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Min Jung Kim Date

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By

Min Jung Kim

MPH

Epidemiology

William McClellan

Faculty Thesis Advisor

Sang Do Shin

Thesis Field Advisor

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By

Min Jung Kim

Bachelor of Science

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Abstract

Neurological prognostication by gender
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By Min Jung Kim

Aim To examine whether neurological recovery of out-of-hospital cardiac arrest (OHCA) patients receiving therapeutic hypothermia (TH) treatment is enhanced for women of childbearing age.

Methods A cross-sectional analysis was conducted using a nationwide surveillance database in Korea of OHCA with presumed cardiac etiology and 15 years or older that occurred and survived to admission between 2008 and 2012. The exposure and outcomes studied were TH treatment and neurological outcome at discharge. Patient characteristics between hypothermia-treated and non-treated groups were compared. Multivariate logistic regression was used to account for the patient characteristics. The association was examined for each stratum of gender, age (<45, 45-65, and >65 years old), and cardiac rhythm. Cardiac rhythms were considered in two different categorizations: 1) shockable/non-shockable rhythm, and 2) VF.VT/PEA/asystole.

Results Total 8,486 OHCA were analyzed. Crude analysis showed that women of childbearing ages treated with TH had enhanced neurological recovery than older aged women and all men. After adjusted, men had stronger association between TH and good neurological recovery than women. The highest association was found in men who are under 45 years of age and have shockable cardiac rhythm (OR=2.00 (1.26, 3.19)). The association between TH and neurological recovery was not statistically significant in all women. The magnitude of association decreased with age. Shockable rhythm was associated with better neurological recovery than non-shockable rhythms in all gender and age groups. Using VF.VT/PEA/asystole categorization of cardiac rhythms, men consistently showed higher ORs than women. In all gender and age groups, having PEA rhythm was associated with better neurological outcome than shockable rhythms (VF/VT) or asystole.

Conclusion The unadjusted association between TH and neurological recovery was the strongest in women of childbearing ages. After adjustment, men had a better neurological outcome than women across all ages. Shockable rhythms were associated with enhanced neurological recovery. Our results suggest that among out-of-hospital cardiac arrest patients, the effect of TH treatment on neurological recovery is greater for men, young ages, and having shockable cardiac rhythm.

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INTRODUCTION

Approximately 300,000 out-of-hospital cardiac arrests (OHCAs) occur in the United States annually with an estimated survival rate of 8%[1]. Globally, the average incidence of OHCA in adults is 55 per 100,000 person-years[2], and the estimated burden of cardiac deaths ranges from 4 to 5 million cases per year[3]. The disease burden of cardiac arrest is driven by not only low survival, but also high frequency of recoveries accompanied with neurological damage[4, 5]. The severity of damage ranges from moderate disability to brain death[6], leaving the majority of recovering patients with significant cognitive deficits. In effort to attenuate the injuries, the International Liaison Committee on Resuscitation (ILCOR) recommends the use of therapeutic hypothermia (TH) in patients after return of spontaneous circulation (ROSC)[7]. Despite increasing recognition of TH for enhanced recovery[6, 8, 9], however, female gender has been frequently associated with underutilization of TH[10-14].

In a population of OHCA patients, enhanced neurological outcome was observed in women of childbearing ages compared with men, whereas the gender-based difference disappeared with increasing age[15]. Similarly, women of childbearing ages had a higher survival rate, and the enhanced survival was not observed in older aged women[16]. Evidence suggests that the prognosis of OHCA patients differ by gender, but whether the gender difference in outcome persists with TH treatment remains unknown. Experimental studies help depict sex hormones as a predictor of clinical outcome during cardiac arrest, suggesting that estrogen exerts neuroprotective effects during ischemic injury[17-20]. Yet no studies have clearly demonstrated the influence of sex hormones in regards to post-resuscitation care. The aim of this study is to examine the gender-based difference in neurological recovery and possible influence of sex hormones on TH efficacy.

Neuroprotective effects of hypothermia

Early studies have postulated mechanisms in which lowering of body temperature mitigates reperfusion injury during cardiac arrest. By artificially dropping body temperature, TH decreases the rate of cerebral metabolism[21] and suppresses the release and uptake of neurotransmitters that are normally activated during ischemia[21, 22]. The consequences of decreased enzymatic activities include reduction of intracellular calcium level, suppression of inflammatory responses, and inhibition of cell apoptosis[23, 24]. Furthermore, TH has been associated with improved axon regeneration and integrity of blood-brain-barrier, thereby mitigating neuronal cell damage[23, 25].

Neuroprotective effects of sex hormones

Predicting outcomes of OHCA by gender remains a challenge, yet empirical evidences have delineated mechanisms through which sex hormones exert neuroprotection against ischemic injury. Observational studies have shown that women who receive hormone replacement therapy benefit from improved cognition and brain function[26, 27]. Experimental models also demonstrate that injection of estradiol (E2) in animals prior to ischemia is associated with protection of brain tissue[17] and enhanced neurological recovery[18-20]. Similarly, higher levels of androgens have been implicated in neuroprotection as progesterone treatments were shown to reduce cerebral damage[28-30]. Furthermore, comparable results have been found in another study using testosterone[31].

Cellular studies illustrate the hormonal pathways through which sex hormones and physiological systems interact during resuscitation.(Figure 1) Estrogen exerts hormonal effects to the cardio-cerebral system through its receptors found in cardiac myocytes[32] and throughout the brain.[33] Subsequently, estrogen mitigates ischemic damage by reducing metabolic rate[34], nitrogen oxide synthase activity[34-36], peroxidation of cell membranes[20, 36], cell apoptosis[34], and inflammation[36]. In addition, estrogen can directly promote synaptic plasticity[34], axon regeneration[36], and integrity of blood-brain-barriers[20, 37]. Such neuroprotective functions of sex hormones agree with the clinical aim of TH, and possible overlap of cellular pathways between sex hormones and TH is expected.

