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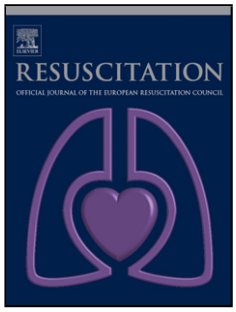
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Abstract

Background:

Optimal hemodynamic goals in post-resuscitation patients are not clear. Previous studies have reported an association between lower heart rate and good outcome in patients receiving targeted temperature management (TTM) after out-of-hospital cardiac arrest.

Methods:

We analyzed heart rate (HR) and outcome data of 504 post-resuscitation patients from the prospectively collected database of the FINNRESUSCI study. One-year neurologic outcome was dichotomized by the Cerebral Performance Category (CPC) to good (1–2) or poor (3–5).

Results:

Of 504 patients, 40.1 % (202/504) had good and 59.9 % (302/ 504) had poor one-year neurologic outcome. Patients with good outcome had lower time-weighted mean HR during the first 48 hours in the ICU (69.2 bpm [59.2-75.1] vs. 76.6 bpm [65.72-89.6], p<0.001) and the first 72 hours in the ICU (71.2 bpm [65.0-79.0] vs. 77.1 bpm [69.1-90.1, p<0.001]). The percentage of HR registrations below HR threshold values (60, 80 and 100 bpm) were higher for patients with good neurologic outcome, p<0.001 for all. Lower time-weighted HR for 0-48 h and 0-72 h, and a higher percentage of HR recordings below threshold values were independently associated with good neurological one-year outcome (p<0.05 for all). When TTM and non-TTM patients were analyzed separately, HR parameters were independently associated with one-year neurologic outcome only in non-TTM patients.

Conclusion:

Lower heart rate was independently associated with good neurologic outcome. Whether HR in post-resuscitation patients is a prognostic indicator or an important variable to be targeted by treatment, needs to be assessed in future prospective controlled clinical trials.

Key words: Postresuscitation; Haemodynamics; Heart rate; Bradycardia; Outcome; Hypothermia; Therapeutic Temperature Management

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Introduction

Intensive care after successful resuscitation has developed markedly during last decade.(1) Despite active research around post-resuscitation care, data on optimal hemodynamics of these patients remain scarce. (2, 3) Recently, two studies reported that better survival and neurologic outcome was associated with lower heart rate (HR) during therapeutic hypothermia (TH). (4, 5) Both therapeutic temperature management (TTM) and vasoactive medications may have an influence on heart rate. Accordingly, we aimed to test the association of heart rate with one-year neurologic outcome in a large prospective FINNRESUSCI data, including both patients treated with and without therapeutic hypothermia.

Methods

The prospective observational FINNRESUSCI study was conducted in 21 Finnish ICUs between March 2010 and February 2011. (6) In this present study, we included 504 patients from 20 of the 21 participating ICUs with available heart rate data. All patients with available heart rate recordings were included in this pre-planned sub-study of the FINNRESUSCI-study (flowchart in ESM Figure 1).

Patients and data collection

The inclusion criteria for FINNRESUSCI study was OHCA, age over 18 years and post-resuscitation care in one of the participating 21 Finnish ICUs. The study protocol was approved by the Ethics Committee of Helsinki University Central Hospital. (6) The use of TTM was decided by the local ICU protocols.

Data were collected prospectively and included patient demographics, factors known at resuscitation, and treatment in the ICU.

Routine data (demographics, the International Classification of Diseases [ICD-10] diagnosis, ICU scores, physiologic measures, and outcomes), data on vasopressor and inotrope use, and all arterial blood gas analyses that were drawn during intensive care treatment were collected prospectively to the Finnish Intensive Care Consortium (FICC) database, maintained by Tieto Ltd (Helsinki, Finland).

Heart rate registration was performed in each of the participating ICUs. The data were then collected along with other data to the FICC database. The heart rate data were registered as 2-15 minute medians in the respective ICUs. 5 ICUs collected data as 15-minute medians, one ICU as 5-minute medians while the other

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15 ICUs collected heart rate data as 2-minute medians. For our analyses the heart rate data retrieved from the FICC database was converted to 10-minute medians for data from ICUs using 2–5-minute medians and the data in 15-minute medians were used for analyses without further filtering. The heart rate of 8 patients (1.6 %) could not be retrieved from the database. One of the 21 participating ICUs did not collect hemodynamic data to the database.

Outcome data

A neurologist (M.T.), blinded to ICU care, determined one-year functional outcome with a telephone interview with the patient, next of kin, or caregiver. Functional outcome was classified using the cerebral performance category (CPC) and dichotomized into good (1–2) or poor (3–5). (7)

Statistical analyses

Data are presented as percentages or medians with interquartile ranges (IQR). We used a Chi-square test or Fisher's exact test, when appropriate for categorical data and the Mann-Whitney U-test, for continuous data.

We identified the heart rate measurements, in addition to the highest and the lowest values during the ICU stay. We calculated the heart rate-time integral for (heart rate value x time of measurement from first measurement in 10 or 15 minute medians) for evaluation of total heart rate burden during the first 48 hours and the first 72 hours in the ICU. By dividing the heart rate-time integral with the aggregate time of the heart rate registrations, we calculated the time-weighted HR values for the first 48 hours and 72 hours. We identified all values below the following heart rate thresholds: in the ICU during the first 48 hours, 60 beats per minute (bpm), 80 bpm, 100 bpm, and calculated the percentage of heart rate registrations during this time interval below these thresholds. We also identified the heart values below heart rate thresholds: 50 bpm, 60 bpm, 70 bpm, 80 bpm, 90 bpm and over 90 bpm, from 500 minutes to 1500 minutes from the first heart rate registration in the ICU and assessed the percentage of heart rate registrations below the thresholds, during this time interval.

We analyzed the ability of time-weighted mean heart rate values for 48 and 72 hours from ICU admission to predict neurologic outcome for all patients and for TTM or non-TTM treated patients respectively using Area under Receiver Operating Characteristics (ROC) curve (AUCs) with 95 % confidence intervals (CI). We estimated the best cut-off value for prediction of one-year outcome of the time-weighted mean heart rate values by Youden index (sensitivity + specificity −1).

