ORIGINAL ARTICLE

Treating Rhythmic and Periodic EEG Patterns in Comatose Survivors of Cardiac Arrest

B.J. Ruijter, H.M. Keijzer, M.C. Tjepkema-Cloostermans, M.J. Blans, A. Beishuizen, S.C. Tromp, E. Scholten, J. Horn, A.-F. van Rootselaar, M.M. Admiraal, W.M. van den Bergh, J.-W.J. Elting, N.A. Foudraine, F.H.M. Kornips, V.H.J.M. van Kranen-Mastenbroek, R.P.W. Rouhl, E.C. Thomeer, W. Moudrous, F.A.P. Nijhuis, S.J. Booij, C.W.E. Hoedemaekers, J. Doorduin, F.S. Taccone, J. van der Palen, M.J.A.M. van Putten, and J. Hofmeijer, for the TELSTAR Investigators*

ABSTRACT

BACKGROUND

Whether the treatment of rhythmic and periodic electroencephalographic (EEG) patterns in comatose survivors of cardiac arrest improves outcomes is uncertain.

METHODS

We conducted an open-label trial of suppressing rhythmic and periodic EEG patterns detected on continuous EEG monitoring in comatose survivors of cardiac arrest. Patients were randomly assigned in a 1:1 ratio to a stepwise strategy of antiseizure medications to suppress this activity for at least 48 consecutive hours plus standard care (antiseizure-treatment group) or to standard care alone (control group); standard care included targeted temperature management in both groups. The primary outcome was neurologic outcome according to the score on the Cerebral Performance Category (CPC) scale at 3 months, dichotomized as a good outcome (CPC score indicating no, mild, or moderate disability) or a poor outcome (CPC score indicating severe disability, coma, or death). Secondary outcomes were mortality, length of stay in the intensive care unit (ICU), and duration of mechanical ventilation.

RESULTS

We enrolled 172 patients, with 88 assigned to the antiseizure-treatment group and 84 to the control group. Rhythmic or periodic EEG activity was detected a median of 35 hours after cardiac arrest; 98 of 157 patients (62%) with available data had myoclonus. Complete suppression of rhythmic and periodic EEG activity for 48 consecutive hours occurred in 49 of 88 patients (56%) in the antiseizure-treatment group and in 2 of 83 patients (2%) in the control group. At 3 months, 79 of 88 patients (90%) in the antiseizure-treatment group and 77 of 84 patients (92%) in the control group had a poor outcome (difference, 2 percentage points; 95% confidence interval, −7 to 11; P=0.68). Mortality at 3 months was 80% in the antiseizure-treatment group and 82% in the control group. The mean length of stay in the ICU and mean duration of mechanical ventilation were slightly longer in the antiseizure-treatment group than in the control group.

CONCLUSIONS

In comatose survivors of cardiac arrest, the incidence of a poor neurologic outcome at 3 months did not differ significantly between a strategy of suppressing rhythmic and periodic EEG activity with the use of antiseizure medication for at least 48 hours plus standard care and standard care alone. (Funded by the Dutch Epilepsy Foundation; TELSTAR ClinicalTrials.gov number, NCT02056236.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Hofmeijer can be contacted at j.hofmeijer@utwente.nl or at the Department of Clinical Neurophysiology, Faculty of Science and Technology, University of Twente, P.O. Box 217, 7500 AE Enschede, the Netherlands.

*A full list of the TELSTAR investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was updated on February 24, 2022, at NEJM.org.

N Engl J Med 2022;386:724-34.
DOI: 10.1056/NEJMoa2115998
Copyright © 2022 Massachusetts Medical Society.

The New England Journal of Medicine
Downloaded from nejm.org at WELCH MEDICAL LIBRARY - JOHNS HOPKINS UNIVERSITY on March 1, 2022. For personal use only. No other uses without permission.
Copyright © 2022 Massachusetts Medical Society. All rights reserved.

Rhythmic and periodic electroencephalographic (EEG) patterns that may reflect electrographic seizures have been reported in 10 to 35% of comatose patients after cardiac arrest. Unequivocal electrographic or clinical seizures are infrequent, whereas generalized periodic discharges are common in these patients[1,2] and have generally been associated with a poor neurologic outcome.[1,3-7] Whether rhythmic and periodic EEG patterns should be treated with antiseizure medications, with the goal of improving the neurologic outcome, is unclear.[8,9]

Uncertainty about the efficacy of treatment has been reflected in surveys showing that approximately one third of neurologists use a stepwise antiseizure-medication strategy to suppress epileptiform EEG activity in nonconvulsive status epilepticus and status epilepticus, one third use these medications in a nonstandardized way, and one third do not use antiseizure medications because of presumed futility of improving the neurologic outcome.[10,11] It has been suggested that the effects of antiseizure medication depend on the specific EEG pattern being treated.[4,5,7]

We conducted the Treatment of Electroencephalographic Status Epilepticus after Cardiopulmonary Resuscitation (TELSTAR) trial to assess whether intensive, stepwise antiseizure and sedative treatment to suppress rhythmic and periodic EEG patterns detected in continuous EEG monitoring would alter the outcomes in comatose patients after cardiac arrest. We hypothesized that the use of antiseizure medication would reduce the incidence of a poor neurologic outcome at 3 months.

Methods

Trial Design

This trial was a pragmatic, multicenter clinical trial with randomized treatment assignments, open-label treatment, and blinded end-point evaluation at 11 intensive care units (ICUs) in the Netherlands and Belgium. Stepwise treatment to suppress rhythmic and periodic EEG patterns on continuously monitored EEG plus standard care was compared with standard care alone in comatose patients after cardiac arrest. The trial was supported by a grant from the Dutch Epilepsy Foundation (NEF14-18), which was not involved in trial design or conduct, data analysis, or manuscript preparation or review.

The trial protocol (available with the full text of this article at NEJM.org) was approved by a central medical ethics committee and by the research boards at each participating center. Written informed consent was obtained from legal representatives of patients before randomization or, from January 10, 2017, was obtained in a deferred manner from the patient if possible, within 24 hours after randomization. Written informed consent for follow-up was obtained from surviving patients or from legal representatives. An independent data and safety monitoring board analyzed safety when 25%, 50%, and 75% of the patients had been enrolled and assessed efficacy when 50% of the patients had been enrolled.

