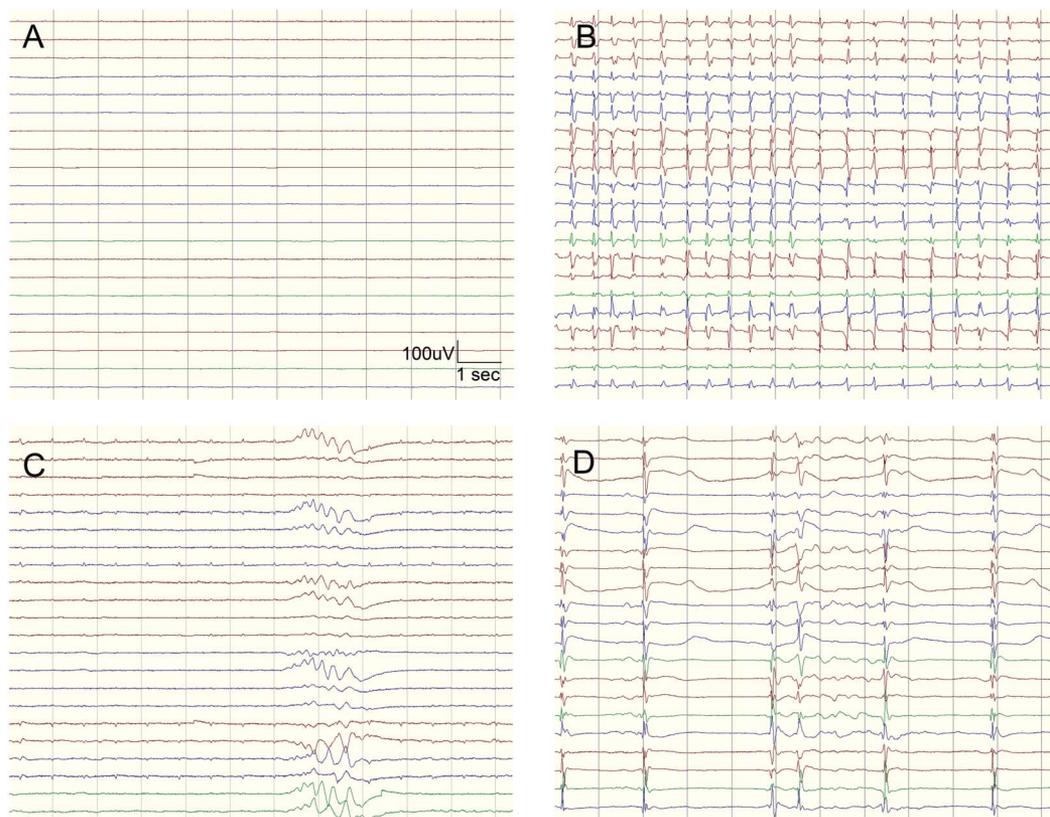
Highly malignant patterns used in the study defined according to the standardized EEG terminology by the American Clinical Neurophysiology Society. (A) Suppressed background (amplitude <10 μV, 100% of the recording) without discharges. (B) Suppressed background with superimposed continuous periodic discharges. (C) Burst-suppression (periods of suppression with amplitude <10 μV constituting >50% of the recording) without discharges. (D) Burst-suppression with superimposed discharges.

Eight patients with prolonged coma (>5 days) did not have an EEG. One of these was brain dead and 2 had absent N20 potentials. In the remaining 5 patients, the reason for missing EEG was unclear. Two of these patients did not have WLST and eventually recovered to CPC 3, 1 died on day 5 of cerebral cause without WLST, 1 died on day 6 due to multiorgan failure without WLST, and 1 died on day 5 of cerebral cause after WLST.

The patients' characteristics are presented in table 1. Patients with EEG were more likely to have a poor outcome.

Characteristics of the patients on the day of EEG registration are presented in table 2. At this time point the majority were deeply comatose. Clinical seizures occurred during the EEG recording in 16%, mostly myoclonus, and 35% of patients had antiepileptic treatment.

Highly malignant EEG. The prognostic ability of the highly malignant patterns is presented in table 3 (primary hypotheses). A highly malignant pattern was reported by the majority of the 4 interpreters (mode value) in 38 patients (37%) and all had a poor neurologic outcome. The sensitivity for a highly malignant pattern to predict a poor outcome was 50% (mode value). Sensitivity varied among the 4 interpreters but specificity was 100% for all individual interpreters (table e-1 on the *Neurology®* Web site at Neurology.org).

