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Clinical paper

Mild therapeutic hypothermia is associated with favourable outcome in patients after cardiac arrest with non-shockable rhythms☆

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ABSTRACT

Aim: Mild therapeutic hypothermia (32–34 °C) improves neurological recovery and reduces the risk of death in comatose survivors of cardiac arrest when the initial rhythm is ventricular fibrillation or pulseless ventricular tachycardia. The aim of the presented study was to investigate the effect of mild therapeutic hypothermia (32–34 °C for 24 h) on neurological outcome and mortality in patients who had been successfully resuscitated from non-ventricular fibrillation cardiac arrest.
Methods: In this retrospective cohort study we included cardiac arrest survivors of 18 years of age or older suffering a witnessed out-of-hospital cardiac arrest with asystole or pulseless electric activity as the first documented rhythm. Data were collected from 1992 to 2009. Main outcome measures were neurological outcome within six month and mortality after six months.
Results: Three hundred and seventy-four patients were analysed. Hypothermia was induced in 135 patients. Patients who were treated with mild therapeutic hypothermia were more likely to have good neurological outcomes in comparison to patients who were not treated with hypothermia with an odds ratio of 1.84 (95% confidence interval: 1.08–3.13). In addition, the rate of mortality was significantly lower in the hypothermia group (odds ratio: 0.56; 95% confidence interval: 0.34–0.93).
Conclusion: Treatment with mild therapeutic hypothermia at a temperature of 32–34 °C for 24 h is associated with improved neurological outcome and a reduced risk of death following out-of-hospital cardiac arrest with non-shockable rhythms.

1. Introduction

The incidence of out-of-hospital cardiac arrest ranges from 37 to 46 per 100,000 events per year.[1] Approximately 25% of all cardiac arrest patients are younger than 65 years of age.[2] The favourable outcomes of patients who are admitted to the hospital range from 11% to 48%, indicating that a large number of patients die after successful resuscitation during their hospital stay or develop severe permanent neurological impairment.[3,4] The only therapy that has been shown to improve survival and neurological outcome after successful resuscitation from sudden cardiac arrest is the induction of mild therapeutic hypothermia for 12–24 h.[5,6]Two large randomised clinical trials investigating the effect of mild hypothermia in cardiac arrest survivors only included patients with primary shockable cardiac rhythms.[5,6] There is a lack of data concerning the effect of mild therapeutic hypothermia in survivors after cardiac arrest with asystole or pulseless electrical activity as the first documented rhythms. Approximately 60–80% of patients who have suffered from an out-of-hospital cardiac arrest present with an initial non-shockable rhythm.[4,7–9] Some preliminary analyses have reported a non-significant reduction in unfavourable outcomes in patients who present with pulseless electrical activity or asystole and who were treated with mild hypothermia.[10–12]

The aim of this retrospective cohort study was to investigate the effect of mild therapeutic hypothermia on neurological outcome and mortality in patients who had been successfully resuscitated from non-ventricular fibrillation cardiac arrest.

2. Methods

This cohort study is based on a cardiac arrest registry that consists of all adult patients who were admitted to the department of emergency medicine of a tertiary-care hospital with cardiac arrest between January 1992 and October 2009. The institutional ethical review board has approved this registry. The data of all patients

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Table 1
Baseline characteristics of the patients.