This trial was an investigator-initiated trial, with no commercial involvement. The executive committee designed the trial. Members of the executive committee and local investigators collected and analyzed the data and wrote the manuscript. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Trial Population

Eligible patients were 18 years of age or older, were comatose (Glasgow Coma Scale score, ≤8; range, 3 to 15, with lower scores indicating worse responses to stimuli) after resuscitation for cardiac arrest, had continuous EEG monitoring started less than 24 hours after the return of spontaneous circulation, and had rhythmic or periodic activity on EEG. Continuous EEG monitoring was standard practice in all participating hospitals, but we did not maintain a case log of all patients with cardiac arrest in these units during the trial. Rhythmic and periodic EEG patterns were defined as periodic discharges, rhythmic delta activity, spike-and-wave or sharp-and-wave EEG patterns, each at a rate of 0.5 Hz or more, irrespective of their spatial evolution across EEG montages or temporal evolution. The minimum duration of continuous activity of these patterns for inclusion in the trial was 30 minutes or, if intermittent, 5 minutes, recurring at least twice at intervals of less than 60 minutes. Detailed inclusion and exclusion criteria are listed under Additional Methods in the Supplementary Appendix (available at NEJM.org).

Trial Interventions

Patients were randomly assigned to receive protocol-defined antiseizure medication plus standard

A Quick Take is available at NEJM.org

The New England Journal of Medicine
Downloaded from nejm.org at WELCH MEDICAL LIBRARY - JOHNS HOPKINS UNIVERSITY on March 1, 2022. For personal use only. No other uses without permission.
Copyright © 2022 Massachusetts Medical Society. All rights reserved.

Table 1. Characteristics of the 172 Patients at Baseline.*

Characteristic	Antiseizure Treatment (N=88)	Control (N=84)†
Demographic characteristics		
Median age (IQR) — yr	64 (56–73)	66 (59–74)
Male sex — no./total no. (%)	60/88 (68)	58/83 (70)
Characteristics of cardiac arrest		
Location of cardiac arrest — no./total no. (%)		
Out of hospital	84/88 (95)	78/83 (94)
In hospital	4/88 (5)	5/83 (6)
Presumed cause of cardiac arrest — no./total no. (%)		
Cardiac	70/88 (80)	64/83 (77)
Other	9/88 (10)	14/83 (17)
Unknown	9/88 (10)	5/83 (6)
Bystander-witnessed cardiac arrest — no./total no. (%)	62/88 (70)	53/83 (64)
First monitored rhythm — no./total no. (%)		
Shockable	51/85 (60)	58/81 (72)
Nonshockable	34/85 (40)	23/81 (28)
Median time from cardiac arrest (IQR) — min		
To start of basic life support	5 (1–8)	5 (3–10)
To return of spontaneous circulation	16 (10–30)	19 (12–25)
Clinical characteristics at randomization		
Median APACHE IV score (IQR)‡	103 (76–119)	106 (87–119)
Nystagmus — no./total no. (%)	2/65 (3)	4/61 (7)
Myoclonus — no./total no. (%)	50/82 (61)	48/75 (64)
Standard care — no./total no. (%)		
Targeted temperature management, 33°C	21/88 (24)	20/83 (24)
Targeted temperature management, 33–36°C	67/88 (76)	63/83 (76)
EEG monitoring		
Median time from return of spontaneous circulation to start of continuous EEG monitoring (IQR) — hr	15 (9.4–19.2)	12 (6.9–17.7)
Median time from resuscitation to onset of RPP (IQR) — hr	36 (27.4–43.3)	33 (25.4–43.9)
EEG pattern at randomization — no./total no. (%)		
Generalized periodic discharges, 0.5–2.5 Hz	68/88 (77)	67/83 (81)
Electrographic seizures, ≥2.5 Hz	9/88 (10)	8/83 (10)
Evolving patterns, 0.5–2.5 Hz§	2/88 (2)	3/83 (4)
Other rhythmic or periodic patterns, 0.5–2.5 Hz	9/88 (10)	5/83 (6)
Background continuity of EEG at start of RPP — no./total no. (%)		
Continuous	56/88 (64)	40/83 (48)
Discontinuous	19/88 (22)	29/83 (35)
Suppressed	13/88 (15)	14/83 (17)
Somatosensory evoked potential — no./total no. (%)		
Evoked potential measured	61/88 (69)	60/83 (72)
N20 bilaterally absent¶	20/61 (33)	17/60 (28)

The New England Journal of Medicine
Downloaded from nejm.org at WELCH MEDICAL LIBRARY - JOHNS HOPKINS UNIVERSITY on March 1, 2022. For personal use only. No other uses without permission.
Copyright © 2022 Massachusetts Medical Society. All rights reserved.

Table 1. (Continued.)

* Patients in the antiseizure-treatment group received intensive antiseizure treatment plus standard care, and patients in the control group received standard care alone. Percentages may not total 100 because of rounding. Regarding characteristics for which median and interquartile range (IQR) are shown, the numbers of patients with missing data were as follows: age, 0 in the antiseizure-treatment group and 1 in the control group; time from cardiac event to start of basic life support, 22 and 18; time from cardiac arrest to return of spontaneous circulation, 26 and 22; Acute Physiology and Chronic Health Evaluation (APACHE) IV score, 17 and 18; time from return of spontaneous circulation to start of continuous electroencephalography (EEG), 0 and 1; and time from resuscitation to onset of rhythmic and periodic pattern (RPP), 0 and 1.

† One patient in the control group gave consent for inclusion in the analysis of the primary outcome but not in any other analyses.

‡ APACHE IV scores range from 0 to 71, with higher scores indicating greater disease severity with a higher risk of death in the short term.