Malignant EEG. The prognostic ability of the malignant features is presented in table 3. A malignant EEG, defined as presence of at least one malignant feature and thus also including the highly malignant patterns, was reported in 89 patients (86%). The sensitivity to predict a poor outcome was 99% with a specificity of 48% (mode values). Sensitivity and specificity varied considerably among the 4 interpreters (table e-1). Regarding the subcategories of malignant features, any malignant periodic or rhythmic pattern showed a higher specificity (100%) to predict a poor outcome compared to any malignant background pattern (74%) or a nonreactive EEG (70%). An isolated finding of a single malignant feature occurred in 30 patients, 17 of whom had a good outcome.

If at least 2 of the 3 malignant subcategories were present in the same EEG, the specificity to predict a

Figure 2   Study flow chart of exclusion from and inclusion into the study
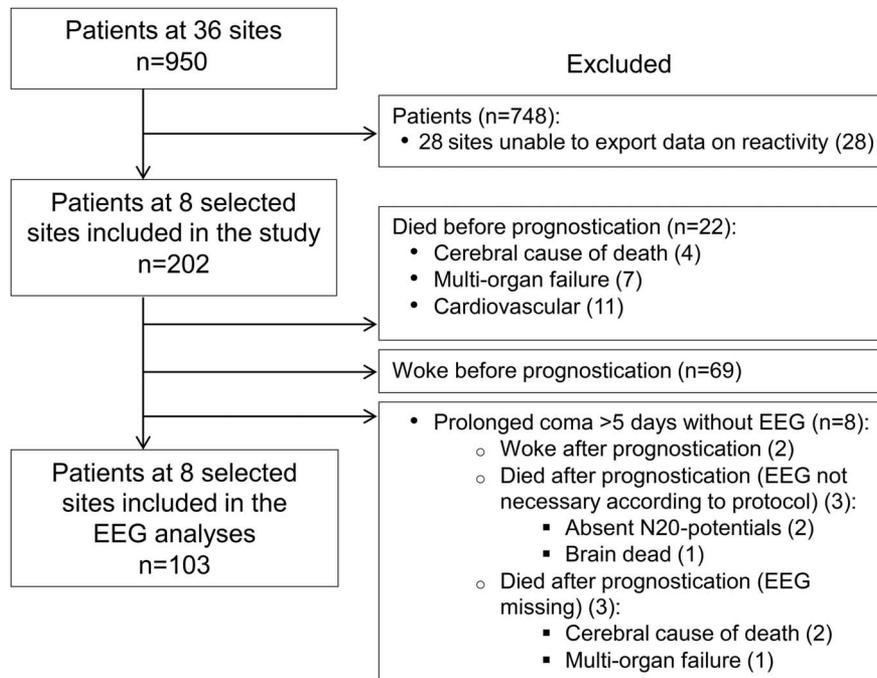
The recommended time point of prognostication was 72 hours after rewarming, corresponding to approximately 108 hours after the cardiac arrest. The most probable cause of death according to the treating physician is reported (cerebral, multi-organ failure, or cardiovascular). Eight study sites were included since they had an EEG system that allowed export of EEG data that included notations regarding testing of reactivity.

poor outcome increased significantly to 96% ($p <$ 0.001), while sensitivity decreased to 76% ($p < 0.001$).

Benign EEG. Fourteen patients (14%) had a benign EEG, defined as a lack of all malignant features. Of these, 13 (93%) had a good outcome. A benign EEG was found in 1% (95% CI 0%–7%) of the 76 patients with a poor outcome and in 48% (95% CI 31%–66%) of the 27 patients with a good outcome.

Eight patients (8%) had a benign and reactive EEG, defined as absence of all malignant features and presence of reactivity to either sound or pain stimuli, and none of these patients had a poor outcome. A benign and reactive EEG was found in none (95% CI 0%–5%) of the patients with a poor outcome and in 30% (95% CI 16%–49%) of the patients with a good outcome.

The ability for a benign EEG to predict good outcome did not significantly differ compared to that of a benign and reactive EEG ($p = 0.08$) in this small sample size.

Level of target temperature management. There were no significant differences between patients treated with 33°C compared to 36°C regarding prevalence or prognostic ability of highly malignant EEG (prevalence $p = 0.58$; sensitivity $p = 0.58$; specificity $p = $ not applicable) or malignant EEG

(prevalence $p = 0.17$; sensitivity $p = 0.64$; specificity $p = 0.81$).