Cardiac rhythms and effect of hypothermia

Cardiac arrests are associated with four types of electrocardiographic (ECG) rhythms: ventricular fibrillation (VF), ventricular trachycardia (VT), pulseless electrical activity (PEA), and asystole. It has been shown that increased survival is mostly likely to be seen in patients with shockable rhythms (VF/VT) compared to non-shockable rhythms (PEA/asystole), and survival is slightly higher with PEA than asystole[38]. When treated with TH, an enhanced neurological outcome is observed in patients presenting VF[8]. In non-shockable rhythms, the beneficial effect of TH has been controversial as some studies observed favorable outcome[13, 39] while others did not[12, 40]. When stratified by gender, a recent study observed that female patients with shockable rhythms have poorer survival than men, whereas the gender effect was insignificant in patients with non-shockable rhythms[11]. Published studies demonstrate that clinical outcomes after cardiac arrest vary by cardiac rhythms, and thus, the effect of TH on neurological outcome must be examined separately by cardiac rhythm type.

Objective

This study hypothesizes that the extent to which TH exerts neuroprotection is augmented by the presence of female sex hormones, and the degree of neurological recovery will differ by gender. The hypothesis will be examined by testing the significance of the following three interaction terms: TH with gender, TH with age, and TH with both gender and age. The three interaction terms will compare the effect of TH in men and women at childbearing ages (<45 years old), menopausal and post-menopausal ages (45-65 years old), and at older ages (>65 years old). We expect that women of childbearing ages would have a high level of female sex hormones and benefit from an enhanced neurological outcome relative to men counterparts. In contrast, it is anticipated that the degree of neurological recovery will be indifferent in patients who are 45 years and older. In addition, because shockable rhythms are associated with enhanced neurological outcome, the interaction between TH and cardiac rhythm will also be considered.

METHODS

Study Design and Data Source

This cross-sectional study was conducted using a nationwide database of emergency medical services(EMS)-assessed OHCAs in the Republic of Korea. In 2007, the Korean Center for Disease Control and Prevention (CDC) initiated a population-based retrospective study, the Cardiovascular Disease Surveillance (CAVAS) Project, which has been recruiting all EMS-assessed and transported OHCAS in the country since 2006. The database has been constructed through review of national EMS database and hospital medical records. The EMS database, which is managed by the National Emergency Management Agency (NEMA), is constructed from ambulance run sheets that are completed by EMS providers following transport of OHCA patients to hospitals. Subsequent outcomes, hospital care, and clinical information of the patients are abstracted from the medical record of each destination hospital by trained medical record reviewers. For quality assurance, the reviewers receive consultation and feedback as needed from medical experts, managers of the fire departments, and epidemiologists. Missing variables are recorded when: 1) the hospital is closed, 2) hospital refuses release of medical records, or 3) there is lack of information on medical records.

Study Setting

In Korea, a national EMS system is coordinated and operated by the fire department and their16 provincial headquarters. Under a single-tiered EMS system, there were 1349 ambulances in 2010 serving approximately 48 million people across the country[41]. All ambulances are operated by emergency medical technicians (EMTs) who provide intermediate level of life support service including CPR, automated external defibrillator (AED), and advanced airway insertion under direct medical control. Due to limited number of qualified and higher level of EMTs, advanced cardiac life support (ACLS) is not widely performed and often only available at hospitals. EMTs cannot stop CPR or declare death without the presence of a physician, and thus, all EMS-assessed patients are mandatorily transported to the emergency department (ED) of the nearest hospitals by EMS protocol. EMTs are trained and certified in either of level 1 (intermediate) or level 2 (basic). Level 1 EMTs hold a degree from EMT schools, pass a national certification examination, and receive mandatory continuing education. Level 1 EMTs can perform airway management using endotracheal intubation or laryngeal mask airway. Level 2 EMTs are trained in fire academies and pass a national certifying examination[42].

All EDs are designated in levels 1 through 4 based on capacity measures of human resources, service levels, availability of equipment, and number of specialists and physicians by EMS act. Level 1 EDs are regional hospitals with the highest capacity, and level 2 EDs are local hospitals with well-equipped emergency services. Both level 1 and 2 EDs are required by law to have emergency physicians available 24 hours a day. Level 3 EDs are small emergency rooms and are usually served by general physicians. Level 4 EDs are community health care centers or hospitals in which no or only minimal emergency care is performed[43]. In Korea, there are currently 20 level 1 EDs, 99 level 2 EDs, about 300 level 3 EDS, and about 400 level 4 non-ED facilities[44].

Study participants

The CAVAS Project started recording the treatment status of TH beginning the year of 2008, and therefore, this study was restricted to the incident cases that occurred between 2008 and 2012. (Figure 2) All cases were EMS-assessed OHCA patients. This study applied the following inclusion criteria: 1) patients who are 15 years or older, 2) patients with presumed cardiac etiology, and 3) patients who survived to admission at hospital (thus eligible to receive TH), and 4) those with known neurological outcome.

Variables

The primary predictor, TH, was recorded for all patients who received TH treatment within 48 hours of admission. For this study, TH was defined as a binary variable (yes and no) and disregarded the differences in techniques, duration, and temperature of individual procedures. In practice, TH was performed to maintain body temperature at 32°C to 34°C, and type of technique was recorded as one of the of the following: external cooling type 1, external cooling type 2, intravascular cooling, internal cooling, and other. External cooling type 1 included the use of cooling blankets, applying ice packs in axillae, or spraying water on body and cooling with fan. Type 2 included the use of machines or a cooling device (i.e., Arctic Sun). Intravascular cooling used cooling catheter device (i.e., CoolGard3000 by Alsius). Internal cooling recorded invasive techniques through installation of cold saline via nasogastric tube or bladder tube, peritoneal lavage, or cold saline IV infusion. All information on TH treatment was recorded by physicians in the ED.