§ Evolving patterns indicate at least two unequivocal, sequential changes in frequency, morphologic characteristics, or location defined as follows: evolution in frequency was defined as at least two consecutive changes in the same direction by at least 0.5 Hz (e.g., from 2 to 2.5 to 3 Hz or from 3 to 2 to 1.5 Hz); evolution in morphologic characteristics was defined as at least two consecutive changes to new morphologic characteristics; and evolution in location was defined as sequentially spreading into or sequentially out of at least two different locations in the standard 10–20 system of electrode placement that was used in nine hospitals and in a 10-electrode configuration used in two hospitals. The two consecutive changes had to be in the same category (frequency, morphologic characteristics, or location) to qualify.

¶ N20 indicates cortical response measured at the scalp as a negative peak at 20 msec after electrical stimulation at the wrist.

care (antiseizure-treatment group) or standard care alone (control group) with the use of the Web-based service ALEA (Clinical Trial Center Maastricht, the Netherlands) in a 1:1 ratio with permuted blocks (block size, 4 to 10) stratified according to center. The antiseizure intervention consisted of a stepwise treatment strategy with the intent of completely suppressing rhythmic and periodic EEG activity on continuous EEG monitoring. Standard care was left to the discretion of the treating physicians but generally followed European guidelines and included targeted temperature management in both trial groups.[12]

In the antiseizure-treatment group, treatment of rhythmic and periodic EEG patterns was based on international guidelines for the treatment of status epilepticus.[13-15] Step 1 was a first antiseizure drug plus a first sedative agent (usually midazolam or propofol), step 2 was a second antiepileptic drug plus a second sedative agent, and step 3 was a high-dose barbiturate; all medications were administered intravenously. Permitted antiseizure medications were phenytoin, valproate, and levetiracetam. Because no antiseizure or sedative drug has been proven superior to another in improving outcomes after status epilepticus, medications were chosen by the treating physician in the doses and infusion rates as indicated in the protocol.[16] The treatment flow chart is available in the Supplementary Appendix under Additional Methods.

The goal of antiseizure treatment was to suppress all rhythmic and periodic EEG activity for at least 48 consecutive hours (defined as >90% of activity suppressed). Each subsequent step was taken as soon as possible when the previous step failed to suppress all this activity. There was no obligation to induce burst suppression on EEG. In the antiseizure-treatment group, treatment was started within 3 hours after detection of rhythmic and periodic EEG patterns. Treatment was guided by a neurologist or clinical neurophysiologist who analyzed the EEG findings and adjusted or changed medication according to the protocol in consultation with the ICU physician. Treating physicians were allowed to follow local protocols for treatment of seizurelike activity, provided that these were in line with the overall stepwise approach. If rhythmic and periodic EEG patterns returned after 48 hours with the use of at least two antiseizure medications, the decision to prolong antiseizure treatment was left to the discretion of the treating physician. In the control group, physicians were allowed to prescribe sedative medication if needed for mechanical ventilation or to suppress clinically manifest myoclonus, irrespective of the EEG findings; additional use of antiseizure drugs was discouraged in the control group.

In both groups, decisions regarding limitation or withdrawal of treatment were based on Dutch guidelines, which were derived from the European guidelines at the time we started the trial.[17] Withdrawal of treatment could be considered during normothermia and while the patient was not receiving sedation if there was incomplete

The New England Journal of Medicine
Downloaded from nejm.org at WELCH MEDICAL LIBRARY - JOHNS HOPKINS UNIVERSITY on March 1, 2022. For personal use only. No other uses without permission.
Copyright © 2022 Massachusetts Medical Society. All rights reserved.

Table 2. Antiseizure Treatment and EEG Response.*

Variable	Antiseizure Treatment (N=88)	Control (N=84)†
	no./total no. (%)	
Treatment details		
Intensive antiseizure treatment started	88/88 (100)	0/83
Intensive antiseizure treatment continued after 24 hr‡	54/88 (61)	0/83
No. of antiseizure drugs used		
0	0/88	75/83 (90)
1	24/88 (27)	5/83 (6)
2	57/88 (65)	3/83 (4)
≥3	7/88 (8)	0/83
No. of sedative drugs used		
0	1/88 (1)	20/83 (24)
1	27/88 (31)	47/83 (57)
2	54/88 (61)	15/83 (18)
≥3	6/88 (7)	1/83 (1)
≥1 Antiseizure drug continued during entire period of ICU admission	85/88 (97)	8/83 (10)
Effect on EEG recordings		
Complete suppression of EEG index activity for ≥48 consecutive hr§	49/88 (56)	2/83 (2)
Complete suppression of EEG index activity for ≥24 consecutive hr	75/88 (85)	10/83 (12)
Suppression of RPPs 0–24 hr after randomization		
Complete	64/88 (73)	3/83 (4)
Partial	20/88 (23)	11/83 (13)
None	4/88 (5)	69/83 (83)
Suppression of RPPs 24–48 hr after randomization‡		
Complete	60/88 (68)	39/83 (47)
Partial	12/88 (14)	14/83 (17)
None	6/88 (7)	9/83 (11)
No EEG recordings available	2/88 (2)	1/83 (1)
Treatment restrictions during ICU admission		
Do not resuscitate	32/88 (36)	36/83 (43)
Withdrawal of life-sustaining treatment	68/88 (77)	65/83 (78)

* Percentages may not total 100 because of rounding. ICU denotes intensive care unit.
† One patient in the control group gave consent for inclusion in the analysis of the primary outcome but not in any other analyses.
‡ A total of 8 of 88 patients (9%) in the antiseizure-treatment group and 20 of 83 patients (24%) in the control group died within 24 hours after randomization.
§ Suppression of index EEG activity for 48 hours was the goal in the antiseizure-treatment group of the trial.

return of brain-stem reflexes and bilateral absence of somatosensory evoked potentials[17]; however, EEG patterns in the previous 72 hours were not taken into account in these decisions.

TRIAL OUTCOMES

The primary outcome was neurologic outcome according to the score on the Cerebral Performance Category (CPC) scale at 3 months, dichotomized as a good outcome (CPC score of 1 [no or mild neurologic disability] or 2 [moderate disability]) or a poor outcome (CPC score of 3 [severe disability], 4 [coma], or 5 [death]).[18] These scores were obtained at 3 months after admission by a standardized telephone interview conducted by an investigator who was unaware of the trial-

The New England Journal of Medicine
Downloaded from nejm.org at WELCH MEDICAL LIBRARY - JOHNS HOPKINS UNIVERSITY on March 1, 2022. For personal use only. No other uses without permission.
Copyright © 2022 Massachusetts Medical Society. All rights reserved.