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We performed a univariable analysis to determine prognostic factors for one-year neurologic outcome. Finally, variables with a p-value <0.1 were entered in a backward logistic regression analysis to evaluate the possible independent associations between heart rate parameters and one-year outcome for all patients. We performed the regression analyses using the enter method and confirmed by performing a backward stepwise conditional regression analyses. The following variables were entered to the analyses: Presence of coronary artery disease, use of epinephrine during CPR, therapeutic hypothermia in ICU, shockable initial rhythm, time to return of spontaneous circulation (ROSC), witnessed cardiac arrest, SAPS 24 score, history of chronic heart failure, coronary angiography during ICU stay. In each of the five separate regression analysis models, we entered one of the following heart rate variables: 1) time-weighted mean heart rate for the first 48 h in the ICU, 2) time-weighted mean heart rate for the first 72 h in the ICU, 3) percentage of heart rate recordings below 60 bpm 4) percentage of heart rate recordings below 80 bpm, and 5) percentage of heart rate recordings below 100 bpm. We performed the regression analyses for all patients and for TTM and non-TTM patients separately.

All statistical analyses were performed using IBM, SPSS statistics 21.0 and 22.0 (IBM, Armonk, NY, USA) or NCSS 8 (East Kaysville, UT, USA) software.

Results

We analyzed a total of 953,560 heart rate registrations from 504 patients, which were converted to 237,889 10- or 15-minute-median heart rate values for the analyses (ESM appendix). The time from OHCA to ICU admission was 119 (90-162) minutes and the time from OHCA to the first heart rate registration was 129 (100-175) minutes (median, IQR)

The baseline and demographic data are shown in Table 1 and ESM Table 3. ICU mortality was 107/504 (21.2 %), hospital mortality 218/504 (43.3 %) and one-year mortality 222/504 (44.0 %). Of the 504 patients, 40.1 % (202/504) had good neurologic outcome (CPC 1-2), while 59.9 % (302/ 504) had poor neurologic outcome (CPC 3-5) at one year. Of the 281 patients with shockable rhythm, 241 (85.8 %) were treated with TH, and of the 223 patients with non-shockable rhythm, 70 (31.4 %) were treated with TH.

Of the study patients, 107 patients died in the ICU. Of these, the last heart rate registration was ≤ 48 hours in 65 patients and ≤ 72 hours in 86 patients, representing death or withdrawal of intensive care during the study period. In 301 patients, the last heart rate registration was done at ≤ 72 hours. Of these 301 patents,

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147 left the hospital alive and 107 had good one-year outcome, representing patients no more requiring ICU treatment, who were transferred to the ward during the study period.

The heart rate data of patients with good and poor outcome are presented in Table 2 and ESM Table 1. Quartiles of time-weighted mean heart rate and outcome are presented in Figure 1 (and ESM figure 2). All heart rate recordings during first 48 hours in ICU stratified to outcome are presented in Figure 2.

In Receiver Operating Characteristic (ROC) analyses of all patients, the area under curve (AUC) of the time-weighted mean heart rate for the first 48 hours was 0.675 (CI 95%, 0.629-0.721) and 0.658 (CI 95%, 0.611-0.705) for the first 72 hours. Of the 307 patients with TTM, time-weighted mean heart rate for the first 48 hours AUC was 0.707 (CI 95%, 0.629-0.785) and 0.591 (CI 95%, 0.528-0.655) for the first 72 hours. Of the 197 patients without TTM time-weighted mean heart rate of first 48 hours AUC was 0.712 (CI 95%, 0.634-0.789) and of first 72 hours 0.606 (CI 95%, 0.543-0.669).

With Youden analyses, the best cut-of value of time-weighted mean heart rate 48 hours for prediction of good one-year neurologic outcome was below 75.0 bpm for all patients, 68.8 bpm for patients with TTM and 76.2 bpm for non-TTM patients.

In multivariable regression analyses (five separate models) lower time-weighted HR for 0-48 h, lower time-weighted HR for 0-72 h, a higher percentage of heart rate recordings below 60 bpm, 80 bpm, and 100 bpm during the first 48 hours were all independently associated with good neurological outcome at one year ($p<0.05$ for all) (Table 3).

When the regression analyses were performed for TTM and non-TTM patients separately, lower time-weighted HR for 0-48 h, lower time-weighted HR for 0-72 h, and lower percentages of heart rate recordings below 80 bpm and 100 bpm during the first 48 hours were all independently associated with good neurological outcome in non-TTM patients ($p<0.05$ for all), but not in patients treated with TTM. The results of the regression analyses are presented in ESM Tables 2, 4 and 5. The results were confirmed by alternatively using tertiles and quartiles of time-weighted HR in the regression analyses.

Data of vasopressor use were available for analyses from 451 patients treated in 18 ICUs, as 3 ICUs did not collect vasopressor data. Of the 451 patients, 359 (79.6 %) received vasopressors or inotropes during the first 48 hours in the ICU. Norepinephrine was used in 297/451 (65.9 %) with a maximum dose of 0.099 µg/kg/min (median, IQR 0.056-0.190) for patients with good outcome and 0.145 µg/kg/min (median, IQR 0.075 -0.273) for patients with poor outcome (p=0.001). Dobutamine was used in 124/451 (27.5 %) and of

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these patients, 65/124 (52.4%) had poor outcome and 59/124 (47.6 %) had good outcome (p=0.17). Furthermore, 30/459 (6.5 %) received dopamine and 18/459 (3.9 %) epinephrine. In patients with dobutamine treatment, time-weighted mean heart rate for the first 48 hours was lower, 69.5 bpm (61.0-78.0) vs. 72.2 bpm (63.6- 85.9), and the percentage of heart rate registrations below 60 bpm was higher, 37.2% (10.3%-58.1%) vs 17.6% (0.0%-53.6%) than in patients with no dobutamine.

Discussion

In this substudy of the observational multicenter FINNRESUSCI study, we found that lower time-weighted mean heart rate during first 48 and first 72 hours, and a higher percentage of heart rate registrations below thresholds 60 bpm, 80 bpm and 100 bpm during the first 48 hours in the ICU were associated with better one-year neurologic outcome. In multivariate regression analyses, lower heart rate was independently associated with good neurologic outcome in the whole study population, as well as in the subgroup of patients not treated with TTM. Of note, lower heart rate was not independently associated with good neurologic outcome in TTM patients (33°C).