Patient's gender, age, and cardiac rhythm were considered as potential effect modifiers of the outcome. Patients were stratified by gender (men and women) and age (<45, 45-65, and >65 years old). Cardiac rhythm was classified according to the initial ECG rhythm which was recorded by the EMT at the scene or physicians in the ED at admission later if not recorded by the EMTs. For the main analysis, cardiac rhythm were reclassified as shockable (VF/VT) and non-shockable (PEA, and asystole) rhythms. Additional clinical covariates included: 1) sociodemographic factors measured by urbanization level and insurance type; 2) measure of service capacity including level of ED (levels 1 through 4); and 3) Utstein risk factors such as presence of witness, place, bystander CPR, EM S CPR, response time interval, scene time interval, transport time interval, pre-hospital defibrillation by EMS provider, ED CPR, and reperfusion therapy.

Urbanization level was measured in two levels (metropolitan and non-metropolitan) using data on population size available at the Korean National Statistics Office. A metropolitan city has a population of over a million, and the rest of the cities with population less than 1,000,000 in size were categorized as non-metropolitan[14]. For each patient, type of health insurance was recorded. By law, most of patients in Korea are covered by national health insurance. Other types of insurance include automobile insurance, occupation compensation insurance, private insurance and government medical aid (class 1 for low income, and class 2 for upper income persons). For analysis, reclassification of insurance type combined national health insurance, automobile insurance, and occupation compensation insurance into a single category of health insurance.

Pre-hospital Utstein factors were recorded by EMT. Presence of witness (yes or no) indicates whether the cardiac arrest occurred in presence of witness. Place of cardiac arrest was recorded as public, private, or unknown. Bystander CPR (yes or no) indicates whether there was an attempt of public to provide CPR to the patient.

For this analysis, a single variable measuring both EMS and ED CPR was considered. Having no EMS and ED CPR (n=17) were assumed as miscoding and were reclassified as having received both EMS and ED CPR. Response time interval measured the time from EMS call received at the dispatcher center and arrival of ambulance to the scene. Scene time interval measured time from arrival of EMS to scene until departure to ED. Transport time interval was measured as the time after EMS left the scene until arrival in ED. Pre-hospital defibrillation (yes or no) recorded the use of a defibrillator by EMT.

CPR in ED (yes or no) records whether a patient received CPR at the destination hospital. Reperfusion therapy (yes or no) indicates the use of treatment procedures, such as intravenous thrombolysis and primary coronary intervention, to restore blood flow in the coronary artery. Both ED CPR and reperfusion therapy were recorded by physicians at destination hospital.

Outcome

The outcome of the study, cerebral performance category (CPC) scale, is a measure of neurological recovery in a scale of 1 to 5. The description of each CPC score is shown in Table 1[45]. CPC scores of 1 and 2 are an indicator of good neurological recovery, and CPC scores 3 and below indicate poor neurological recovery. CPC scores were recorded at discharge by physicians at the destination hospital. Because physicians are not usually mandated to record CPC score in medical record, CPC scale in the surveillance database was often evaluated based on the patient's condition available in the medical record. For this analysis, neurological outcome was considered as a dichotomous variable (good or poor neurological recovery). All patients who did not survive to discharge were classified as having bad neurological outcome.

Analysis

In effort to understand the underlying population, proportions of the patients surviving to discharge were calculated for each stratum of gender, age, and cardiac rhythms. The distribution of TH treatment types utilized by men and women were compared.

Descriptive statistics of the study variables were calculated for all subjects, and separately for patients treated with TH and not treated with TH. Means of continuous variables and percentages of categorical variables are reported. Descriptive statistics were also calculated by the outcome status. ORs and their 95% confidence intervals (CIs) were calculated between TH status and each of the covariates. T-test was used to assess the difference of continuous variables between TH-treated and non-treated groups.

Association between neurological outcome and the following variables were assessed: gender, age, and cardiac rhythm. ORs and their 95% CIs were calculated for each stratum of the three variables.

To test the hypothesis, 1 three-way interaction term and 3 two-way interaction terms were considered: TH*gender*age, TH*gender, TH*age, and TH*cardiac rhythm. Strata-specific crude associations between TH and neurological outcome were examined for the variables involved in interaction (gender, age and cardiac rhythm). Then, a multivariable logistic regression model was conducted by considering all covariates and interaction terms. A hierarchically well-formulated model with all interactions terms of interest was constructed. All the terms in this model were assessed for multicollinearity; a term was dropped from the model for multicollinearity if it had conditional index (CNI)>30 and variance decomposition proportion (VDP)>0.5. Subsequently, a chunk test was carried out to compare a full model with all potential interaction terms and a no-interaction model. If the chunk test was significant at $\alpha=0.05$, it was assumed that at least one of the interaction terms in the full model was significant. Then, the significance of each interaction term was tested by backward elimination procedure. A three-way interaction term (TH*gender*age) was tested first, followed by two-way interaction terms (TH*gender, TH*age, and TH*cardiac rhythm). When an interaction term showed statistical significance ($p<0.05$), all of its lower-order terms were retained in the model. If a chunk test was significant but none of the interaction terms were statistically significant on its own, we assumed that each interaction term in the full model exerted an overall interaction effect and retained all interaction terms in the model. The resulting model was considered as the gold standard (GS) model. Confounding was then assessed by comparing the estimates of all possible subset models to the GS model. A final model was chosen by considering both accuracy (OR is within ±10% of the GS OR) and precision (narrower CI). Finally, the adjusted ORs for each stratum were calculated. All data were analyzed by SAS 9.3 (SAS Institute Inc, NC, USA).

This study was conducted using a dataset without human identifiers. The Emory University Institutional Review Board (IRB) determined that this study does not constitute human subjects research and provided with a letter of exemption for IRB review.