Sedation. Ongoing or residual sedation affected the level of consciousness in 56% of the patients on the day of the routine EEG, according to the treating physician. In 36%, sedation was ongoing during recording of the EEG. There were no significant differences regarding prognostic ability of highly malignant EEG (sensitivity $p = 0.81$; specificity $p = $ not applicable) or malignant EEG (sensitivity $p = 0.44$; specificity $p = 0.21$) between patients with ongoing sedation and those without ongoing sedation.

DISCUSSION EEG is a standard investigation to assess prognosis after cardiac arrest, but its reliability may be limited by lack of consensus on definitions of malignant patterns[8–10] and by interrater variability.[11,12] We found that the proposed highly malignant EEG patterns reliably predicted a poor outcome in our cohort of comatose post–cardiac arrest patients. These patterns were previously found to have substantial interrater and intrarater reliability[11] and the sensitivity to detect patients with poor prognosis was 50%, exceeding that of SSEP and absent ocular reflexes.[19] Since routine EEG is a generally available, noninvasive examination, these findings, if verified in a different cohort, may enhance the safe use of EEG as a key

Table 1   **Patient characteristics**

	EEG performed (n = 103)	All patients (n = 202)
Age, y, mean ± SD	67 ± 10	67 ± 11
Male, n (%)	80 (78)	160 (79)
Comorbidities before randomization, n (%)		
Ischemic heart disease	32 (31)	53 (26)
Arterial hypertension	57 (55)	92 (46)
Previous transient ischemic attack or stroke	11 (11)	18 (9)
Diabetes mellitus	17 (17)	35 (17)
Asthma or chronic obstructive pulmonary disease	12 (12)	20 (10)
Epilepsy	1 (1)	2 (1)
Malignancy	2 (2)	2 (1)
Pre-cardiac arrest CPC 1[a]	96 (93)	187 (93)
Pre-cardiac arrest CPC 2	7 (7)	14 (7)
Cardiac arrest-related variables		
Bystander witnessed cardiac arrest, n (%)	96 (93)	181 (90)
Shockable first rhythm,[b] n (%)	74 (72)	151 (75)
Time to return of spontaneous circulation,[c] min, median (IQR)	30 (21-45)	26 (18-43)
Admission variables, n (%)		
Glasgow Coma Scale (motor), median (IQR)	1 (1-2)	1 (1-3)
Seizures before cardiac arrest	1 (1)	5 (2)
Seizures after resuscitation	3 (3)	5 (2)
Randomized to TTM 33°C, n (%)	52 (50)	103 (51)
Outcome		
Poor neurologic outcome,[d] n (%)	76 (74)	109 (54)

Abbreviations: CPC = Cerebral Performance Category scale; IQR = interquartile range; TTM = Target Temperature Management.

[a] Pre-cardiac arrest CPC was unknown for one patient.

[b] Ventricular fibrillation, nonperfusing ventricular tachycardia, or unknown rhythm responsive to shock.

[c] For unwitnessed arrests, time intervals were calculated from emergency call to event.

[d] Best CPC 3-5 during hospital stay or at follow-up 180 days after the cardiac arrest.

component in decisions on continuation or withdrawal of life-sustaining therapy. Nevertheless, it is strongly advisable to combine the EEG findings with other tests to perform a multimodal prognostication.[7]

Standardization of EEG interpretation is critical for reproducibility of clinical studies, meta-analyses, and application of these results into everyday clinical practice. Therefore, the use of an international well-defined terminology, such as the ACNS EEG terminology, is strongly recommended.

The highly malignant patterns used in this study were strictly defined according to the ACNS EEG terminology and adhere closely to previously described malignant patterns.[8–10]

Our secondary hypothesis that a malignant EEG should nearly always be associated with a poor outcome[16] was discarded due to lack of specificity and considerable variability between interpreters. Our results therefore discourage the use of isolated findings

of a malignant feature in decisions on WLST. Combination of at least 2 malignant features from diverse malignant subcategories significantly increased the specificity to 96%, indicating that such combinations, if confirmed in another cohort, may be of use to predict a poor prognosis.