Optimal hemodynamic targets during post-resuscitation care are still largely unknown (2, 3) (8). Large prospective studies on optimal hemodynamic parameters, such as blood pressure (3, 9) and cardiac output (10, 11) are lacking. There are scarce data on optimal heart rate targets, and indications for e.g. pacing or vasoactive medications to treat post-resuscitation bradycardia or tachycardia are not clear. (2)

Heart rate may be modified by several factors during post-resuscitation intensive care. Mild hypothermia initially leads to activation of the sympathetic nerve system with a subsequent increase in venous return, followed by mild sinus tachycardia. Further lowering of the body temperature during therapeutic hypothermia causes the heart rate to drop progressively. At temperatures of approximately 33°C, normal heart rate is 35-45 bpm, due to changes in the rate of spontaneous depolarization of cardiac pacemaker cells, conduction of myocardial impulses and duration of action potentials.(12) In addition, hypothermia may lead to changes in sympathetic and autonomous nervous system function, leading to subsequent changes in heart rate.(13) On the other hand, use of ß-agonists generally increases the heart rate. Vasoactive medications, particularly catecholamines like dobutamine, epinephrine and dopamine accelerate the heart rate, potentially causing tachycardia.(14)

In patients not receiving therapeutic hypothermia, the differences in heart rate and their associations with outcome may not be attributed only to changes in body temperature. Use of ß-blockers prior to cardiac

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arrest may plausibly lower the heart rate significantly during the first days after resuscitation. Use of ß-blockers is associated with better outcome in patients with chronic heart failure (15, 16) and after myocardial infarction(17, 18). Thus, it is possible that medications have a role in the better outcome with lower heart rate also after resuscitation. The use of ß-agonists may also affect heart rate after cardiac arrest. In the present study however, use of dobutamine was not associated with higher heart rates, nor with worse outcome. However, dobutamine was plausibly initiated for treatment of marked bradycardia and the outcome of this patient group could not be assessed without the dobutamine effect, which plausibly raised the heart rate of these patients. Norepinephrine may also to a lesser degree affect heart rate. Higher norepinephrine doses of patients with poor outcome might be a consequence of more severe hemodynamic compromise in patients not surviving.

In the cohort of Thomsen et al (5), patients with post-resuscitation bradycardia had less previous heart failure and higher admission ejection fraction (EF). In our previous study (11) two-thirds of post-resuscitation patients developed transient myocardial depression, presenting as low stroke volume and cardiac index. It seems plausible that bradycardia is physiological and well tolerated, if the cardiac function is normal, but less well tolerated in patients with pre-existing or post-resuscitation induced impaired contractility.

As bradycardia is a normal physiological response to therapeutic hypothermia, lack of this response could potentially reflect other underlying pathologies, or more severe brain injury due to cardiac arrest, impairing the outcome of these patients. (5) In patients not treated with hypothermia, higher heart rate may also be caused by a more severe degree of post-cardiac arrest syndrome and brain injury with concomitant autonomous dysfunction.(19, 20) These injuries may also be linked to lower heart rate variability, related to increased sympathetic excitation, depressed vagal activity, or reduced responsiveness of sinus nodal cells to neural modulation. Preserved heart rate variability has been presented as a marker of intact autonomic regulation and less cerebral injury in experimental and clinical studies of cardiac arrest. (21, 22)

It has been suggested that the pathophysiology of the sepsis-like post-cardiac arrest syndrome includes shock-induced endotheliopathy, which is correlated with sympatho-adrenal hyperactivation. (23) Thus, heart rate could be a marker of the severity of the systemic ischemia-reperfusion injury. In a post-hoc study of the TTM –study of patients receiving hypothermia treatment (33°C or 36 °C), circulating catecholamines and markers of endothelial damage inter correlated, and predicted long-term mortality. High plasma epinephrine was the only biomarker studied that was associated with mortality at all time points. (24) In a previous substudy of 278 FINNRESUSCI patients, we have earlier shown that levels of heparin-binding protein were associated both with early death and one-year neurologic outcome.(25, 26)

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Lower heart rate was independently associated with good outcome in patients without TTM, but not in patients treated with TTM, although the median heart rate was lower in these patients. TTM at 33°C and deep sedation used during TTM lower the heart rate and might attenuate the association of HR and outcome in this patient group. However, in the present study, the TTM and non-TTM patients were not identical due to the patient selection process. Most of the patients treated with TTM were resuscitated from shockable rhythm, which is a prognostic indicator in itself. (26) Furthermore, the etiology of the cardiac arrest might be different in shockable and non-shockable arrests and, thus, modify the HR response.

Lower heart rate is associated with better outcome, but without prospective trial it is not possible to conclude, whether is it a prognostic marker, or whether lowering of heart rate could be a treatment target. If trying to modify the heart rate with e.g. ß-blockers, optimal treatment targets for different patient groups would have to be defined. Plausibly HR targets should be individualized, taking in account e.g. TTM target temperature, degree of sympathico-adrenal hyperactivation, hemodynamic status, and left ventricular function.

The strength of the present study lies in the comprehensive heart rate data collected in a large multicenter study covering the majority of Finnish OHCA patients during one year. In contrast to previous studies reporting associations of bradycardia with neurologic outcome in patients treated with therapeutic hypothermia (4, 5), the present study includes patients both with and without therapeutic hypothermia. Furthermore, in addition to detailed heart rate data, we also analyzed rigorous data of vasoactive medications.

Our study has some limitations. First, information of medication prior to OHCA and hospitalization was not collected and could therefore not be retrieved for analyses in this sub-study. Therefore, the association of prior ß-blocker medication, heart rate and outcome could not be assessed. Also other medications during intensive care than vasoactives, such as sedatives and antiarrhytmics, may have caused changes in HR. Second, we did not collect data on cardiac function (cardiac output or ventricle function) for the assessment of whether patients with preserved cardiac function tolerate bradycardia. Third, we did not collect data on heart rate variability, which has been presented as a marker of preserved autonomous function. Fourth, detailed temperature data were not collected. Fifth, there was some variation between ICUs both on methods providing TH and on the selection of patients for TH. The decision to use TH for some of the patients with non-shockable initial rhythm may have affected the results, considering the association of HR and outcome, as TH in itself lowers HR. Sixth, in the median filtering process used in data analysis,

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some extreme values of heart rate may have lost (ESM appendix and table 1). Furthermore, death or discharge from the ICU before the end of the 48 hour study period could have potentially biased the results.

Conclusions

Lower heart rate during the first 48 and 72 hours and a higher percentage of lower heart rate registrations during the first 48 hours in ICU were associated with better one-year neurologic outcome in post-resuscitation patients. Lower heart rate was independently associated with good neurologic outcome in the whole population. When TTM and non-TTM patients were analyzed separately, lower heart rate was independently associated with good neurologic outcome only in non-TTM patients. Whether heart rate in post-resuscitation patients is a prognostic indicator or a variable to be targeted by treatment, needs to be assessed in future prospective clinical trials.

Conflict of Interest

No conflict of interest.