	Non-hypothermia (*N* = 239)	Hypothermia (*N* = 135)	*p*
Age (years)			
Median	60	58	0.239
Interquartile range	48–70	43–68	
Female sex; no./total no. (%)	97/239 (41)	38/135 (28)	0.019
Medical history; no./total no. (%)			
Diabetes	51/239 (21)	25/135 (19)	0.593
Coronary heart disease	56/239 (23)	29/135 (22)	0.702
Cerebrovascular disease	10/239 (4)	6/135 (4)	1.000
Chronic obstructive lung disease	41/239 (17)	20/135 (15)	0.544
Presumed origin of arrest; no./total no. (%)			
Presumed cardiac origin	113/239 (47)	61/135 (45)	0.746
Presumed pulmonary origin	56/239 (23)	39/135 (29)	0.267
Unknown origin	26/239 (11)	17/135 (13)	0.617
Other	44/239 (18)	18/135 (13)	0.247
Pulseless electrical activity; no./total no. (%)	110/239 (46)	71/135 (53)	0.237
Basic life support provided by bystander; no./total no. (%)	55/239 (23)	31/135 (23)	1.000
No flow time (interval between collapse and start of life support) (min)			
Median	2	3	0.048
Interquartile range	0–8	0–9	0.376
Low-flow time (interval between start of life support until ROSC[a]) (min)			
Median	9	9	0.061
Interquartile range	15–22	17–29	
Total epinephrine dose (mg)			
Median	3	3	0.189
Interquartile range	2–5	1–4	
Shockable rhythm[b] during life support; no./total no. (%)	67/239 (28)	47/135 (35)	0.198
GCS[c] on admission			
Median	3	3	0.144
Interquartile	3–3	3–3	
pH on admission to ED[d]			
Median	7.12	7.12	0.276
Interquartile range	6.97–7.27	6.98–7.22	
Lactate on admission ED[d] (mmol/l)			
Median	10.9	10.3	0.232
Interquartile range	7.9–14.8	7.5–13.8	

[a] Return of spontaneous circulation.
[b] Ventricular fibrillation or pulseless ventricular tachycardia.
[c] Glasgow Coma Scale.
[d] Emergency department.

were prospectively documented according to the 'Utstein Style Criteria', which are the recommended guidelines for cardiac arrest and cardiopulmonary resuscitation outcome reporting.[13]

2.1. Patient selection criteria

We included patients with 18 years of age or older, with a witnessed out of hospital cardiac arrest of non-traumatic origin, with a non-shockable initial cardiac rhythm (asystole or pulseless electric activity) and a restoration of spontaneous circulation. Patients who died during the first 24 h after restoration of spontaneous circulation were excluded. Patients with a Glasgow coma scale of greater than 8 after restoration of spontaneous circulation as well as patients with limited neurological and overall functionality [cerebral performance categories (CPC) and overall performance categories (OPC) >2] before cardiac arrest were not included. A performance score of 1 (good function) or 2 (moderate disability) on a 5-category scale was considered as a good functionality; the other categories were 3 (severe disability), 4 (a vegetative state), and 5 (death).[14–16] Furthermore, patients with a known cerebrovascular origin of cardiac arrest and patients with a core temperature of <30 °C upon emergency department admission were also excluded.

2.2. Endpoints

The primary endpoint was the best neurological outcome within a six-month observational period. Patients with good recovery or moderate disability had sufficient cerebral function to live independently and work at least part-time. The secondary end point was overall mortality at six months.

2.3. Treatment

All patients received standard intensive care. Patients were sedated by the administration of Midazolam (0.125 mg/kg of body weight per hour) and Fentanyl (0.002 mg/kg/h). Paralysis was induced by the intravenous administration of pancuronium (0.1 mg/kg every 2 h) or rocuronium (0.5 mg/kg/h). Each patient's temperature upon admission was measured with an infrared tympanic thermometer, an oesophageal probe, or a Foley catheter. Patients treated with hypothermia were cooled to a target temperature of 33 °C ± 1 °C by the use of surface, invasive, or combined cooling techniques. The temperature was maintained at 32–34 °C for 24 h.

2.4. Statistical analysis

Continuous variables are reported as the median and interquartile range. Categorical variables are presented as absolute and relative frequencies. Primary and secondary outcomes were binary, and the chi-square test was used to compare the outcomes between experimental groups. For normally distributed continuous variables, the Student's *T*-Test was performed. To test non-normally distributed variables, we used the Kruskal–Wallis Test. A multivariate logistic regression model was used to determine whether the association between the intervention and the primary and