RESULTS

Between 2008 and 2012, there were 112,895 EMS-assessed OHCAs in CAVAS database. (Figure 2) Approximately 92% (104,231) were excluded due to age (<15), non-cardiac etiology, and death before admission to hospital. Of the remaining patients, 2% (178) had unknown CPC and time interval. The final cohort comprised of 8,486 subjects eligible for analysis.

In this cohort, men were more likely to survive to discharge than women across all strata of age and cardiac rhythms. (Table 2) In terms of TH treatment techniques, the most frequently used method of TH in both genders was external cooling type I (38% in female and 42% in male), followed by external cooling type II. (Figure 3) Intravascular cooling was used in less than 13% and 11% of female and male, respectively. The types of TH method were not statistically different for men and women (p=0.5182).

TH was performed in 1,140 subjects (13.4%). (Table 3) Approximately two thirds of the cohort was men (5,656 of 8,486). Men were more likely to receive TH (74% in TH-treatment group vs. 66% in non-treatment group) compared to women (26% in TH-treatment group vs. 35% in non-treatment group). Among all TH-treated patients, 20% were under age 45, 44% were between 45 and 65, and 36% were over 65 years of age. In non-treatment group, smaller proportion of patients was under age 45 (14%), and higher proportion was over 65 (44%). Prevalence of shockable rhythm (VF/VT) was higher than non-shockable rhythms in TH-treated group (27% vs. 16%).

Most patients were covered by health insurance (85%), and only 32 of 7172 cases (0.4%) did not have any insurance. TH-treated group had higher prevalence of health insurance compared to non-treated group (90% vs. 84%).

TH-treated group was more than two times likely to have received bystander CPR than non-treated group (24% vs. 10%). More TH-treated patients were likely to have had cardiac arrest in a public place (31% vs. 21%) and had been witnessed at the time of incidence (76% vs. 68%) than patients who were not treated with TH. The mean response time, scene time, and transport time intervals did not differ much between TH-treatment and non-treatment groups. On average, the response time interval for all patients was 6.65 minutes (±3.56), and the mean time for arrival of EMS was 6.58 minutes (±4.41). On average, patients were transported to hospitals in 8.23 minutes (±8.66) after leaving the scene.

More than one third of the patients treated with TH had been treated at level 1 ED, while only 14% of patients not treated with TH were at level 1 ED. Proportions of patients receiving CPR from EMS and in ED were similar for TH-treatment and non-treatment groups. EMS defibrillation was more frequently done in patients not receiving TH (82%) than patients receiving TH (64%). Reperfusion therapy was done in 13% of TH-treated patients and 10% of patients not receiving TH.

15% (1235/8486) of all patients in the cohort recovered good neurological function. (Table 4) Proportion of patients with good neurological outcome was higher in TH-treated group than non-treated group (23% vs. 13%). Men were almost twice more likely to have good neurological outcome than women (OR=2.04, 95% CI=1.76, 2.35). Presentation of good neurological outcome was most frequent in patients under 45 years of age (OR=4.01, 95% CI=3.35, 4.80), followed by 45-65 years of age (OR=2.89, 95% CI=2.49, 3.36). In terms of cardiac rhythm type, patients with shockable rhythms had the highest proportion of good neurological outcome (37%), followed by asystole (10%) and PEA (9%). The association for good neurological recovery between PEA and asystole was not significant (OR=0.92, 95% CI=0.72, 1.18).

Crude associations between TH treatment and neurological outcome are reported in Table 6. The crude ORs for each stratum of gender, age, and cardiac rhythm were different. Women under age 45 showed greater ORs for having good neurological outcome compared to men in both shockable (women OR=4.38 vs. men OR=1.73) and non-schockable rhythms (women OR=2.34 vs. men OR=1.67). In age between 45 and 65, the association was greater for men than women in both shockable (men OR=1.57 vs. women OR=0.67) and non-shockable rhythms (men OR=1.53 vs. women OR=1.44). In age over 65, the association between TH treatment and neurological outcome was greater for women in shockable (women OR=3.27 vs. men OR=2.37) and non-shockable (women OR=0.90 vs. men OR=0.66) rhythms.

Estimates of the final multivariate model accounting for all significant predictors, confounders, and effect modifiers are presented in Table 5. In multicollinearity assessment, the highest CNI was 31.5823, and the corresponding VDPs for all variables were less than 0.5. No terms indicated multicolinearity, and all were kept in the model. Chunk test, which compared the likelihood ratios of a full model with all potential interaction terms (TH*gender, TH*age, TH*cardiac rhythm, and TH*gender*age) and a no-interaction model resulted in a p-value of 0.1228, indicating that the four interaction terms together are not statistically significant. Backward elimination on the interaction terms dropped the three-way interaction term (TH*gender*age) and its lower-order component term (gender*age). A subsequent chunk test comparing a full model with two-way interaction terms (TH*gender, TH*age, and TH*cardiac rhythm) observed a statistically significant difference (p=0.0191) between the two models. Backward elimination procedure dropped all interaction terms one at a time at $\alpha=0.05$. Considering the significance result of the chunk test, it was assumed that each interaction variable in the model exerted an overall interaction effect. Consequently, all interaction terms that were initially tested in the chunk test were kept in the so-called GS model. Then, confounding assessment dropped the following variables from the GS model: urbanization level, place of event, response time interval, scene time interval, and transport time interval. Dropping the three variables resulted in narrower CI as well as OR estimates that are within 10% from the estimates of the GS model.

Strata-specific multivariate associations between hypothermia and neurological outcome are reported in Table 6. After adjusting for all confounders and effect modifiers, the difference in ORs between men and women became smaller in magnitude. The direction of association was changed for <45 and >65 age groups. Men had higher adjusted OR than women in all strata of age and cardiac rhythm. In both genders, the magnitude of association between TH and good neurological recovery decreased with age. In men, the effect of TH was only significant for patients younger than 45, and the highest associations was observed with shockable rhythm (OR=2.01 (1.26, 3.19)) followed by non-shockable rhythm (OR=1.73 (1.12, 2.68)). In women, all adjusted ORs were not statistically significant.