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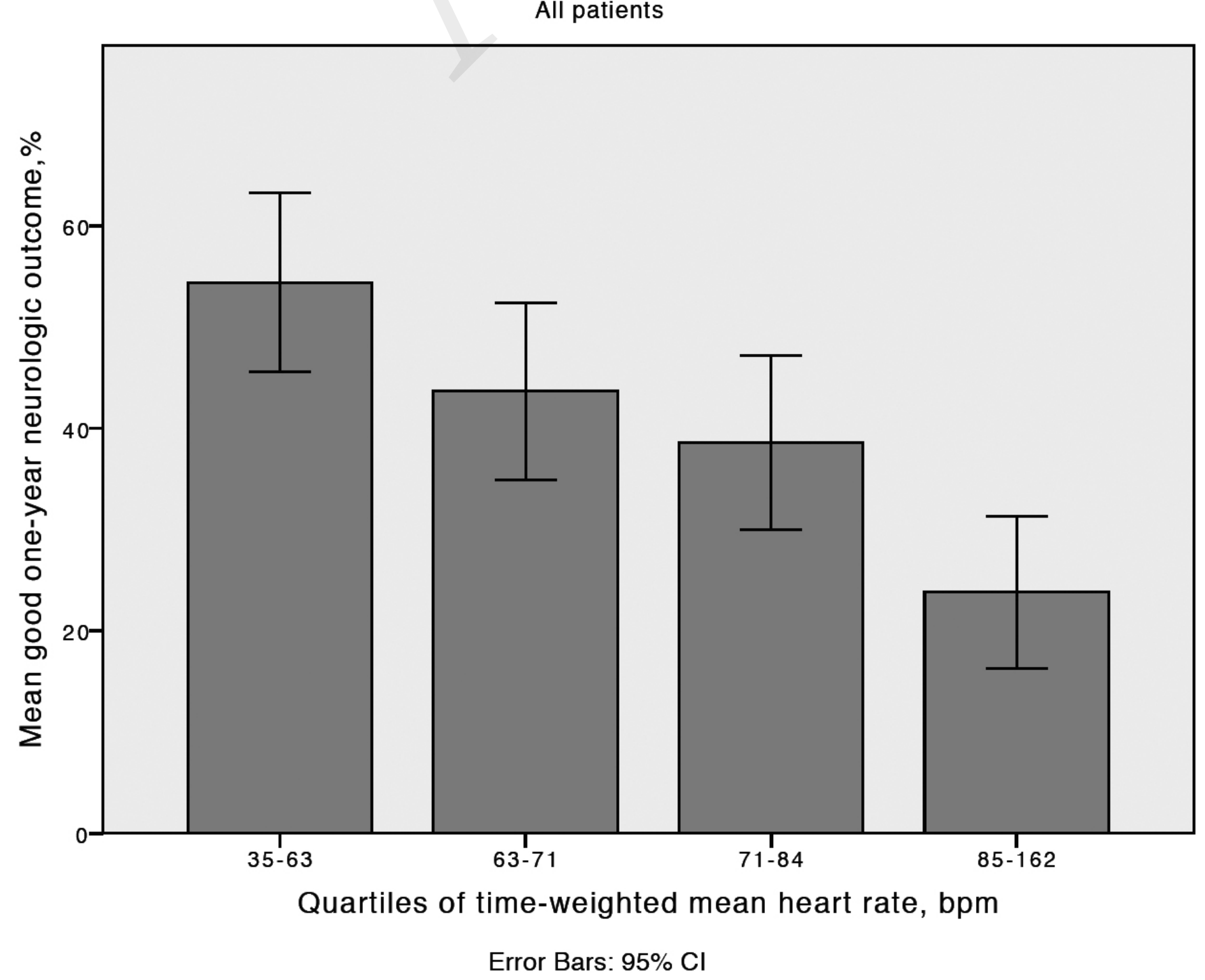
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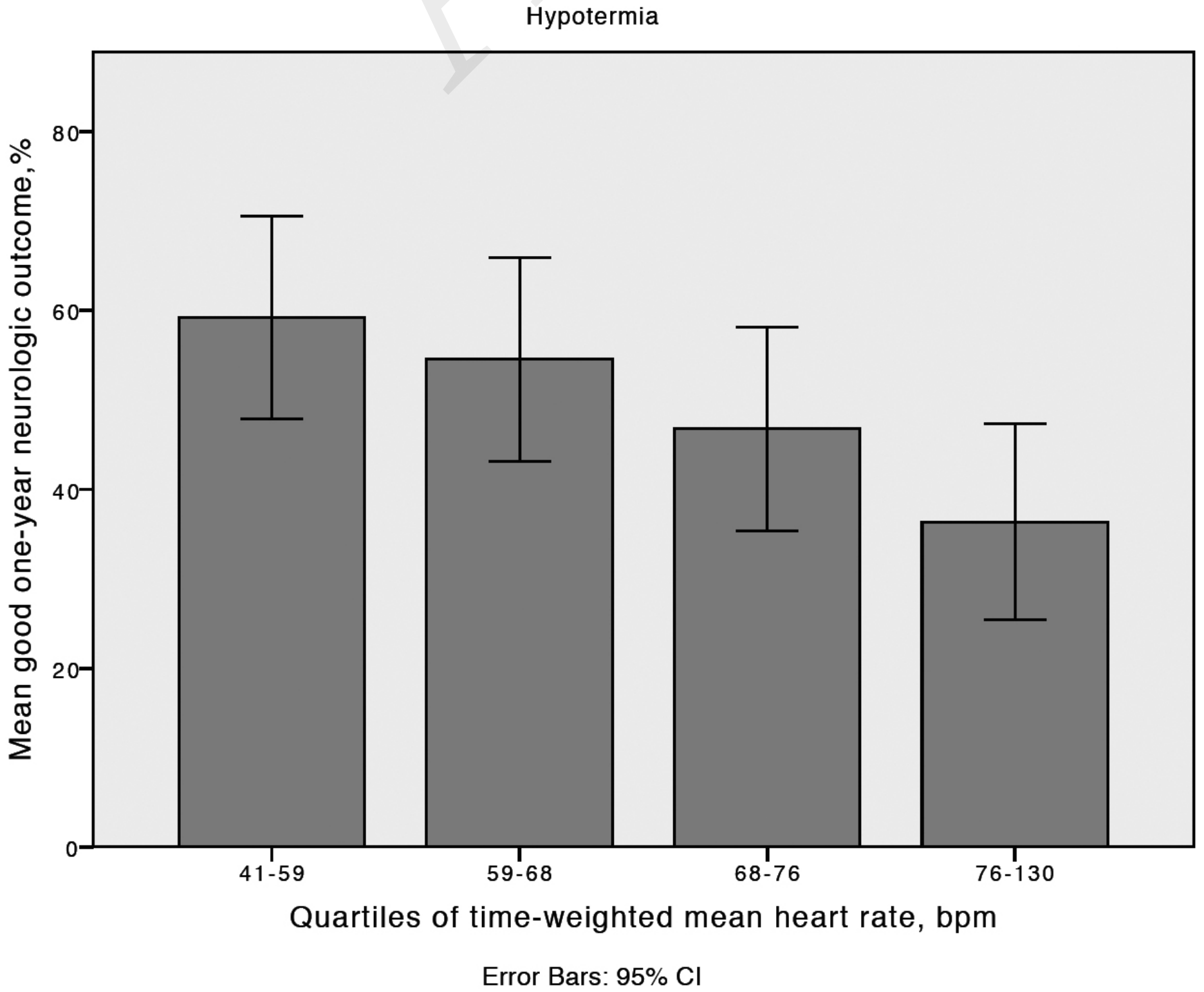
Figure legends