Low-voltage background (most background activity <20 μV) was a common pattern with several false-positive predictions, in contrast to the highly malignant pattern of suppressed background (all background activity <10 μV), which had a specificity of 100% for predicting poor outcome. This is of considerable importance since 20 μV has been used as a limit of the background voltage for predicting a poor outcome.[8–10,21,22]

Our results highlight that the degree of discontinuity is an important predictor of prognosis. A discontinuous background (suppression periods constituting 10%–49%) resulted in some false-positives (for 2 individual interpreters) while a burst-suppression

Table 2	Patient characteristics on the day of EEG recording (n = 103)	
		Values
Time to EEG, hours after cardiac arrest, median (IQR)		77 (53-102)
Variables on day of EEG		
GCS motor, median (IQR)[a]		2 (1-3)
Myoclonic seizures, n (%)		31 (30)
Tonic/clonic seizures, n (%)		9 (9)
Variables during EEG, n (%)		
Ongoing clinical seizures		16 (16)
Myoclonic seizures		10 (10)
Tonic/clonic seizures		1 (1)
Ongoing sedation		37 (36)
Propofol		26 (25)
Midazolam		7 (7)
Pentothal/thiopental		0 (0)
Other (clonidine, ketobemidone, fentanyl, remifentanil)		16 (16)
Ongoing antiepileptic medication		36 (35)
Monotherapy		27 (26)
Combinations		9 (9)

Abbreviations: GCS = Glasgow Coma Scale; IQR = interquartile range.
[a] Patients not assessable due to sedation were excluded.

background (suppression periods constituting 50%–99%) was a reliable predictor of poor prognosis for all 4 interpreters. This is in concordance with a recent retrospective single-center study using the same standardized ACNS terminology that found a zero false-positive rate for burst-suppression to predict a poor outcome.[22] However, that study also reported no false-positives for a low-voltage background 24 hours after cardiac arrest or later, which was not the case in our study using 4 interpreters from different centers.

A proposed malignant pattern is the alpha-theta coma pattern,[23–25] which has a nonreactive background with a reversed anterior-posterior gradient (pathologic distribution of the background activity). A reversed anterior-posterior gradient could per se not reliably predict a poor outcome in our study.

There is no consensus on the definition of postanoxic electrographic seizure activity, but several investigators using different definitions have shown a strong correlation to poor outcome.[26–30] All 5 patients who had unequivocal electrographic seizure activity during the limited time period of the routine EEG had a poor outcome in this study. In contrast, abundant periodic discharges were not inevitably associated with a poor outcome for the individual interpreters (table e-1), but no patients with periodic discharges on a suppressed background (<10 μV) according to any interpreter had a good outcome.

The treatment of epileptiform activity was not defined in the protocol and not included in the intervention of this trial. Whether patients with electrographic status epilepticus may benefit from antiepileptic medication is unclear and currently addressed in a separate randomized trial.[31] Since continuous EEG monitoring was not available in most centers of this study, it is likely that some patients with intermittent electrographic seizures were missed.

It is well-known that EEG activity is affected by sedation[32] and in sufficient doses it may cause burst-suppression, but whether sedation in clinically used doses affects the prognostic value of malignant EEG patterns is unknown. Lacking detailed data on the amount of sedation used, we found that the majority of patients were still considered affected by sedation by the reporting physician at the time of EEG, which is close to the recommended time point for neurologic prognostication in recent guidelines.[7] However, the predictive ability of our malignant patterns was not significantly affected by ongoing sedation.

Background reactivity was previously found to have strong prognostic implications in several single-center studies.[23,33–35] We found only fair interrater agreement for this variable among our 4 interpreters.[11] It is therefore not surprising that the specificity for an unreactive EEG varied considerably among our interpreters. False predictions of a poor outcome ranged from none to the majority of patients among the interpreters. This might reflect different traditions in assessing reactivity in different centers, since the interpreter who had the highest specificity also had the lowest sensitivity and vice versa. A more conservative approach when stating absence of reactivity by the former interpreter compared to the latter may partly explain the differences. More strict definitions, standardized stimuli, video recordings, bedside assessments, use of muscle relaxants, or quantitative measurements[36] could possibly improve agreement and specificity. Awareness of the limitations of reactivity as a prognostic tool is important.