Table 3. Primary, Secondary, and Safety Outcomes (Intention-to-Treat Population).*

Outcome	Antiseizure Treatment (N=88)	Control (N=84)	Measure of Effect†		P Value
			Calculation	Value (95% CI)	
Primary outcome					
CPC score of 3, 4, or 5 at 3 mo — no. (%)	79 (90)	77 (92)	Risk difference	2 (–7 to 11)	0.68
Secondary outcomes‡					
CPC score at 3 mo§			Common odds ratio	1.19 (0.56 to 2.53)	
CPC score of 2 to 5 at 3 mo — no. (%)	86 (98)	82 (98)	Risk difference	0 (–5 to 4)	
CPC score of 4 or 5 at 3 mo — no. (%)	71 (81)	70 (83)	Risk difference	3 (–9 to 14)	
Death at 3 months — no. (%)	70 (80)	69 (82)	Risk difference	3 (–9 to 14)	
Mean length of stay in the ICU (95% CI) — days	8.7 (6.7 to 10.7)	7.5 (5.5 to 9.4)			
Mean duration of mechanical ventilation (95% CI) — days	7.8 (6.1 to 9.5)	6.6 (4.9 to 8.4)			
Serious adverse events until 3 mo					
Any serious adverse event — no. (%)	73 (83)	72 (86)	Chi-square test		0.62
Death after withdrawal of life-sustaining treatment — no./total no. (%)	68/88 (77)	65/83 (78)	Chi-square test		0.87
Death, other cause — no. (%)	2 (2)¶	4 (5)‖	Fisher's exact test		0.44
Patients with other serious adverse events — no. (%)	8 (9)	9 (11)	Chi-square test		0.72
No. of other serious adverse events	10	11			

* Scores on the Cerebral Performance Category (CPC) scale range from 1 to 5, with 1 indicating no or mild neurologic disability, 2 moderate disability, 3 severe disability, 4 coma, and 5 death. For mean length of stay in the ICU and mean duration of mechanical ventilation, data were missing for one patient in the control group.

† Risk difference was defined as the between-group difference (control group minus antiseizure-treatment group) in percentage points.

‡ For secondary outcomes, there was no prespecified plan for adjustment of the width of confidence intervals for multiple comparisons, and no definite conclusions can be drawn from these data.

§ The between-group difference in the distribution of CPC scores was analyzed with logistic-regression analysis of the ordinal data. The effect measure is the common odds ratio from the ordinal logistic-regression model. A value greater than 1 indicates lower CPC scores in the antiseizure-treatment group than in the control group.

¶ Two patients died from a new cardiac arrest.

‖ Two patients died from a new cardiac arrest, one from coronavirus disease 2019, and one from an unreported cause.

group assignments and EEG pattern. Secondary outcomes were mortality at 3 months, length of stay in the ICU, and duration of mechanical ventilation. Safety outcomes included any serious adverse events. Outcomes at 6 and 12 months have not yet been analyzed. Treating physicians were aware of the trial-group assignments and reported serious adverse events to the principal investigator by e-mail.

EEG MONITORING

Continuous EEG monitoring was initiated within 24 hours after resuscitation as part of standard care in participating ICUs and continued for at least 3 days, until discharge from the ICU or until rhythmic and periodic EEG activity was extinguished. The standard international 10–20 system of electrode placement (in nine hospitals) or a limited montage with 10 electrodes (in two hospitals) was used according to local protocols. EEG recordings were checked every 3 hours by a neurologist, clinical neurophysiologist, or clinical neurophysiology technician. The diagnosis of rhythmic and periodic EEG patterns was made by the attending neurologist or clinical neurophysiologist. Guidance was given by typical examples of eligible EEG patterns on our website, at yearly meetings to discuss these patterns, and on a 24/7 online platform through which we were able to exchange EEG information and provide advice in real time if requested.

The final classifications of EEG patterns at baseline and suppression of activity were determined by central reading of EEGs by the first

The New England Journal of Medicine
Downloaded from nejm.org at WELCH MEDICAL LIBRARY - JOHNS HOPKINS UNIVERSITY on March 1, 2022. For personal use only. No other uses without permission.
Copyright © 2022 Massachusetts Medical Society. All rights reserved.

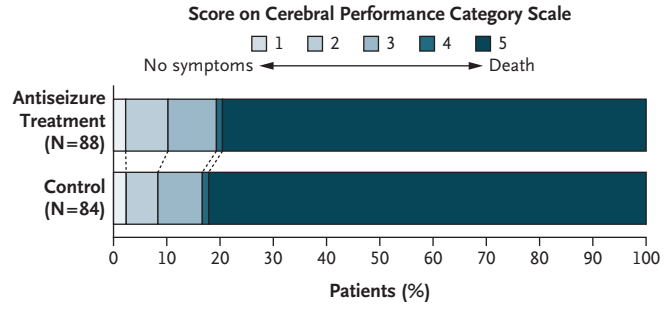

Figure 1. Cerebral Performance Category Scores at 3 Months (Intention-to-Treat Population).

Patients in the antiseizure-treatment group received intensive antiseizure treatment plus standard care, and patients in the control group received standard care alone. Scores on the Cerebral Performance Category scale range from 1 to 5, with 1 indicating no or mild neurologic disability, 2 moderate disability, 3 severe disability, 4 coma, and 5 death.

two and last two authors, who were aware of the trial-group assignments. They classified the EEG pattern at inclusion as electrographic seizures (discharges at ≥2.5 Hz), evolving patterns (0.5 to 2.5 Hz), generalized periodic discharges (0.5 to 2.5 Hz), or other periodic patterns (0.5 to 2.5 Hz), with continuous, discontinuous, or suppressed background activity. They classified the treatment effect on the index EEG activity in both groups as complete suppression (>90%), partial suppression (50 to 90%), or no suppression (<50%).