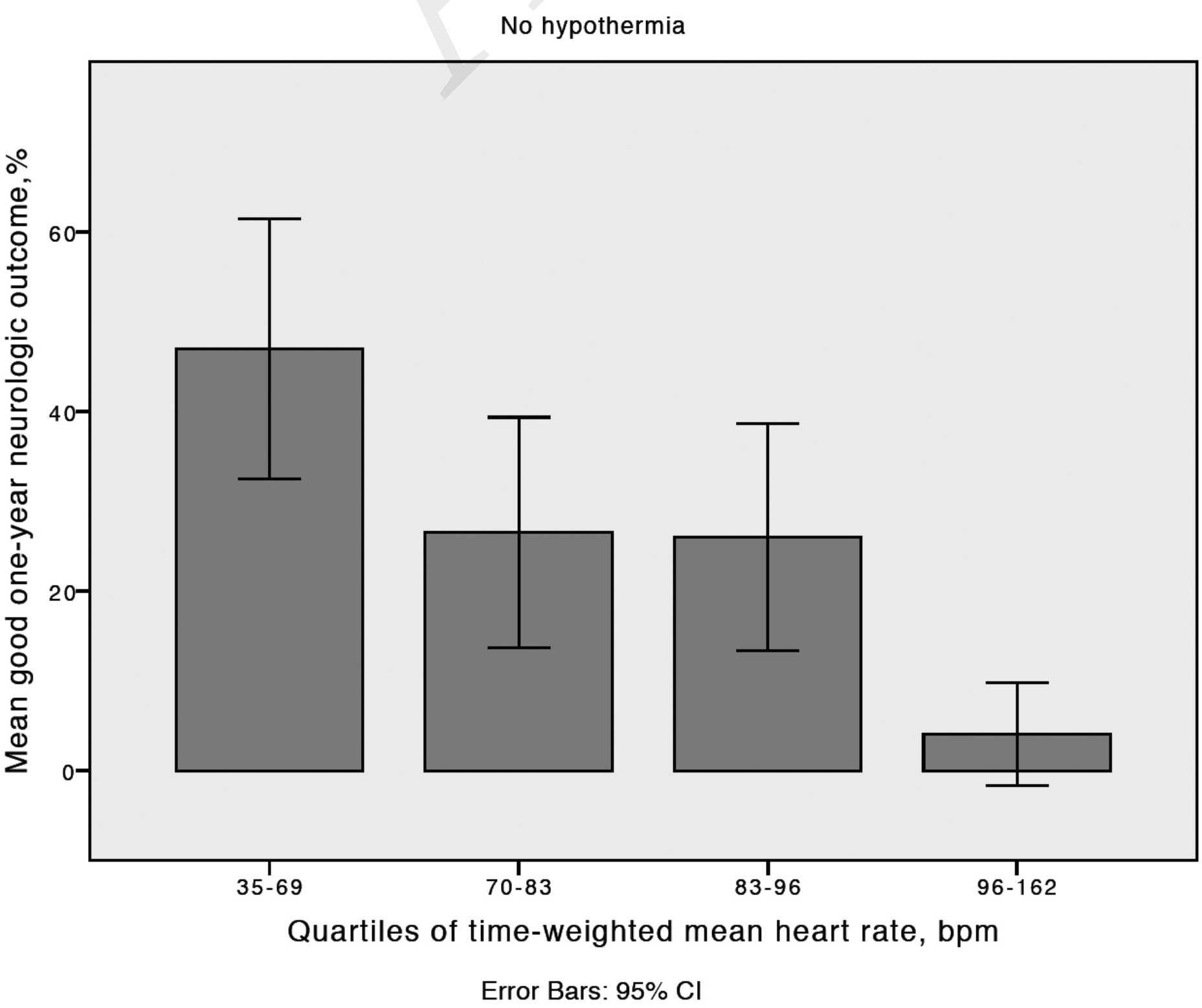
Figure 1. Quartiles of time-weighted mean heart rate during the first 48 h in ICU and good one-year neurologic outcome in 1a) all patients, 1b) patients treated with TH (33°C) and 1c) patients treated with no TTM.