We termed EEGs that lacked any malignant features as benign, according to our prespecified definitions. The proportion of patients with a poor outcome who had a benign EEG was very low (1%), which is an important finding since few markers indicating a good prognosis are available. However, it is important to recognize that many patients with good outcome lacked a benign EEG due to presence of some malignant EEG features and that the definition of good outcome includes a significant proportion of patients with mild cognitive impairment.[37]

An important limitation of our study is that the local EEG report was available at the neurologic evaluation. Although treatment-refractory postanoxic status

Table 3 Ability of highly malignant and malignant patterns to predict poor outcome

EEG patterns	No. (%) (n = 103)	Sensitivity	Specificity	True-positive	False-positive	True-negative	False-negative
≥1 highly malignant pattern[a]	38 (37)	50 (39–61)	100 (88–100)	38	0	27	38
Suppressed background without discharges	19 (18)	25 (17–36)	100 (88–100)	19	0	27	57
Suppressed background with continuous PDs	4 (4)	5 (2–13)	100 (88–100)	4	0	27	72
Burst-suppression (suppression >50%)	15 (15)	20 (12–30)	100 (88–100)	15	0	27	61
≥1 malignant feature[b]	89 (86)	99 (93–100)	48 (31–66)	75	14	13	1
≥2 malignant features[c]	59 (57)	76 (66–85)	96 (82–99)	58	1	26	18
Malignant periodic or rhythmic pattern	33 (32)	43 (33–55)	100 (88–100)	33	0	27	43
Abundant PDs	30 (29)	40 (29–51)	100 (88–100)	30	0	27	46
Abundant rhythmic spike-and-wave	4 (4)	5 (2–13)	100 (88–100)	4	0	27	72
Unequivocal seizure	5 (5)	7 (3–15)	100 (88–100)	5	0	27	71
Malignant background	69 (67)	82 (71–89)	74 (55–87)	62	7	20	14
Discontinuous (suppression >10%)	43 (42)	57 (45–67)	100 (88–100)	43	0	27	33
Low-voltage	52 (50)	65 (53–74)	89 (72–96)	49	3	24	27
Reversed anterior-posterior gradient	12 (12)	13 (7–23)	93 (77–98)	10	2	25	66
Unreactive EEG[d]	65 (63)	88 (78–94)	70 (48–86)	59	6	14	8

Abbreviation: PD = periodic discharge.
Sensitivity and specificity presented as mode values of the 4 interpreters with 95% confidence intervals. True-positives = tested pattern is present and outcome is poor; false-positives = tested pattern is present and outcome is good; true-negatives = tested pattern is absent and outcome is good; false-negatives = tested pattern is absent and outcome is poor.
[a] Suppressed background without discharges; suppressed background with continuous periodic discharges; burst-suppression.
[b] Abundant periodic discharges; abundant rhythmic spike-and-wave; unequivocal seizure; discontinuous background; low-voltage background; reversed anterior-posterior gradient; unreactive EEG.
[c] From different malignant subcategories (malignant periodic or rhythmic patterns; malignant background; unreactive EEG) present in the same EEG.
[d] Reactivity for both pain and sound stimuli was tested in 87 patients.

epilepticus was the only EEG criterion that justified withdrawal of treatment according to the TTM trial protocol,[17] other EEG features in the local EEG report may have had influence, causing a self-fulfilling prophecy. Importantly, all 4 EEG readers in this study were blinded to outcome and all clinical data.

Another limitation is that our EEG investigations are limited to patients who failed to wake up when the active temperature control phase was over. Thus we lack data on spontaneously awakening patients, but we hypothesize that the occurrence of malignant EEG patterns would be highly unlikely in awake patients. Exclusion of early awakening patients with favorable prognosis[38] explains the worse prognosis among patients with EEG recordings in our study. Yet this cohort is likely to be representative of comatose patients eligible for an EEG for prognostication after cardiac arrest.

The power of the study is limited by the exclusion of sites that could not export EEG data of reactivity. This selection of centers allows for homogenous high-quality data and the possibility to confirm findings, apart from reactivity, in the remaining cohort. We recruited our EEG specialists from different countries and centers without prior collaboration, which

would increase the generalizability of our results. We recognize that all 4 EEG readers are specialists in clinical neurophysiology with 10–14 years of experience in reading EEGs and that we cannot conclude on the transferability of our results to less experienced readers.

All EEGs were performed after rewarming and the majority within 2–4 days after the cardiac arrest and we stress that our results are representative for this time period only. It has previously been shown that some of our malignant patterns can occur during the early phase after resuscitation and ongoing target temperature management among survivors with good outcome.[26,39]

A highly malignant EEG pattern, defined according to the standardized ACNS EEG terminology, predicted poor outcome in half of patients who remained in a coma after rewarming without false-positives. If replicated in a larger cohort, ideally with blinding of the EEGs to the treating physician, these patterns are promising candidates to be included in a multimodal prognostication algorithm. On the other hand, an isolated finding of a single malignant feature could not be used to predict poor outcome. For these patients, prognostication must rely on other methods. A benign EEG was conversely highly predictive of a

good functional outcome. Neither the level of temperature management nor ongoing sedation in clinically used doses significantly affected the prognostic ability of these patterns.