An additional model was analyzed by dividing non-shockable rhythms into PEA and asystole (Table 7). Using the same analytic method as above, all two-way interaction terms were tested and remained in the model. Confounding assessment dropped the following variables from the GS model: urbanization level, place of event, and transport time interval. Interpretation of ORs for some strata are not reliable due to due to limited cell size (<5) after stratification.(Table 5b). Male gender and young age (<45 years old) were associated with higher odds of having good neurological recovery. In both genders across age, having PEA rhythm was associated with the highest ORs, followed by VF/VT and asystole. The highest associations was observed in patients under 45 years of age with PEA rhythm (men OR=3.56 (1.87, 6.80) and women OR=2.95 (1.44, 6.02)). The effect of TH in asystole was small in magnitude and not statistically significant for both genders across all age groups.

DISCUSSION

Our study demonstrated that there is a gender-modified effect of TH treatment on neurological outcome. We showed that the strength of association between TH and neurological recovery differ by gender, age, and cardiac rhythm. Across all age groups, women were less likely to benefit from hypothermia treatment than men. In both genders, better neurological outcome was observed with younger age and having shockable cardiac rhythm. This is an important finding implying that women are less likely to benefit from TH treatment despite relatively higher underlying levels of estrogen. Additionally, after further stratifying non-shockable rhythms into PEA and asystole, significant associations between TH and good neurological recovery was observed for patients with PEA, which was unexpectedly stronger than the associations for VF/VT and asystole.

Crude analysis showed that women of childbearing age have the highest odds of benefiting from TH compared to older aged women and men of any ages. After menopause, however, such protective effect of TH was no longer greater for women but men. In age over 65, TH became more effective for women compared to male counterparts. After adjustment, the dose-response relationship of the “estrogen effect” was no longer observed, and women of childbearing age did not show enhanced neurological outcome. Young men were more likely to recover good neurological function than young women as well as older men.

It is possible that men experience an “androgen effect” during cardiac arrest. A previous cohort study found significant association between high testosterone level (≥300ng/dl) and good neurological outcome at six months after cardiac arrest.[46] Furthermore, administering progesterone in animal models has been associated with neuronal cell protection following ischemic injury.[47, 48] A similar animal study showed that progesterone protects brain cells against ischemic injury through GABA receptor activity.[49] These findings suggest that androgen may exert neuroprotection during ischemic injury, and men could benefit from having higher levels of male sex hormones compared to women in cardiac arrest.

Nevertheless, the male advantage observed after multivariate adjustment may be associated with the underlying gender differences in demographic and clinical characteristics. Clinical and demographic factors underlying the gender disparities in TH delivery and outcome are likely to be complex. Our data showed that male OHCA patients are more likely to live in metropolitan area, receive bystander CPR, have cardiac arrest in a public place, and receive reperfusion therapy. Men also benefited from shorter time intervals for EMS arrival and transport to hospital. It is possible that the gender differences in such pre-hospital factors put men at a higher probability of good recovery.

In our database, higher proportion of men arrived in ED with ROSC compared to women, and it was further translated into higher survival to discharge in men. Although TH is generally recommended in patients after ROSC with witnessed VF/VT[7], patients in our database were treated with TH even when they were not witnessed or VF/VT. Previous clinical trials examining the effect of TH restricted their studies to patients who had restored spontaneous circulation after being witnessed and with VF/VT.[8] Another study has also shown that the impact of TH on neurological recovery is most obvious when spontaneous circulation was regained within 30 minutes of collapse.[6] Our study did not make adjustment for the variations in pre-hospital ROSC, and whether the gender-difference in ROSC distribution in time had an effect on neurological outcome and survival is unknown.

Furthermore, we observed that men have higher rates of survival to discharge than women across all ages and cardiac rhythm types. Similar to the association between TH and good neurological recovery, survival rate is also greater for men, young ages, and having shockable rhythm. It should be noted that VF/VT rhythms have been frequently associated with higher survival rate after cardiac arrest,[8] and it is possible that a large proportion of patients with VF/VT recover good neurological outcome regardless of treatment status. The effect of TH in shockable rhythms may be somewhat related to the underlying rhythm type than the TH treatment itself. Whether there were any pre-hospital and clinical factors that predisposed the differences in neurological outcome and survival is unknown.

We also observed differences in neurological recovery by types of cardiac rhythm. An enhanced neurological outcome following TH was observed in shockable rhythm, and this difference persisted after stratified by gender. In both men and women, good neurological recovery was observed in shockable rhythms, although the effect in women was not statistically significant.

Of interest, an additional model with four types of cardiac rhythm (VF/VT/PEA/Asystole) showed an enhanced neurological recovery in patients with PEA compared to asystole. Our study implies that treatment with TH may improve neurological outcome in patients with non-shockable rhythms.

We also observed a stronger association between TH and good neurological recovery for PEA than for shockable rhythm (VF/VT). This is an unusual finding that do not agree with previous evidence[50]. However, it should be noted that VF/VT rhythms have been frequently associated with higher survival rate after cardiac arrest,[8] and it is possible that a large proportion of patients with VF/VT recover good neurological outcome regardless of treatment status. The effect of TH in shockable rhythms may be somewhat related to the underlying rhythm type than the TH treatment itself. Furthermore, our analysis on non-shockable rhythm is subject to modeling issues such as small sample size as well as multiple tests leading to an inflated type I error. This finding of good results in PEA rhythm, however, may encourage providers to consider expanded indication for TH rather than current recommendation guidelines.

There are several other limitations to our study. This study did not consider multi-levels of socioeconomic status, although insurance types and urbanization allowed for some control of the non-clinical patient variations. Lower socioeconomic status has been associated with higher rates of mortality from cardiac arrest[51] as well as access to resuscitation efforts, and adjusting for these patient variations may be necessary.