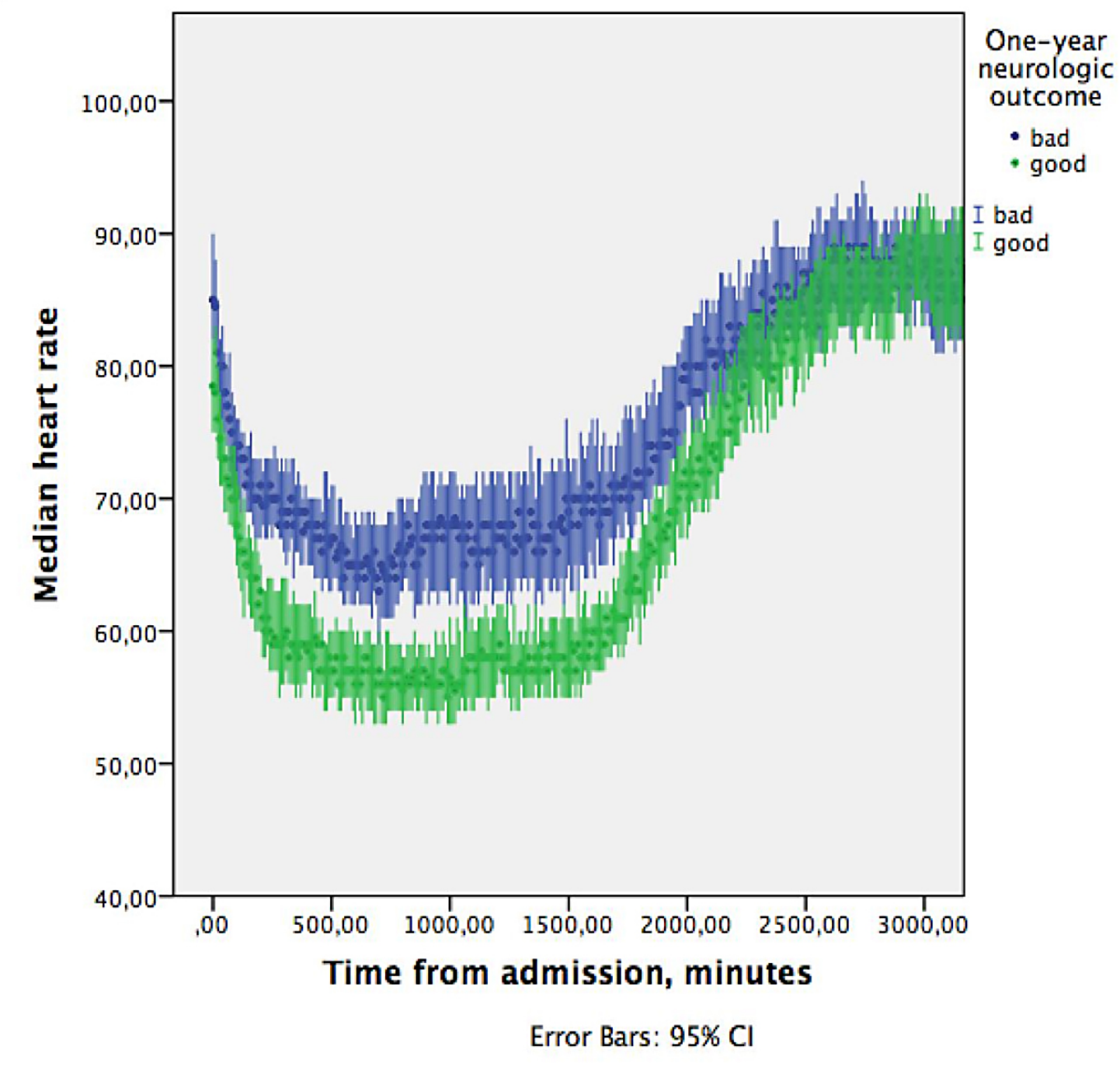
Figure 2. Heart rate recordings during first 48 hours in ICU stratified to one-year neurologic outcome (CPC 1–2 good, CPC 3–5 poor outcome). 2a) All post-resuscitation patients, 2b) patients treated with TH (33°C), 2c) patients with no TTM.

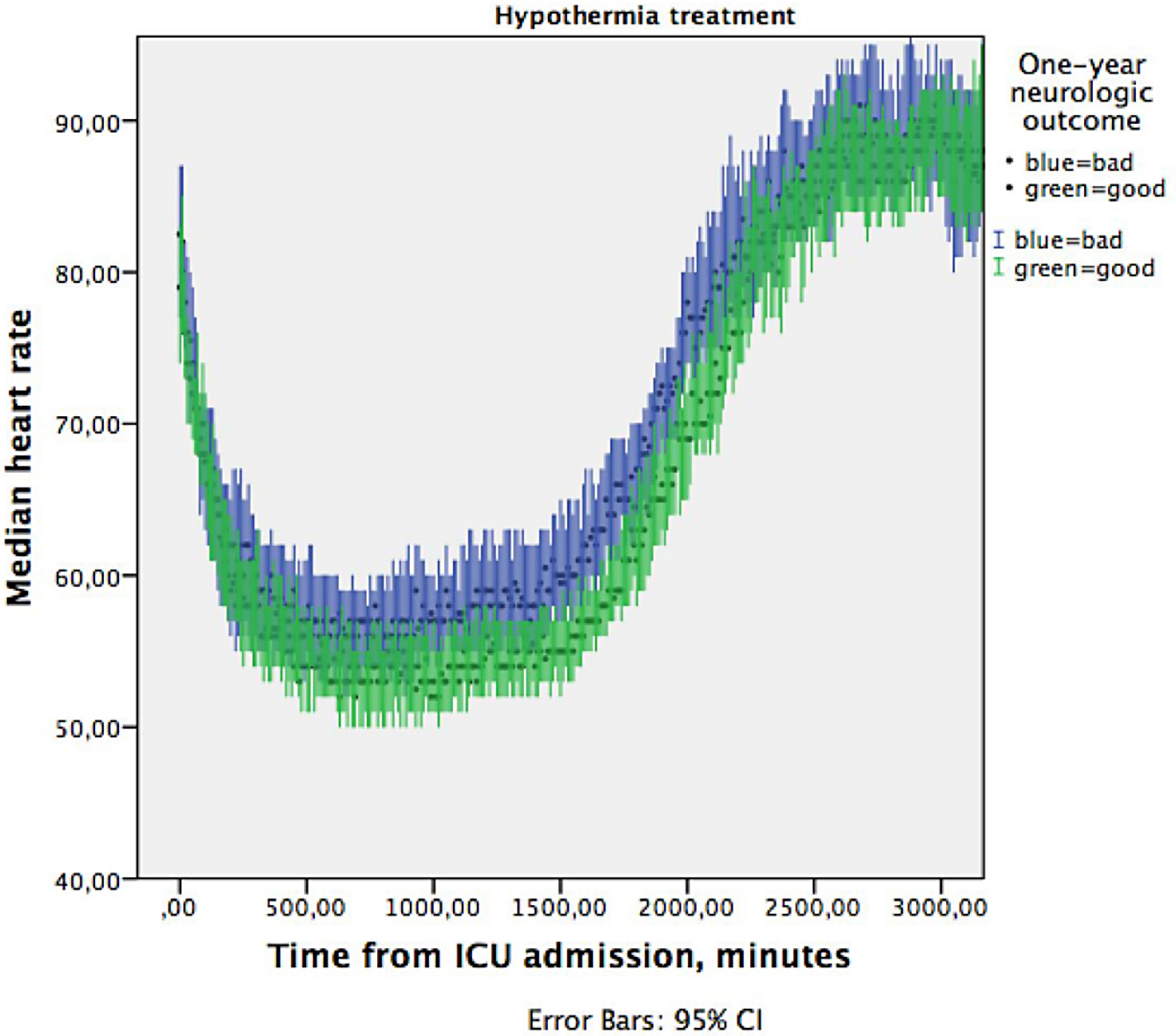
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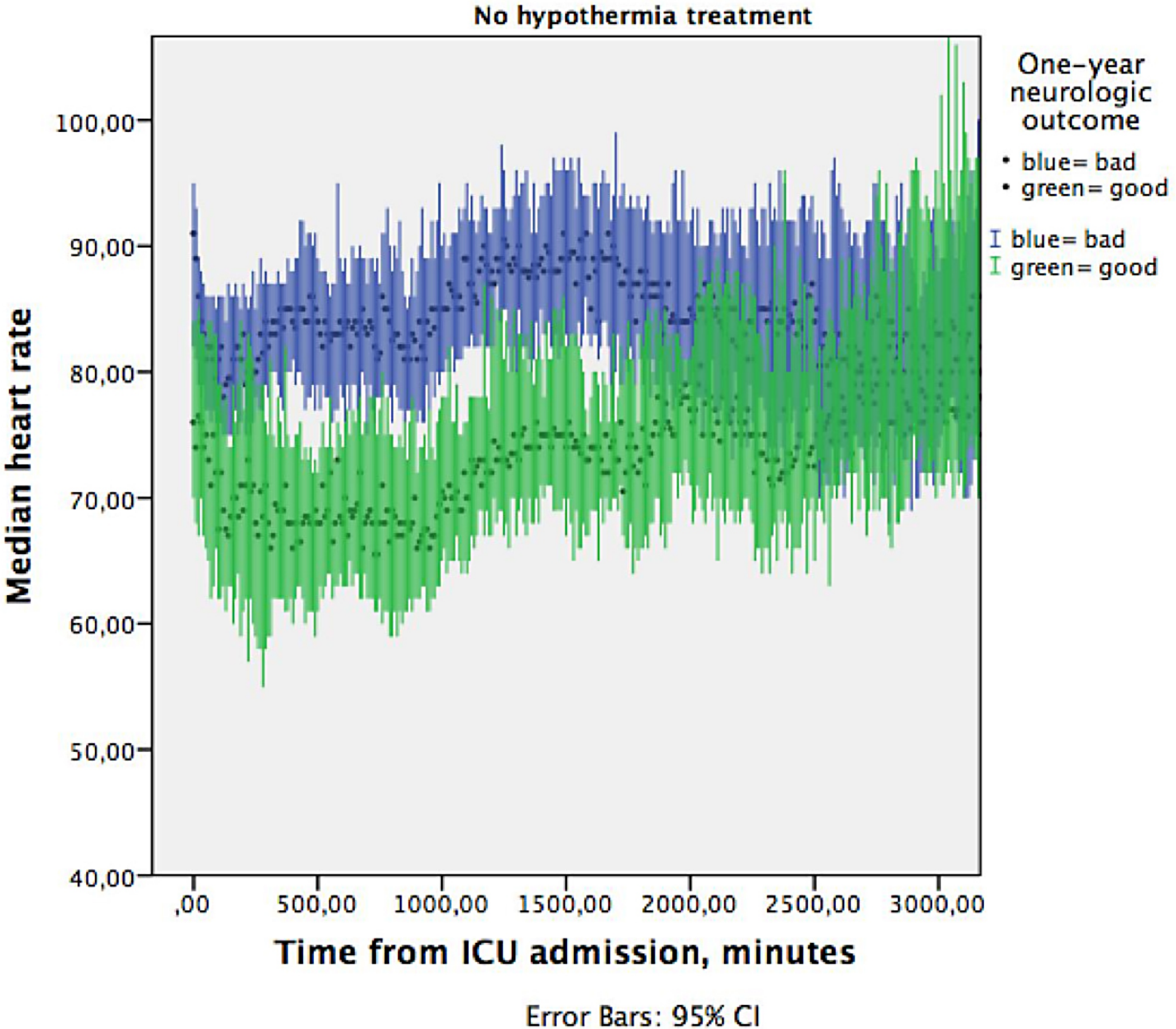