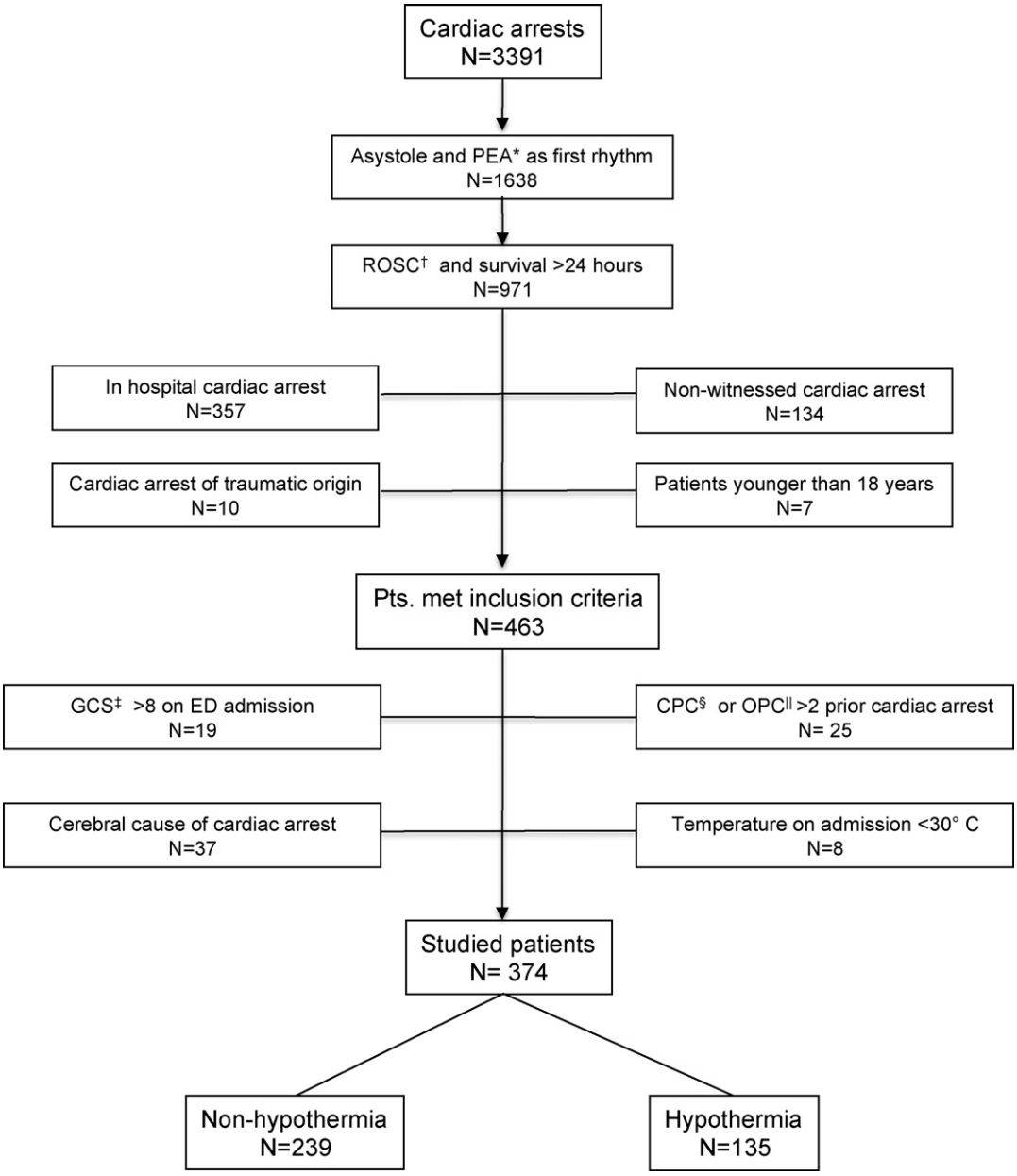

Fig. 1. Flowchart of case selection. *Pulseless electric activity. †Restoration of spontaneous, circulation. ‡Glasgow Coma Scale. §Ceberal Performance Category. ‖Overall Performance Category.