AUTHOR AFFILIATIONS

Divisions of Clinical Neurophysiology (E.W., I.R.), Intensive and Perioperative Care (H.F.), and Neurology (T.C.), Department of Clinical Sciences, Lund University, Sweden; Department of Neurology (A.O.R.), CHUV and University of Lausanne, Switzerland; Departments of Neurology/Clinical Neurophysiology (A.-F.v.R.) and Intensive Care Medicine (J. Horn), Academic Medical Center, University of Amsterdam, the Netherlands; Neurophysiology Center (T.W.K.), Roskilde University Hospital, Roskilde, Denmark; R&D Centre Skane (S.U.), Skane University Hospital, Lund; Department of Anaesthesia and Intensive Care (N.N.), Intensive Care Unit, Helsingborg Hospital, Sweden; Department of Intensive Care (A.Å.), Liverpool Hospital, Sydney, New South Wales, Australia; Department of Clinical Sciences (D.E.), Lund University, Sweden; Department of Anesthesiology, Pharmacology and Intensive Care (Y.G.), Geneva University Hospital, Switzerland; Departments of Cardiology (C.H., J.K.) and Cardiothoracic Anesthesiology (M.W.), The Heart Centre, and Copenhagen Trial Unit, Centre of Clinical Intervention Research (J.W.), Copenhagen University Hospital Rigshospitalet, Denmark; Department of Anesthesiology (J. Hovdenes), Oslo University Hospital, Rikshospitalet, Norway; Department of Intensive Care, Medical Center Leeuwarden (M.K.), the Netherlands; Intensive Care Unit (T.P.), Santa Maria degli Angeli, Pordenone, Italy; Department of Anesthesiology and Intensive Care (P.S.), Centre Hospitalier de Luxembourg; and Adult Critical Care (M.P.W.), University Hospital of Wales, Cardiff, UK.

AUTHOR CONTRIBUTIONS

E.W., I.R., A.O.R., A.-F.v.R., T.W.K., J.Horn, N.N., and T.C. are members of the EEG group of the TTM trial. E.W., I.R., A.O.R., A.-F.v.R., T.W.K., and T.C. designed the EEG analyses. S.U. is the statistician of the EEG analyses. E.W., A.O.R., A.-F.v.R., and T.W.K. performed the EEG interpretations. In the TTM trial: N.N. is principal investigator; H.F. is senior investigator; N.N., H.F., T.C., J.Horn, A.Å., D.E., Y.G., C.H., J.Hovdenes, J.K., M.K., T.P., P.S., M.W., J.W. and M.P.W. are members of the steering group. E.W. and T.C. drafted the manuscript, which was critically revised for intellectual content and finally approved by all coauthors.

DISCLOSURE

E. Westhall receives academic support from the County Council of Skåne. A. Rossetti receives support by the Swiss National Research Foundation (CR32I3_143780) and received research support from UCB Pharma and SAGE Pharmaceuticals. A. van Rootselaar reports no disclosures. T. Wesenberg Kjaer is principal investigator in trials with Widex A/S and has received honoraria from Eisai and UCB Pharma for lectures. J. Horn receives government research support (ZonMw no. 92003586) and support from the Dutch Heart Foundation (no. 2007B039) and serves on the scientific advisory board of Bard Medical. S. Ullén reports no disclosures. H. Friberg receives support from the Swedish National Health System (ALF), serves as European editor of *Therapeutic Hypothermia and Temperature Management*, is a member of the editorial board of *Resuscitation*, and has received honoraria for lectures from Bard Medical and Natus Inc. N. Nielsen receives support from the Swedish National Health System (ALF). I. Rosén and A. Åneman report no disclosures. D. Erlinge has received minor speaker fees or advisory board compensation from ZOLL, AstraZeneca, and Lilly. Y. Gasche reports no disclosures. C. Hassager receives grant support from the Interreg IVA ØKS program; honorarium for lectures from AstraZeneca, Teva, Novartis, and ViCare Medical; and travel support to congresses from Novartis. J. Hovdenes, J. Kjaergaard, and M. Kuiper report no disclosures. T. Pellis has received speakers honorarium from Bard Medical. P. Stammet and M. Wanscher report no disclosures. J. Wetterslev's institution, Copenhagen Trial Unit (CTU), received an unrestricted grant from TRYGFONDEN in Denmark for involvement in the TTM Trial. M. Wise was funded 40% WTE during the study by a National Institute for Social Care and Health Research (NISCHR) Academic Health Science Collaboration (AHSC) Clinical Research Fellowship; received travel costs from the British Thoracic Society, Intensive Care Society, Scottish Intensive Care Society, and Orion Ltd.; received royalties from Wiley Publishing; received honorarium for lecturing at educational meetings from Fisher & Paykel and Merck; serves on the advisory board for Kalobius Pharmaceuticals, Bard; and is Editor of *BMJ Open Respiratory Research*. T. Cronberg receives academic support from the County Council of Skåne. Go to Neurology.org for full disclosures.