Simplified classification of variables may have also led to loss of potentially important information. This study used a broad standard of exposure and disregarded different methods and times utilized for TH. Whether or not there is a meaningful difference between subgroups of TH is unknown.

In addition, patients' cardiac rhythm types are rarely monitored under close observation throughout treatment process. A patient initially found in VF may ultimately switch to asystole over time, and thus, the categorization of ECG rhythms is not always bound to be accurate.

Lastly, our multivariate model did not adjust for clinical variations such as competing risks and comorbidity factors. Previous studies have found that women who survive OHCA are less likely to have underlying coronary artery disease and more likely to have abnormally structured heart than men.[52] Moreover, the incidence of cardiac arrest with PEA rhythm is increasing in trend, and it may be that PEA is related to non-cardiac diseases, whereas VF is more associated with coronary disease.[53] Future studies about whether such clinical variations and disease factors modify TH effect would be beneficial.

CONCLUSION

This study highlights the significant differences in the effect of TH on neurological outcome by gender. In a nationwide OHCA database, the odds of having good neurological recovery following TH treatment were greater for women of childbearing ages than male counterparts. When adjusted for sociodemographic and pre-hospital factors, men were more likely to recover good neurological function than women. In both men and women, increasing age and having non-shockable rhythm were associated with less favorable neurological outcome. The observed gender difference in TH outcome underscores the need to further examine the clinical and physiological characteristics in women to understand their response to TH treatment.

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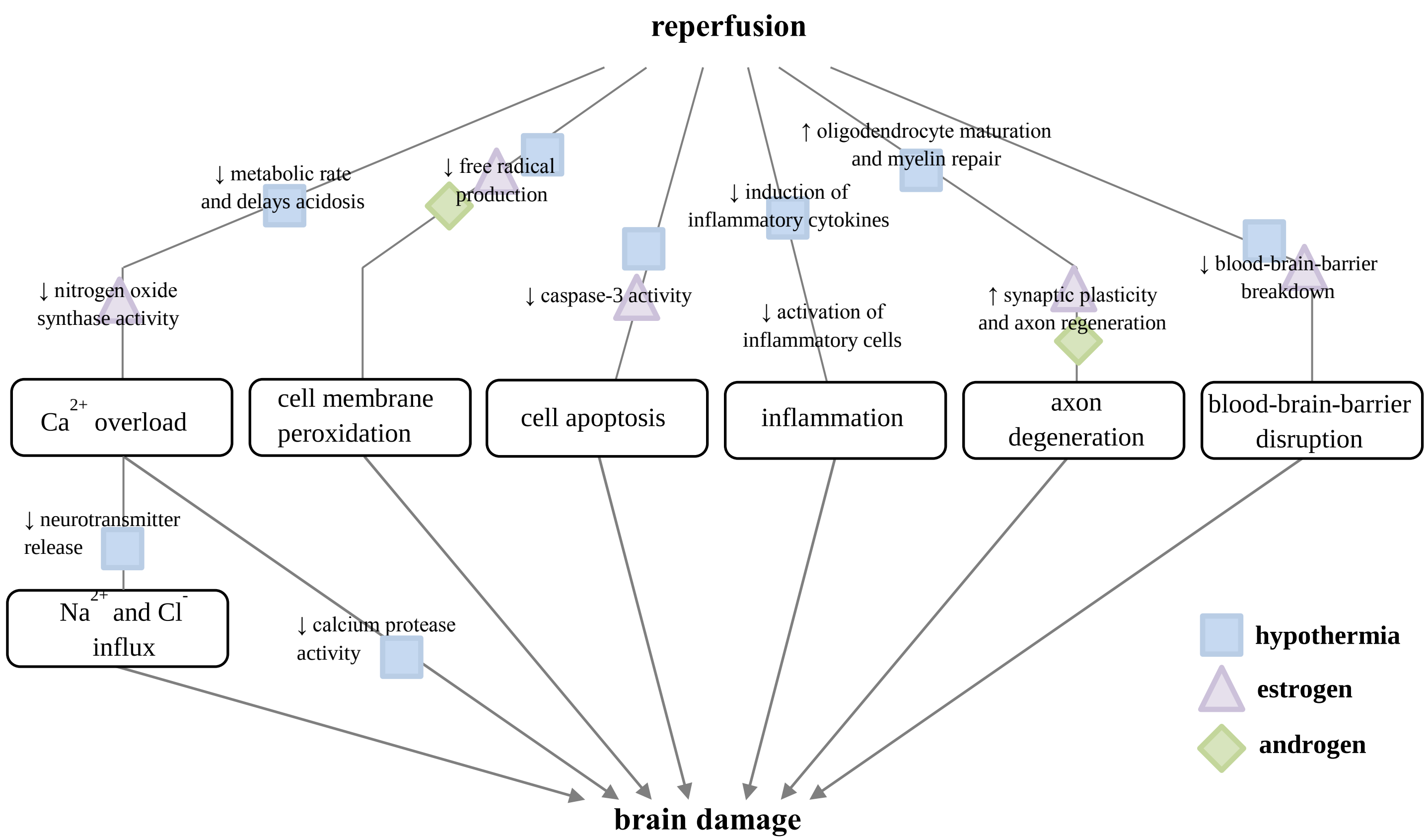
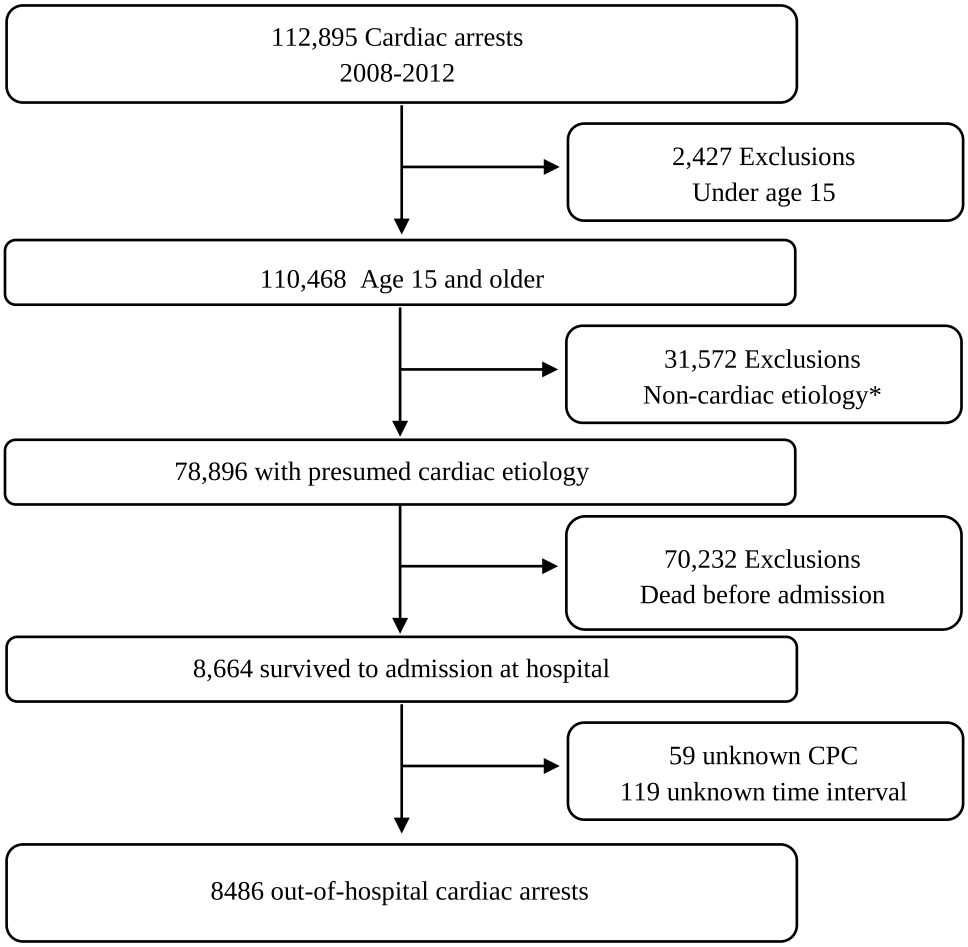
Figure 1. Mechanisms of neuroprotection by hypothermia treatment and proposed roles of sex hormones during reperfusion injury.