STATISTICAL ANALYSIS

We calculated a sample size of 172 patients: 84 per group on the basis of a prevalence of a poor outcome of 99% derived from uncontrolled cohorts,[19,20] a presumed lower incidence of a poor outcome in the antiseizure-treatment group than in the control group by 7 percentage points, an alpha level of 5%, a beta level of 80%, and one-tailed testing as well as two additional patients per group to compensate for a planned interim analysis after 86 patients had been enrolled.[21] The statistical analysis plan (available with the protocol at NEJM.org) was finalized before the database was locked and before data were analyzed.

The primary analysis was a single comparison between the two trial groups with regard to the dichotomized primary outcome according to the intention-to-treat principle, expressed as the risk difference (between-group difference in percentage points) of a poor outcome, including the corresponding 95% confidence interval. The level of statistical significance for the difference in the primary outcome was P=0.0429 to accommodate a single interim analysis of efficacy that used O'Brien–Fleming boundaries.[21]

Secondary analyses of the primary outcome included risk differences of a poor outcome for all other dichotomous outcomes on the CPC scale, as well as the shift across CPC scores in the direction of a better outcome in the antiseizure-treatment group, analyzed by means of multivariable ordinal logistic regression and expressed as a common odds ratio. For secondary outcomes, between-group differences were analyzed by means of independent-samples t-tests, Mann–Whitney tests, or Fisher exact tests, where appropriate. Because there was no prespecified plan for adjustment of the widths of confidence intervals for multiple comparisons of secondary outcomes, no definite conclusions can be drawn from these data. There was no prespecified plan for the handling of missing data. We performed prespecified per-protocol analyses involving all patients who received antiseizure drugs as compared with those who did not receiving antiseizure drugs. We planned multivariable logistic-regression analysis to adjust for imbalances in baseline prognostic variables between the antiseizure-treatment group and the control group, if applicable.

Treatment-effect modification was explored in prespecified subgroups defined by seizure type at inclusion (electrographic seizures, evolving patterns, generalized periodic discharges, or other), background continuity at inclusion (continuous, discontinuous, or suppressed), and time of onset of rhythmic and periodic EEG patterns (≤24 hours, >24 to <48 hours, or ≥48 hours after the return of spontaneous circulation), but the trial was not powered for these subgroups. An additional post hoc exploratory subgroup analysis was added according to generalized periodic discharges as compared with nongeneralized periodic discharges in EEG patterns at inclusion, as suggested by findings reported in the literature.[9] All analyses were performed with the use of MATLAB software, version 2021a (MathWorks).

RESULTS

BASELINE CHARACTERISTICS

Between May 1, 2014, and January 24, 2021, continuous EEG recordings were started in 2528 patients, rhythmic and periodic EEG activity was detected in 354, and 172 were included in the

The New England Journal of Medicine
Downloaded from nejm.org at WELCH MEDICAL LIBRARY - JOHNS HOPKINS UNIVERSITY on March 1, 2022. For personal use only. No other uses without permission.
Copyright © 2022 Massachusetts Medical Society. All rights reserved.

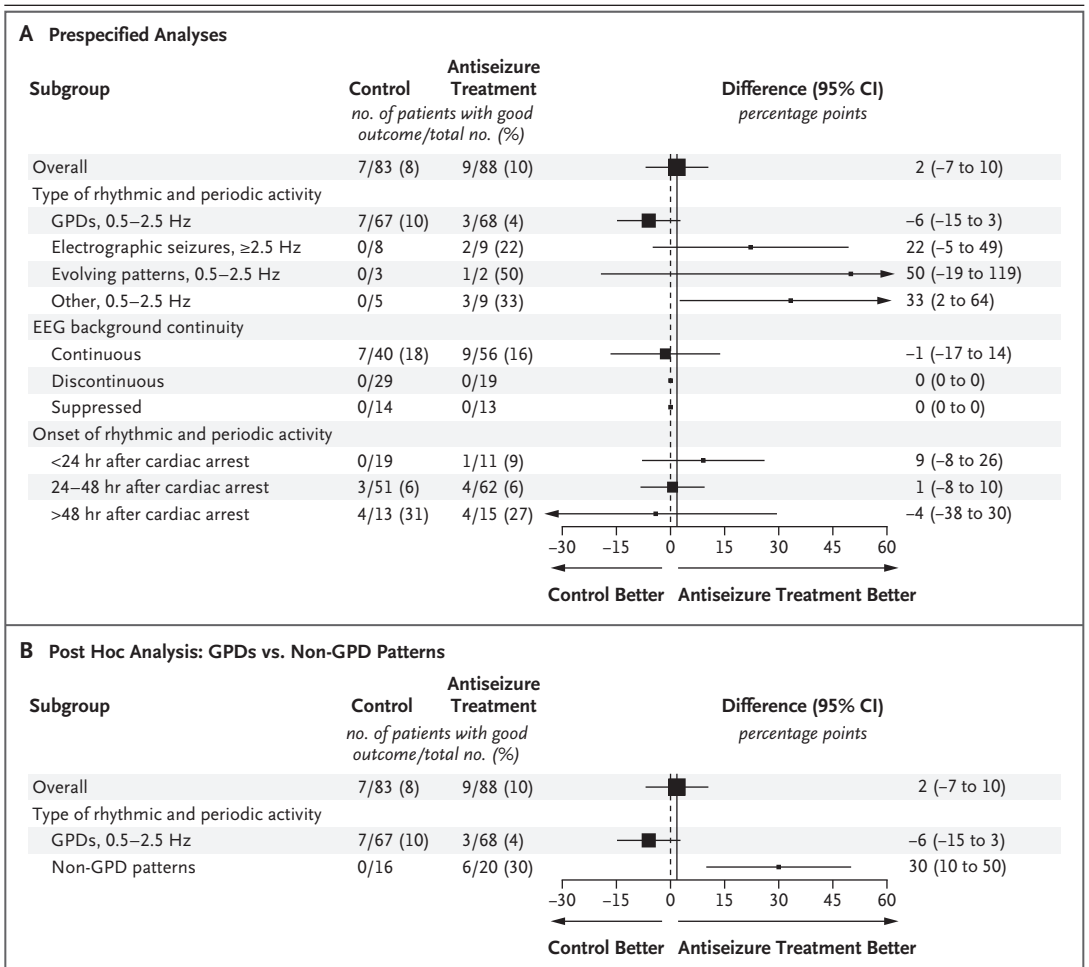

Figure 2. Subgroup Analyses.