secondary outcomes (neurological recovery and mortality) was confounded by baseline differences between the study groups. We included all possible confounders which, from a clinical point of view, may be associated with the outcomes: sex, age, bystander basic life support (yes/no), presumed cardiac cause of cardiac arrest (yes/no), pulmonary cause of cardiac arrest (yes/no), no flow time (time from collapse to start of life support [min]), low flow time (time from start of life support until restoration of spontaneous circulation [min]), history of diabetes (yes/no), chronic obstructive pulmonary disease (yes/no), cerebral vascular insufficiency (yes/no), pulseless electric activity as the first monitored rhythm (yes/no), total epinephrine dose, shockable rhythm during life support (yes/no), and GCS on admission. Continuous variables were examined for any possible linear associations with the outcome. To keep the most parsimonious model, we excluded confounders that did not change the effect size of the primary risk factors by more than 1% from the final model and did not significantly change the goodness-of-fit model. The goodness-of-fit was assessed by the Hosmer–Lemeshow Test. We tested for interactions with the primary risk factor, assuming significant interactions at $p \leq 0.05$. If interactions were present, we further explored them via stratification of the effect modifiers. SPSS software (version 16.0, SPSS Inc., Chicago, IL) and STATA (version 8.2, StataCorp, College Station, TX) were used to analyse the data.

3. Results

During an observational period from 1992 to 2009, 3391 patients with cardiac arrest were seen at the emergency department and documented in the registry. Out of these, 374 patients were analysed. The flow chart of case selection is shown in Fig. 1. Mild therapeutic hypothermia was induced in 135 patients. At baseline (Table 1), there were no statistically significant differences

Table 2
Timing of cooling therapy and cooling methods.

	Min	IQR
Time to cooling initiation	85	43–140
Time to temperature <34 °C	174	89–247
Cooling method	***N***	**%**
Surface	35	26
Invasive	62	46
Combined	25	18
Other	13	10

between the two groups except that there were less female patients in the group that was treated with hypothermia.

3.1. Cooling

In the hypothermia group, 35 patients (26%) were cooled with surface cooling, 87 patients (64%) were cooled with invasive cooling devices or combined techniques, and 13 patients (10%) were cooled with other methods. A median of 85 min (interquartile range: 43–140) elapsed from the restoration of spontaneous circulation to cooling initiation (Table 2). The target temperature was reached in a median time of 174 min (interquartile range: 89–247). The temperature curves for the non-hypothermia and hypothermia groups are shown in Fig. 2.

3.2. Outcome

A total of 47 out of the 135 patients (35%) in the hypothermia group had favourable neurological outcomes within six months, as compared to 55 of the 239 (23%) in the non-hypothermia group (odds ratio: 1.79; 95% confidence interval: 1.12–2.84). After adjusting for confounders, the odds ratio for favourable neurological outcome was 1.84 (95% confidence interval: 1.08–3.13).

The six-month mortality after cardiac arrest was 180 out of the 239 patients in the non-hypothermia group (75%) in comparison to 82 out of the 135 patients (61%) who were treated with mild hypothermia (odds ratio: 0.51; 95% confidence interval: 0.33–0.80).

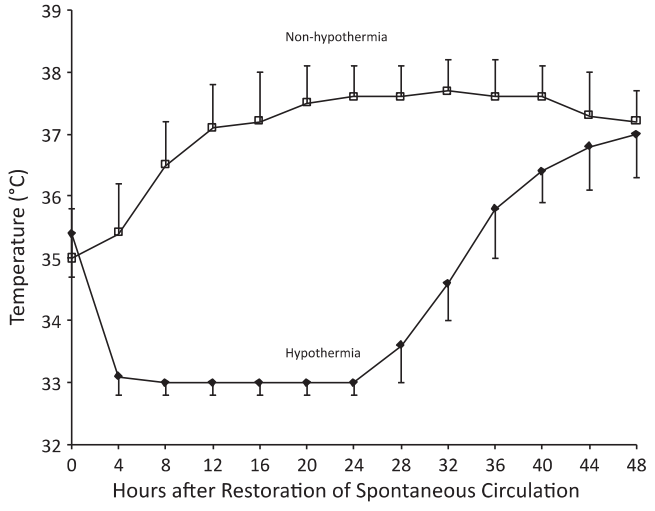

Fig. 2. Temperatures in the non-hypothermia and hypothermia groups. The T-bars indicate the 75th percentile in the non-hypothermia group and the 25th percentile in the hypothermia group. The target temperature in the hypothermia group was 32–34 °C, and the duration of cooling was 24 h. Only patients with recorded temperatures were included in the analysis. The graph was computed out of 1318/1755 (70%) datasets in the hypothermia group and 921/3107 (30%) in the non-hypothermia group.