During reperfusion, brain damage is induced by one or more of the pathways involving: a) calcium overload and subsequent ionic imbalance; b) peroxidation of cell membrane; c) cell apoptosis; d) inflammatory responses; e) axon degeneration; f) disruption of blood-brain-barrier integrity. Antagonistic effects induced by hypothermia and sex hormone against these reperfusion mechanisms are described above.

Figure 2. Inclusion criteria of OHCA from CAVAS database, 2008-2012.



* Those with non-cardiac etiologies (trauma, drowning, poisoning, asphyxia, hanging and other) were excluded from the study.

Table 1. Cerebral Performance Category (CPC) Scale.

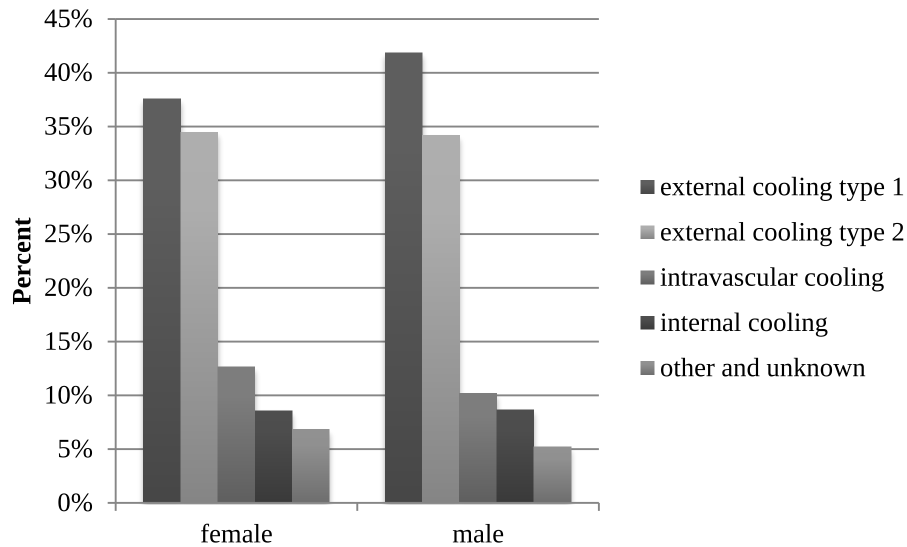
CPC 1 (Good cerebral performance)	Conscious, able to work. Might have mild neurologic or psychological disability.
CPC 2 (Moderate cerebral disability)	Conscious, able to perform daily activities independently and work in a sheltered facility.
CPC 3 (Severe cerebral disability)	Conscious, require assistance due to cognitive deficit. Includes severe dementia or paralysis.
CPC 4 (Coma or vegetative state)	Unconscious, does not respond to external stimulus.
CPC 5 (brain death)	Apnea, areflexia, EEG silence.

Table 2. Proportion of patients survived to discharge, stratified by gender, age and cardiac rhythm.

	Survival to discharge, n / Total, N (%)			
	Women		Men	
Total	820/2,830	(29.0%)	2,372/5,656	(41.9%)
<45				
VF/VT[a]	42/69	(60.9%)	167/222	(75.2%)
PEA[b]	9/40	(22.5%)	30/71	(42.3%)
Asystole	92/284	(32.4%)	238/553	(43.0%)
45-65				
VF/VT	71/112	(63.4%)	448/626	(71.6%)
PEA	26/84	(31.0%)	101/231	(43.7%)
Asystole	196/724	(27.1%)	722/1826	(39.5%)
>65				
VF/VT	56/139	(40.3%)	153/314	(48.7%)
PEA	45/172	(26.2%)	75/225	(33.3%)
Asystole	283/1206	(23.5%)	438/1588	(27.6%)

[a] VF: ventricular fibrillation, VT: ventricular trachycardia.
[b] PEA: pulseless electrical activity.