The trial was not powered to analyze subgroups, and these results should be considered exploratory. One patient in the control group gave consent for inclusion in the analysis of the primary outcome but not in any other analyses. The between-group difference was calculated as antiseizure-treatment group minus control group. Black squares indicate point estimates of effects, dotted vertical lines indicate no effect, and solid vertical lines indicate the overall effect in the antiseizure-treatment group. EEG denotes electroencephalography, and GPD generalized periodic discharge.

trial, with 88 assigned to the antiseizure-treatment group and 84 to the control group (Fig. S1 in the Supplementary Appendix). A total of 72 patients were not enrolled because their EEG recordings were not interpreted rapidly enough to be included. All included patients had complete follow-up at 3 months. There was one interim analysis after 86 patients had been enrolled.

The median age of the patients was 65 years (interquartile range, 57 to 74), and 118 (69%) were men. Rhythmic and periodic EEG patterns started at a median of 35 hours (interquartile range, 27 to 44) after cardiac arrest, and 98 of 157 patients (62%) had myoclonus. Approximately 80% of the patients in both groups had generalized periodic discharges, and 10% had electrographic seizures. Baseline characteristics were similar in the two groups (Tables 1 and S2). The representativeness of trial patients is shown in Table S1.

EEG RESPONSE

All the patients in the antiseizure-treatment group and 8 in the control group were treated with at least one antiseizure medication. All the patients who were assigned to the antiseizure-treatment group received the intended treatment strategy. Complete suppression of paroxysmal EEG activity for the 24 hours after randomization was achieved in 64 of 88 patients (73%) in

The New England Journal of Medicine
Downloaded from nejm.org at WELCH MEDICAL LIBRARY - JOHNS HOPKINS UNIVERSITY on March 1, 2022. For personal use only. No other uses without permission.
Copyright © 2022 Massachusetts Medical Society. All rights reserved.

the antiseizure-treatment group and in 3 of 83 patients (4%) in the control group. Complete suppression of the index EEG activity for 48 consecutive hours at any time after the start of treatment occurred in 49 of 88 patients (56%) in the antiseizure-treatment group and in 2 of 83 patients (2%) in the control group (Tables 2 and S3). Suppression for more than 24 hours is shown in Table 2. Examples of the rhythmic and periodic activity encountered in the trial are shown in Figure S4. The typical evolution of generalized periodic discharges is illustrated in Figure S5: these started with low-frequency activity (<0.5 Hz) and gradually evolved toward frequencies of discharges that met our trial inclusion criteria, on time scales of hours.

OUTCOMES

At 3 months, 79 of 88 patients (90%) in the antiseizure-treatment group and 77 of 84 patients (92%) in the control group had a poor outcome as defined by a CPC score of 3, 4, or 5 (difference, 2 percentage points; 95% confidence interval [CI], −7 to 11; P=0.68) (Table 3). Results were similar for per-protocol analyses (Table S4). At 3 months, 70 of 88 patients (80%) in the antiseizure-treatment group and 69 of 84 patients (82%) in the control group had died (difference, 3 percentage points; 95% CI, −9 to 14); however, mortality within 24 hours after randomization was 9% in the antiseizure-treatment group and 24% in the control group (Table 3). Survival curves are shown in Figure S3. All but one death within 24 hours after randomization occurred after withdrawal of life-sustaining treatment. Two patients in each group had a second cardiac arrest; one patient in the control group died more than 24 hours after randomization as a result of a second cardiac arrest. The distribution of CPC scores was similar in the two groups (common odds ratio, 1.19; 95% CI, 0.56 to 2.53) (Fig. 1). The mean length of stay in the IUC was 8.7 days in the antiseizure-treatment group and 7.5 days in the control group (Table 3). The incidence of withdrawal of life-sustaining treatment was approximately 77% in both trial groups (Table 2). The timing of withdrawal of life-sustaining treatment ranged from 1 to 33 days after ICU admission; in the first 24 hours, withdrawal occurred in 2% of the patients in the antiseizure-treatment group and in 13% of those in the control group (Fig. S2).

SAFETY

The incidence of serious adverse events in the overall population was 145 of 172 patients (84%); serious adverse events were similar in incidence and type in the two trial groups (Tables 3 and S5). Adverse events of lesser degree than serious adverse events, such as hypotension, were not systematically recorded.

EXPLORATORY SUBGROUP ANALYSES

Visual inspection of subgroup plots (Fig. 2A) suggested that for the most common type of EEG activity, generalized periodic discharges, the antiseizure-treatment group may have had a smaller proportion of good outcomes than the control group, but the trial was not powered to make conclusions from these subgroup results and the results are exploratory. Post hoc analyses of outcomes of generalized periodic discharges as compared with all other patterns are shown in Figure 2B.

DISCUSSION

In this trial involving comatose patients after cardiac arrest who had rhythmic and periodic EEG patterns, intensive antiseizure treatment adapted from protocols for status epilepticus did not result in fewer poor outcomes at 3 months than standard treatment. Sedative medications were used in both the antiseizure-treatment group and the control group to support mechanical ventilation or suppress myoclonus, which may have led to cessation of rhythmic and periodic EEG activity in the standard-care group that reduced the differences in the incidence of EEG and clinical outcomes between the two groups. The antiseizure intervention was associated with a slightly longer length of stay in the ICU and a longer duration of mechanical ventilation. Overall mortality was 81%, similar to findings in observational studies involving patients who were comatose after cardiac arrest.[5,6,22-25] A total of 10% of the patients in the antiseizure-treatment group and 8% of those in the control group in our trial had a good neurologic recovery.

In a previous observational study, stepwise, intensive treatment resulted in a good outcome in 16 of 36 patients (44%) with rhythmic and periodic EEG patterns other than generalized periodic discharges, as compared with none of 13 patients with generalized periodic discharges.[9]

The New England Journal of Medicine
Downloaded from nejm.org at WELCH MEDICAL LIBRARY - JOHNS HOPKINS UNIVERSITY on March 1, 2022. For personal use only. No other uses without permission.
Copyright © 2022 Massachusetts Medical Society. All rights reserved.