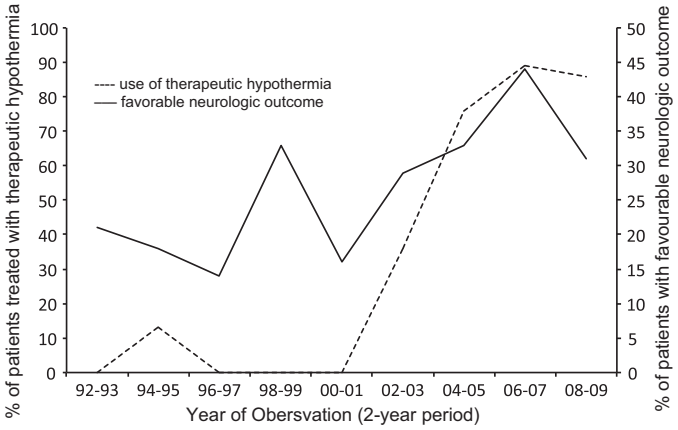

Fig. 3. Percentage of patients treated with therapeutic hypothermia (dotted line) and percentage of all patients with favourable neurologic outcome (solid line) over time percentiles of the observational period. Favourable neurologic outcome was observed in 40/186 patients (22%) in the first five percentiles (pre-hypothermia period) and in 62/188 patients (33%) in the last five percentiles (hypothermia period) ($p = 0.02$).

After adjusting for confounders, the odds ratio for death in the hypothermia group was 0.56 (95% confidence interval: 0.34–0.93) in comparison to the non-hypothermic group (Table 3). Changes in the use of therapeutic hypothermia and changes in primary outcome over the observational period are shown in Fig. 3.

4. Discussion

Treatment with mild therapeutic hypothermia at temperatures between 32 °C and 34 °C for 24 h is associated with an improved neurological outcome and a reduced risk of death during a six-month observational period in patients who were successfully resuscitated from out-of-hospital cardiac arrests of non-traumatic origin with asystole or pulseless electrical activity as the first documented rhythm. This association remains unchanged after adjustment for confounders. The fact that patients with various causes of cardiac arrest were included in our trial strongly supports hypothermia as the therapy of choice for all comatose cardiac arrest survivors irrespective of the first monitored rhythm.

Our cardiac arrest database includes more than 3000 cardiac arrest patients who were followed-up by healthcare professionals up to six months after the event by personal visit or a standard telephone interview. Detailed patient data at admission, including 'low-flow' times, 'no-flow' times, and a medical history, were documented. Data were obtained through meticulous communications with the dispatch centre, the emergency physicians, the paramedics on scene, bystanders, and relatives.

This study has a few limitations that are worth mentioning. This study was derived from an observational and descriptive registry, and the database therein comprises only patients who were admitted to our department. Because this was not a randomised study, selection bias might have occurred. The final decision to cool a patient was left to the discretion of the attending physician. Therefore, it is possible that a higher proportion of patients with expected bad outcomes were not cooled. We attempted to compensate for this possible bias by adjusting for all known confounders that may have influenced our results. Furthermore we excluded all patients that died during the first 24 h after return of spontaneous circulation. This criterion was chosen because in patients with hemodynamic instability, therapeutic hypothermia might not have been established because of possible bad outcome. Another significant limitation of our study is that patients who were

Table 3
Outcome and multivariable logistical regression for favourable neurological outcome and death.

	Non-hypothermia (no./total no. (%))	Hypothermia (no./total no. (%))	Odds ratio (95% CI[a])	*p*
Favourable neurological outcome[b,c]	55/239 (23)	47/135 (35)	1.84 (1.08–3.13)	0.024
Death[d]	180/239 (75)	82/135 (61)	0.56 (0.34–0.93)	0.025

An adjustment for multiple confounders included age, sex, presumed cardiac cause of arrest, presumed pulmonary cause of arrest, pulseless electrical activity as the primary rhythm, no flow time (time from collapse to the initiation of life support), low-flow time (time from the start of life support to restoration of spontaneous circulation), total dose of epinephrine, shockable rhythm during life support, and GCS on admission.