All patients
Mean good one-year neurologic outcome,%
60
40
20
0
35-63
63-71
71-84
85-162
Quartiles of time-weighted mean heart rate, bpm
Error Bars: 95% CI


Hypotermia
Mean good one-year neurologic outcome,%
80
60
40
20
0
41-59
59-68
68-76
76-130
Quartiles of time-weighted mean heart rate, bpm
Error Bars: 95% CI


No hypothermia
Mean good one-year neurologic outcome, %
60
40
20
0
35-69
70-83
83-96
96-162
Quartiles of time-weighted mean heart rate, bpm
Error Bars: 95% CI


One-year neurologic outcome
bad
good
bad
good
Median heart rate
100,00
90,00
80,00
70,00
60,00
50,00
40,00
,00
500,00
1000,00
1500,00
2000,00
2500,00
3000,00
Time from admission, minutes
Error Bars: 95% CI


Hypothermia treatment
Median heart rate
90,00
80,00
70,00
60,00
50,00
40,00
,00
500,00
1000,00
1500,00
2000,00
2500,00
3000,00
Time from ICU admission, minutes
One-year neurologic outcome
• blue=bad
• green=good
I blue=bad
I green=good
Error Bars: 95% CI


No hypothermia treatment
Median heart rate
100,00
90,00
80,00
70,00
60,00
50,00
40,00
,00
500,00
1000,00
1500,00
2000,00
2500,00
3000,00
Time from ICU admission, minutes
One-year neurologic outcome
• blue= bad
• green= good
I blue= bad
I green= good
Error Bars: 95% CI

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Table 1. Demographic data of the patients, presented as median (IQR) or count (percentage).

Variable	All patients N=504	Good outcome N=202	Bad outcome N=302	p-value
Age, years	63.0 (54.3-72.0)	61.0 (54.0-67.0)	64.0 (55.8-73.0)	<0.001
Male gender, %	386/504 (76.6)	160/202 (79.2)	226/302 (74.8)	0.28
Female gender, %	118/504 (23.4)	42/202 (20.8)	76/302 (25.2)	
Time to ROSC, minutes	20.0 (13.0-28.0)	16.0 (10.8-23.0)	23.0 (15.0-30.0)	<0.001
BMI, kg/m^2	26.2 (24.5-29.3)	26.2 (24.5-29.3)	26.2 (24.3-29.3)	0.56
SAPS 24 score, points	59.0 (44.0-69.0)	47.0 (35.8-61.0)	63.0 (55.0-73.0)	<0.001
APACHE II score, points	29.0 (24.0-34.0)	25.0 (18.0-30.3)	31.0 (27.0-37.0)	<0.001
Witnessed, %	449/504 (81.9)	190/202 (94.1)	259/302 (85.8)	0.003
Shockable rhythm, %	297/504 (54.2)	166/202 (82.2)	131/302 (43.4)	<0.001
Epinephrine during CPR, %	336/504 (61.3)	102/202 (50.5)	234/302 (77.5)	<0.001
Coronary artery disease, %	149/504 (27.2)	47/202 (23.3)	102/302 (33.8)	0.013
Hypertension, %	207/504 (37.8)	79/202 (39.1)	128/302 (42.4)	0.52
Chronic heart failure, %	72/504 (13.1)	20/202 (9.9)	52/302 (17.2)	0.027
Chronic renal failure, %	13/504 (2.4)	2/202 (1.0)	11/302 (3.6)	0.086
Diabetes, %	103/504 (18.8)	34/202 (16.8)	69/302 (22.8)	0.12
Pacemaker, %	9/504 (1.6)	0/202 (0.0)	9/302 (3.0)	0.013
Severe sepsis in ICU, %	16/504 (2.9)	4/202 (2.0)	12/302 (4.0)	0.30
Pneumonia in ICU, %	178/504 (32.5)	79/202 (39.1)	99/302 (32.8)	0.15
Coronary angiography during ICU stay, %	81/504 (14.8)	57/202 (28.2)	24/302 (7.9)	<0.001
PCI during ICU stay	42 /504 (7.7)	32/202 (15.8)	10/302 (3.3)	<0.001
Therapeutic hypothermia, %	307/504 (56.0)	151/202 (74.8)	156/302 (51.7)	<0.001
ICU length of stay, days	2.0 (1.0-4.0)	2.0 (2.0-4.0)	2.0 (1.0-3.0)	<0.001