In our trial, generalized periodic discharges were the most common aberrant EEG pattern, present in approximately 80% of the patients. As in some other studies, generalized periodic discharges typically started with low frequencies (<0.5Hz), with a gradual evolution toward frequencies that met our inclusion criteria over a period of hours.[3,6] This pattern differs from the usual evolution of seizures in status epilepticus, which is characterized by rapid onset of EEG abnormalities, evolving over seconds.[26] Data from several studies suggest that generalized periodic discharges in postanoxic encephalopathy may be a direct expression of severe ischemic brain damage rather than of epilepsy.[27,28]

Exploratory subgroup analyses suggested that there may have been fewer good outcomes with the antiseizure intervention in patients with generalized periodic discharges than in those with other patterns.[9] However, no conclusions can be drawn from these results, because the trial was underpowered for these analyses.

Trial physicians were allowed to decide to withdraw antiseizure or life-sustaining treatment after 48 hours of intensive antiseizure treatment. Treatment for longer than 48 hours has been advocated in the type of patient included in the trial.[29,30] In the aforementioned observational study, the mean duration of treatment was approximately 5 days,[9] as compared with the mean duration of ICU treatment in our antiseizure-treatment group of approximately 9 days, during which antiseizure medications were continued in all the patients in the group.

Strengths of our trial include a prospective, randomized design; the use of continuous EEG monitoring; and outcome assessors who were unaware of the trial-group assignments. Limitations are that mortality within 24 hours was higher in the control group than in the antiseizure-treatment group, and we cannot rule out the possibility that decisions with respect to withdrawal of life-sustaining treatment were not balanced between the trial groups, which potentially resulted in poorer outcomes in the control group. Furthermore, patients in the antiseizure-treatment group more often received sedative medication as part of the antiseizure treatment regimen, and withdrawal of life-sustaining treatment may have been delayed in this group. Treating physicians in the trial were aware of the trial-group assignments, which may have influenced choice regarding medication treatment choices and decisions about withdrawal of care. The final classification of seizure types and degree of suppression of index EEG activity was determined by experienced EEG readers who were aware of the trial-group assignments. Finally, the wide confidence interval around the point estimate for the between-group difference in the primary outcome cannot rule out benefit or harm of aggressive antiseizure treatment in these patients.

In comatose patients after cardiac arrest with rhythmic and periodic EEG activity, intensive antiseizure treatment over a period of at least 48 hours did not improve neurologic outcomes at 3 months, but the wide confidence interval for the primary outcome may not rule out modest benefit or harm.

Supported by a grant from the Dutch Epilepsy Foundation (NEF14-18).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Barry J. Ruijter, M.D., Ph.D., Hanneke M. Keijzer, M.Sc., Marleen C. Tjepkema-Cloostermans, Ph.D., Michiel J. Blans, M.D., Albertus Beishuizen, M.D., Ph.D., Selma C. Tromp, M.D., Ph.D., Erik Scholten, M.D., Janneke Horn, M.D., Ph.D., Anne-Fleur van Rootselaar, M.D., Ph.D., Marjolein M. Admiraal, Ph.D., Walter M. van den Bergh, M.D., Ph.D., Jan-Willem J. Elting, M.D., Ph.D., Norbert A. Foudraine, M.D., Ph.D., Francois H.M. Kornips, M.D., Vivianne H.J.M. van Kranen-Mastenbroek, M.D., Ph.D., Rob P.W. Rouhl, M.D., Ph.D., Elsbeth C. Thomeer, M.D., Walid Moudrous, M.D., Frouke A.P. Nijhuis, M.D., Suzanne J. Booij, M.D., Cornelia W.E. Hoedemaekers, M.D., Ph.D., Jonne Doorduin, Ph.D., Fabio S. Taccone, M.D., Ph.D., Job van der Palen, Ph.D., Michel J.A.M. van Putten, M.D., Ph.D., and Jeannette Hofmeijer, M.D., Ph.D.

The authors' affiliations are as follows: the Department of Clinical Neurophysiology, Technical Medical Center (B.J.R., M.C.T.-C., M.J.A.M.P., J. Hofmeijer), and the Section of Cognition, Data, and Education (J.P.), University of Twente, and the Departments of Neurology and Clinical Neurophysiology (M.C.T.-C., M.J.A.M.P.), the Intensive Care Center (A.B.), and the Department of Epidemiology (J.P.), Medisch Spectrum Twente, Enschede, the Departments of Neurology (H.M.K., J. Hofmeijer) and Intensive Care (M.J.B.), Rijnstate Hospital, Arnhem, the Departments of Intensive Care Medicine (H.M.K., C.W.E.H.) and Neurology (H.M.K., J.D.) and the Donders Institute for Brain, Cognition, and Behavior (H.M.K.), Radboud University Medical Center, and the Department of Neurology, Canisius Wilhelmina Hospital (F.A.P.N., S.J.B.), Nijmegen, the Departments of Neurology and Clinical Neurophysiology (S.C.T.) and Intensive Care (E.S.), St. Antonius Hospital, Nieuwegein, the Department of Neurology, Leiden University Medical Center, Leiden (S.C.T.), the Amsterdam Coma Group (J. Horn, A.-F.R., M.M.A.), the Department of Intensive Care (J. Horn), and the Department of Neurology and Clinical Neurophysiology (A.-F.R., M.M.A.), Amsterdam University Medical Center, Amsterdam, the Departments of Critical Care

The New England Journal of Medicine
Downloaded from nejm.org at WELCH MEDICAL LIBRARY - JOHNS HOPKINS UNIVERSITY on March 1, 2022. For personal use only. No other uses without permission.
Copyright © 2022 Massachusetts Medical Society. All rights reserved.