REFERENCES

1. Atwood C, Eisenberg MS, Herlitz J, Rea TD. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. Resuscitation 2005;67:75–80.
2. Dragancea I, Rundgren M, Englund E, Friberg H, Cronberg T. The influence of induced hypothermia and delayed prognostication on the mode of death after cardiac arrest. Resuscitation 2013;84:337–342.
3. Samaniego EA, Persoon S, Wijman CA. Prognosis after cardiac arrest and hypothermia: a new paradigm. Curr Neurol Neurosci Rep 2011;11:111–119.
4. Oddo M, Rossetti AO. Predicting neurological outcome after cardiac arrest. Curr Opin Crit Care 2011;17:254–259.
5. Friberg H, Cronberg T, Dunser MW, Duranteau J, Horn J, Oddo M. Survey on current practices for neurological prognostication after cardiac arrest. Resuscitation 2015;90:158–162.
6. Deakin CD, Nolan JP, Soar J, et al. European Resuscitation Council guidelines for resuscitation 2010 Section 4: adult advanced life support. Resuscitation 2010;81:1305–1352.
7. Sandroni C, Cariou A, Cavallaro F, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. Intensive Care Med 2014;40:1816–1831.
8. Wijdicks EF, Hijdra A, Young GB, Bassetti CL, Wiebe S. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2006;67:203–210.
9. Sandroni C, Cavallaro F, Callaway CW, et al. Predictors of poor neurological outcome in adult comatose survivors of

cardiac arrest: a systematic review and meta-analysis: part 2: patients treated with therapeutic hypothermia. Resuscitation 2013;84:1324–1338.

10. Sandroni C, Cavallaro F, Callaway CW, et al. Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: a systematic review and meta-analysis: part 1: patients not treated with therapeutic hypothermia. Resuscitation 2013;84:1310–1323.

11. Westhall E, Rosen I, Rossetti AO, et al. Interrater variability of EEG interpretation in comatose cardiac arrest patients. Clin Neurophysiol 2015;126:2397–2404.

12. Gaspard N, Hirsch LJ, LaRoche SM, Hahn CD, Westover MB, Critical care EEGMRC: interrater agreement for critical care EEG terminology. Epilepsia 2014; 55:1366–1373.

13. Hirsch LJ, LaRoche SM, Gaspard N, et al. American clinical neurophysiology Society's standardized critical care EEG terminology: 2012 version. J Clin Neurophysiol 2013;30:1–27.

14. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. N Engl J Med 2013;369: 2197–2206.

15. Cronberg T, Lilja G, Horn J, et al. Neurologic function and health-related quality of life in patients following targeted temperature management at 33°C vs 36°C after out-of-hospital cardiac arrest: a randomized clinical trial. JAMA Neurol 2015;72:634–641.

16. Westhall E, Rosen I, Rossetti AO, et al. Electroencephalography (EEG) for neurological prognostication after cardiac arrest and targeted temperature management: rationale and study design. BMC Neurol 2014;14:159.

17. Nielsen N, Wetterslev J, Al-Subaie N, et al. Target temperature management after out-of-hospital cardiac arrest: a randomized, parallel-group, assessor-blinded clinical trial: rationale and design. Am Heart J 2012; 163:541–548.

18. Cronberg T, Horn J, Kuiper MA, Friberg H, Nielsen N. A structured approach to neurologic prognostication in clinical cardiac arrest trials. Scand J Trauma Resusc Emerg Med 2013;21:45.