[a] Confidence interval.

[b] A favourable neurological outcome was defined as a cerebral-performance category of 1 (good recovery) or 2 (moderate disability). None were lost to follow-up.

[c] Hosmer–Lemeshow $\chi^2 = 10.56$, $p = 0.23$, indicating a good model fit, $n = 374$.

[d] Hosmer–Lemeshow $\chi^2 = 6.352$, $p = 0.61$, indicating a good model fit, $n = 374$.

not treated with hypothermia had a trend towards hyperthermia, which may be associated with a poorer outcome.[17]

The use of mild therapeutic hypothermia after cardiac arrest has become a clinical standard following the reports of two large, prospective, randomised, and controlled trials that were conducted in 2002.[5,6] Nevertheless, these two landmark studies only included patients with ventricular fibrillation or pulseless ventricular tachycardia as the first monitored rhythm. There is only one prospective, randomised trial, which was conducted by Hachimi-Idrissi et al., that includes patients with only an initial non-shockable rhythm.[10] This study was not able to show a significant advantage in terms of neurological or overall outcome of treatment with mild therapeutic hypothermia; however, a trend towards better outcomes was indicated. Because it was primarily designed as a feasibility trial, the study by Hachimi-Idrissi et al. might have been too underpowered to demonstrate a significant outcome improvement in the hypothermia group.

In a retrospective study Holzer et al. were able to show a positive effect of mild hypothermia in cardiac arrest survivors irrespective of the initial rhyhtm.[18] Several studies were not able to show a significant improvement in neurologic outcome via the use of induced hypothermia in patients presenting with asystole or pulseless electrical activity.[11,12,19] In 2007, a study by Kim et al. showed a possible deleterious effect of mild therapeutic hypothermia in cardiac arrest survivors with asystole or pulseless electric activity as the first documented rhythm.[20] Favourable outcomes in patients with initial non-shockable rhythms was 9% in the hypothermia group in comparison to 23% in the non-hypothermia group, although this difference was not statistically significant. A failure to show the benefit of cooling could be explained by several factors. This prospective trial was designed as a pilot trial to investigate the induction of mild hypothermia in the pre-hospital setting and not as an outcome study concerning the effect of hypothermia in non-shockable rhythm cardiac arrests. While cooling was initiated outside of the hospital with cold saline, the maintenance of hypothermia in the hospital was up to the physician's preference, and more than a third of the patients did not receive maintenance cooling. In contrast, in our study, therapeutic hypothermia was strictly maintained for 24 h according to our local standards. Therefore, our results are more reliable regarding the positive effect of a continuous hypothermic treatment for 24 h, as recommended by current resuscitation guidelines.[21,22] A recently published analysis by Dumas et al. showed no improvement in neurological outcome when mild therapeutic hypothermia was applied in patients after non-ventricular fibrillation cardiac arrest.[23] As compared to our registry, follow-up was performed until hospital discharge and the proportion of cardiac arrests due to cardiac causes was inversely distributed. This might be due our rigorous in- and exclusion criteria, which correspond to those in the HACA-Trial.[5] A prospective randomised trial that focuses on the effects of mild hypothermia in cardiac arrest survivors with non-shockable rhythms is still missing. However our results add to the amount of evidence in favour of hypothermia as a beneficial treatment for these patients, and they show that mild hypothermia is an effective treatment in cardiac arrest survivors who present with pulseless electric activity or asystole. The authors feel that the presently available evidence and the pathophysiology of the effect of hypothermia on neurons justify the application of mild therapeutic hypothermia in all patients after cardiac arrest, regardless of the initial rhythm.[24–26]

5. Conclusion

Treatment with mild therapeutic hypothermia at a temperature of 32–34 °C for 24 h is associated with an improved neurological outcome and a reduced risk of death in patients following out-of-hospital cardiac arrest with an initial non-shockable rhythm. Nevertheless, the need for a prospective randomised clinical trial in this patient population to recommend the use of mild hypothermia after cardiac arrest is evident.

Conflict of interest statement

The authors declare that they have no financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work.

Role of the funding source

There have been no study sponsors, who could have had a role in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

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