(W.M.B.) and Neurology and Clinical Neurophysiology (J.W.J.E.), University Medical Center Groningen, University of Groningen, Groningen, the Departments of Intensive Care (N.A.F.) and Neurology (F.H.M.K.), VieCuri Medical Center, Venlo, the Departments of Clinical Neurophysiology (V.H.J.M.K.-M.) and Neurology (R.P.W.R.), Maastricht University Medical Center, and the Academic Center for Epileptology Kempenhaeghe and Maastricht UMC+ (V.H.J.M.K.-M., R.P.W.R.), Maastricht, and the Department of Neurology, Maasstad Hospital, Rotterdam (E.C.T., W.M.) — all in the Netherlands; and the Department of Intensive Care, Erasme University Hospital, Université Libre de Bruxelles, Brussels (F.S.T.).

REFERENCES

1. Rossetti AO, Logroscino G, Liaudet L, et al. Status epilepticus: an independent outcome predictor after cerebral anoxia. Neurology 2007;69:255-60.
2. Hirsch LJ, Fong MWK, Leitinger M, et al. American Clinical Neurophysiology Society's standardized critical care EEG terminology: 2021 version. J Clin Neurophysiol 2021;38:1-29.
3. Ruijter BJ, van Putten MJAM, Hofmeijer J. Generalized epileptiform discharges in postanoxic encephalopathy: quantitative characterization in relation to outcome. Epilepsia 2015;56:1845-54.
4. Rossetti AO, Oddo M, Liaudet L, Kaplan PW. Predictors of awakening from postanoxic status epilepticus after therapeutic hypothermia. Neurology 2009;72:744-9.
5. Barbella G, Lee JW, Alvarez V, et al. Prediction of regaining consciousness despite an early epileptiform EEG after cardiac arrest. Neurology 2020;94(16):e1675-e1683.
6. Westhall E, Rosén I, Rundgren M, et al. Time to epileptiform activity and EEG background recovery are independent predictors after cardiac arrest. Clin Neurophysiol 2018;129:1660-8.
7. Backman S, Westhall E, Dragancea I, et al. Electroencephalographic characteristics of status epilepticus after cardiac arrest. Clin Neurophysiol 2017;128:681-8.
8. Young GB, Gilbert JJ, Zochodne DW. The significance of myoclonic status epilepticus in postanoxic coma. Neurology 1990;40:1843-8.
9. Beretta S, Coppo A, Bianchi E, et al. Neurologic outcome of postanoxic refractory status epilepticus after aggressive treatment. Neurology 2018;91(23):e2153-e2162.
10. Abend NS, Dlugos DJ, Hahn CD, Hirsch LJ, Herman ST. Use of EEG monitoring and management of non-convulsive seizures in critically ill patients: a survey of neurologists. Neurocrit Care 2010;12:382-9.
11. Bouwes A, Kuiper MA, Hijdra A, Horn J. Induced hypothermia and determination of neurological outcome after CPR in ICUs in the Netherlands: results of a survey. Resuscitation 2010;81:393-7.
12. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. Intensive Care Med 2015;41:2039-56.
13. Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012;17:3-23.
14. Rossetti AO, Lowenstein DH. Management of refractory status epilepticus in adults: still more questions than answers. Lancet Neurol 2011;10:922-30.
15. Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr 2016;16:48-61.
16. Chamberlain JM, Kapur J, Shinnar S, et al. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. Lancet 2020;395:1217-24.
17. 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;40:1816-31.
18. Cummins RO, Chamberlain DA, Abramson NS, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. Circulation 1991;84:960-75.
19. Hofmeijer J, Tjepkema-Cloostermans MC, Blans MJ, Beishuizen A, van Putten MJAM. Unstandardized treatment of electroencephalographic status epilepticus does not improve outcome of comatose patients after cardiac arrest. Front Neurol 2014;5:39.
20. Cloostermans MC, van Meulen FB, Eertman CJ, Hom HW, van Putten MJAM. Continuous electroencephalography monitoring for early prediction of neurological outcome in postanoxic patients after cardiac arrest: a prospective cohort study. Crit Care Med 2012;40:2867-75.
21. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
22. Lamartine Monteiro M, Taccone FS, Depondt C, et al. The prognostic value of 48-h continuous EEG during therapeutic hypothermia after cardiac arrest. Neurocrit Care 2016;24:153-62.
23. Legriel S, Hilly-Ginoux J, Resche-Rigon M, et al. Prognostic value of electrographic postanoxic status epilepticus in comatose cardiac-arrest survivors in the therapeutic hypothermia era. Resuscitation 2013;84:343-50.
24. Elmer J, Rittenberger JC, Faro J, et al. Clinically distinct electroencephalographic phenotypes of early myoclonus after cardiac arrest. Ann Neurol 2016;80:175-84.
25. Faro J, Coppler PJ, Dezfulian C, et al. Differential association of subtypes of epileptiform activity with outcome after cardiac arrest. Resuscitation 2019;136:138-45.
26. Jirsa VK, Stacey WC, Quilichini PP, Ivanov AI, Bernard C. On the nature of seizure dynamics. Brain 2014;137:2210-30.
27. Tjepkema-Cloostermans MC, Hindriks R, Hofmeijer J, van Putten MJAM. Generalized periodic discharges after acute cerebral ischemia: reflection of selective synaptic failure? Clin Neurophysiol 2014;125:255-62.
28. Ruijter BJ, Hofmeijer J, Meijer HGE, van Putten MJAM. Synaptic damage underlies EEG abnormalities in postanoxic encephalopathy: a computational study. Clin Neurophysiol 2017;128:1682-95.
29. Beretta S, Coppo A. Post-cardiac arrest patients with epileptiform EEG: better selection for better treatment. Neurology 2020;94:685-6.
30. Westhall E, Rundgren M, Lilja G, Friberg H, Cronberg T. Postanoxic status epilepticus can be identified and treatment guided successfully by continuous electroencephalography. Ther Hypothermia Temp Manag 2013;3:84-7.

Copyright © 2022 Massachusetts Medical Society.

The New England Journal of Medicine
Downloaded from nejm.org at WELCH MEDICAL LIBRARY - JOHNS HOPKINS UNIVERSITY on March 1, 2022. For personal use only. No other uses without permission.
Copyright © 2022 Massachusetts Medical Society. All rights reserved.