19. Dragancea I, Horn J, Kuiper M, et al. Neurological prognostication after cardiac arrest and targeted temperature management 33 degrees C versus 36 degrees C: results from a randomised controlled clinical trial. Resuscitation 2015;93:164–170.

20. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1975;1:480–484.

21. Hofmeijer J, Beernink TM, Bosch FH, Beishuizen A, Tjepkema-Cloostermans MC, van Putten MJ. Early EEG contributes to multimodal outcome prediction of postanoxic coma. Neurology 2015;85:137–143.

22. Sivaraju A, Gilmore EJ, Wira CR, et al. Prognostication of post-cardiac arrest coma: early clinical and electroencephalographic predictors of outcome. Intensive Care Med 2015;41:1264–1272.

23. Crepeau AZ, Rabinstein AA, Fugate JE, et al. Continuous EEG in therapeutic hypothermia after cardiac arrest: prognostic and clinical value. Neurology 2013;80:339–344.

24. Grindal AB, Suter C, Martinez AJ. Alpha-pattern coma: 24 cases with 9 survivors. Ann Neurol 1977;1:371–377.

25. Kaplan PW, Genoud D, Ho TW, Jallon P. Etiology, neurologic correlations, and prognosis in alpha coma. Clin Neurophysiol 1999;110:205–213.

26. Rundgren M, Westhall E, Cronberg T, Rosen I, Friberg H. Continuous amplitude-integrated electroencephalogram predicts outcome in hypothermia-treated cardiac arrest patients. Crit Care Med 2010;38:1838–1844.

27. Rundgren M, Rosen I, Friberg H. Amplitude-integrated EEG (aEEG) predicts outcome after cardiac arrest and induced hypothermia. Intensive Care Med 2006;32:836–842.

28. Rossetti AO, Logroscino G, Liaudet L, et al. Status epilepticus: an independent outcome predictor after cerebral anoxia. Neurology 2007;69:255–260.

29. Rossetti AO, Oddo M, Liaudet L, Kaplan PW. Predictors of awakening from postanoxic status epilepticus after therapeutic hypothermia. Neurology 2009;72:744–749.

30. Legriel S, Bruneel F, Sediri H, et al. Early EEG monitoring for detecting postanoxic status epilepticus during therapeutic hypothermia: a pilot study. Neurocrit Care 2009;11:338–344.

31. Ruijter BJ, van Putten MJ, Horn J, et al. Treatment of electroencephalographic status epilepticus after cardiopulmonary resuscitation (TELSTAR): study protocol for a randomized controlled trial. Trials 2014;15:433.

32. Sessler CN, Grap MJ, Ramsay MA. Evaluating and monitoring analgesia and sedation in the intensive care unit. Crit Care 2008;12(suppl 3):S2.

33. Rossetti AO, Oddo M, Logroscino G, Kaplan PW. Prognostication after cardiac arrest and hypothermia: a prospective study. Ann Neurol 2010;67:301–307.

34. Rossetti AO, Carrera E, Oddo M. Early EEG correlates of neuronal injury after brain anoxia. Neurology 2012;78: 796–802.

35. Oddo M, Rossetti AO. Early multimodal outcome prediction after cardiac arrest in patients treated with hypothermia. Crit Care Med 2014;42:1340–1347.

36. Noirhomme Q, Lehembre R, Lugo Zdel R, et al. Automated analysis of background EEG and reactivity during therapeutic hypothermia in comatose patients after cardiac arrest. Clin EEG Neurosci 2014;45:6–13.

37. Lilja G, Nielsen N, Friberg H, et al. Cognitive function in survivors of out-of-hospital cardiac arrest after target temperature management at 33°C versus 36°C. Circulation 2015;131:1340–1349.

38. Fugate JE, Wijdicks EF, White RD, Rabinstein AA. Does therapeutic hypothermia affect time to awakening in cardiac arrest survivors? Neurology 2011;77:1346–1350.

39. Tjepkema-Cloostermans MC, Hofmeijer J, Trof RJ, Blans MJ, Beishuizen A, van Putten MJ. Electroencephalogram predicts outcome in patients with postanoxic coma during mild therapeutic hypothermia. Crit Care Med 2015;43:159–167.

Neurology®

Standardized EEG interpretation accurately predicts prognosis after cardiac arrest

Erik Westhall, Andrea O. Rossetti, Anne-Fleur van Rootselaar, et al.

This information is current as of February 10, 2016

AMERICAN ACADEMY OF
NEUROLOGY®