ROSC= return of spontaneous circulation, Epinephrine= epinephrine given during resuscitation, SAPS II score = simplified acute physiology score, APACHE II = Acute Physiology and Chronic Health Evaluation II, PCI= percutaneous coronary intervention, BMI = body mass index

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Table 2. Heart rate data of the patients, presented as median (IQR).

variable	Good outcome	Poor outcome	p
Minimum heart rate in ICU, bpm	45.0 (39.0-52.0)	50.0 (40.0-63.0)	<0.001
Maximum heart rate in ICU, bpm	115.0 (101.8-131.0)	124.0 (108.0-142.0)	<0.001
Time-weighted mean heart rate 48 h	69.2 (59.2-75.1)	76.6 (65.72-89.6)	<0.001
Time-weighted mean heart rate 72 h	71.2 (65.0-79.0)	77.1 (69.1-90.1)	<0.001
Percentage of heart rate recordings below 60 bpm, 48 h	42.7 (13.6-60.5)	11.9 (0.0-47.2)	<0.001
Percentage of heart rate recordings below 80 bpm, 48 h	80.6 (63.5-91.9)	63.2 (25.6-85.2)	<0.001
Percentage of heart rate recordings below 100 bpm, 48 h	99.0 (92.4-100.0)	93.0 (75.3-99.3)	<0.001
Percentage of heart rate recordings below 50 bpm, 500-1500 min	53.5 (20.4-93.1)	35.6 (9.9-79.2)	0.015
Percentage of heart rate recordings below 60 bpm, 500-1500 min	90.5 (48.5-100.0)	67.3 (25.0-97.0)	0.001
Percentage of heart rate recordings below 70 bpm, 500-1500 min	98.5 (97.4-100.0)	93.6 (41.6- 100.0)	0.002
Percentage of heart rate recordings below 80 bpm, 500-1500 min	100.0 (97.4-100.0)	98.0 (54.2-100.0)	<0.001

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Table 3. Multivariate regression analyses regarding associations between heart rate and good one-year neurologic outcome.

All patients, N=504	Model 1. Time-weighted mean HR 0-48 h		Model 2. Time-weighted mean HR 0-72 h		Model 3. Percentage of HR recordings below 60 bpm		Model 4. Percentage of HR recordings below 80 bpm		Model 5. Percentage of HR recordings below 100 bpm	
Variable	OR (CI95%)	p	OR (CI95%)	p	OR (CI95%)	p	OR (CI95%)	p	OR (CI95%)	p
Coronary artery disease	0.41 (0.24-0.71)	0.001	0.41 (0.24-0.70)	0.001	0.42 (0.25-0.73)	0.002	0.41 (0.24-0.71)	0.001	0.42 (0.25-0.72)	0.001
Witnessed	1.60 (0.74-3.49)	0.23	1.61 (0.74-3.50)	0.23	1.59 (0.74-3.42)	0.24	1.67 (0.76-3.6)	0.199	1.58 (0.73-3.42)	0.25
ROSC delay	0.99 (0.97-1.02)	0.58	0.99 (0.97-1.02)	0.55	0.99 (0.97-1.02)	0.46	0.99 (0.97-1.02)	0.60	0.99 (0.97-1.02)	0.46
Epinephrine	0.47 (0.27-0.81)	0.007	0.47 (0.27-0.81)	0.007	0.46 (0.26-0.79)	0.005	0.45 (0.26-0.78)	0.004	0.46 (0.26-0.79)	0.005
SAPS II score	0.95 (0.94-0.97)	<0.001	0.95 (0.94-0.97)	<0.001	0.95 (0.94-0.97)	<0.001	0.95 (0.94-0.97)	<0.001	0.96 (0.94-0.97)	<0.001
PCI during ICU stay	2.46 (1.05-5.74)	0.038	2.46 (1.06-5.72)	0.037	2.48 (1.06-5.79)	0.036	2.56 (1.09-5.99)	0.031	2.27 (0.99-5.21)	0.054
Chronic heart failure	1.05 (0.52-2.14)	0.89	1.05 (0.52-2.14)	0.89	1.02 (0.50-2.08)	0.95	1.0 (0.49-2.04)	1.00	1.02 (0.50-2.08)	0.96
Shockable primary rhythm	2.40 (1.32-4.37)	0.004	2.43 (1.33-4.42)	0.004	2.63 (1.45-4.76)	0.001	2.38 (1.30-4.35)	0.005	2.52 (1.38-4.59)	0.003
TH treatment	1.80 (1.32-4.37)	0.062	2.02 (1.11-3.69)	0.022	1.86 (1.00-3.48)	0.051	1.88 (1.02-3.47)	0.044	2.09 (1.15-3.79)	0.016
Time-weighted mean heart rate 0-48 h	0.97 (0.96-0.99)	0.004								
Time-weighted mean heart rate 0-72 h			0.97 (0.96-0.99)	0.005						
HR % below 60 bpm					2.65 (1.07-6.57)	0.035				
HR % below 80 bpm							3.88 (1.55-9.68)	0.004		
HR % below 100 bpm									5.95 (1.20-29.64)	0.029

HR= heart rate, ROSC= return of spontaneous circulation, Epinephrine= epinephrine given during resuscitation, SAPS II score = simplified acute physiology score II, TH treatment= therapeutic hypothermia, PCI= percutaneous coronary intervention, shockable= primary heart rhythm shockable, TW mean= time-weighted mean, HR%= percentage of heart rate recording below threshold.