Figure 3. Type of therapeutic hypothermia treatment utilized by gender.



* Chi-square test statistic is 3.2416 (p-value=0.5182).

Type of technique for every therapeutic hypothermia treatment was recorded as one of the following: external cooling type 1, external cooling type 2, intravascular cooling, internal cooling, and other. External cooling type 1 included the use of cooling blankets, applying ice packs in axillae, or spraying water on body and cooling with fan. Type 2 included the use of machines or a cooling device (i.e., Arctic Sun). Intravascular cooling used cooling catheter device (i.e., CoolGard3000 by Alsius). Internal cooling recorded invasive techniques through installation of cold saline via nasogastric tube or bladder tube, peritoneal lavage, or cold saline IV infusion.

Table 3. Demographic, clinical characteristics, and risk factors of the study population, 2008-2012.

Characteristic	Total (N=8486)		hypothermia (N=1140)		No hypothermia (N=7346)		OR (95% CI)[a]
Age, n (%)							
<45 years old	1239	(14.6)	233	(20.4)	1006	(13.7)	1.83 (1.53, 2.18)
45-65 years old	3603	(42.5)	497	(43.6)	3106	(42.3)	1.26 (1.10, 1.45)
>65 years old	3644	(42.9)	410	(36.0)	3234	(44.0)	Referent
Gender, n(%)							
Men	5656	(66.7)	847	(74.3)	4809	(65.5)	1.52 (1.75, 1.32)
Women	2830	(33.3)	293	(25.7)	2537	(34.5)	Referent
Initial ECG[b], n (%)							
VF/VT[c]	1482	(17.5)	303	(26.6)	1179	(16.0)	2.10 (1.81, 2.44)
PEA[d]	823	(9.7)	163	(14.3)	660	(9.0)	2.02 (1.67, 2.44)
Asystole	6181	(72.8)	674	(59.1)	5507	(75.0)	Referent
Metropolitan, n (%)							
Yes	4666	(55.0)	735	(64.5)	3931	(53.5)	1.58 (1.38, 1.79)
No	3820	(45.0)	405	(35.5)	3415	(46.5)	Referent
Insurance, n (%)							
health insurance[e]	7204	(84.9)	1022	(89.6)	6182	(84.2)	1.33 (0.99, 1.78)
medical aid class 1 and 2	781	(9.2)	63	(5.5)	718	(9.8)	0.70 (0.48, 1.04)
no insurance	32	(0.4)	3	(0.3)	29	(0.4)	0.83 (0.24, 2.82)
other and unknown	469	(5.5)	52	(4.6)	417	(5.7)	Referent
Bystander CPR, n (%)							
Yes	984	(11.6)	277	(24.3)	707	(9.6)	3.01 (2.58, 3.52)
No	7502	(88.4)	863	(75.7)	6639	(90.4)	Referent
Place of OHCA[f], n (%)							
Public	1890	(22.3)	350	(30.7)	1540	(21.0)	1.88 (1.48, 2.42)
Private	5788	(68.2)	703	(61.7)	5085	(69.2)	1.15 (0.90, 1.45)
Other	808	(9.5)	87	(7.6)	721	(9.8)	Referent
Presence of witness, n (%)							
Yes	5833	(68.7)	861	(75.5)	4972	(67.7)	1.47 (1.28, 1.70)
No	2653	(31.3)	279	(24.5)	2374	(32.3)	Referent
ED[g] level, n (%)							
level 1	1443	(17.0)	428	(37.5)	1015	(13.8)	30.89 (19.59, 48.71)
level 2	5558	(65.5)	692	(60.7)	4866	(66.2)	10.37 (6.63, 16.24)
level 3	1485	(17.5)	20	(1.8)	1465	(19.9)	Referent
Time interval, mean (SD)[h]							
Response interval, minutes	6.65	(3.56)	6.46	(2.86)	6.68	(3.66)	0.21 (0.00, 0.44)
Scene interval, minutes	6.58	(4.41)	6.67	(4.22)	6.56	(4.44)	-0.10 (-0.38, 0.17)
Transport interval, minutes	8.23	(8.66)	8.55	(9.19)	8.18	(8.57)	-0.37 (-0.91, 0.17)

Table 3 - continued

Characteristic	**Total (N=8486)**		**hypothermia (N=1140)**		**No hypothermia (N=7346)**		OR (95% CI)[a]
EMS[i] and ED CPR, n (%)							
Both EMS and ED CPR[j]	6585	(77.6)	869	(76.2)	5715	(77.8)	1.09 (0.85, 1.38)
EMS CPR only	1243	(14.6)	190	(16.7)	1053	(14.3)	1.29 (0.97, 1.70)
ED CPR only	659	(7.8)	81	(7.1)	578	(7.9)	Referent
EMS defibrillation, n (%)							
Yes	6780	(79.9)	727	(63.8)	6053	(82.4)	2.66 (2.32, 3.04)
No	1706	(20.1)	413	(36.2)	1293	(17.6)	Referent
Reperfusion therapy, n (%)							
Yes	876	(10.3)	151	(13.2)	725	(9.9)	1.39 (1.56, 1.68)
No	7610	(89.7)	989	(86.8)	6621	(90.1)	Referent

[a] Odds ratio (OR) and 95% confidence interval (CI) compares the odds of receiving TH for each demographic and clinical characteristic.
[b] ECG: electriocardiographic rhythm.
[c] VF: ventricular fibrillation, VT: ventricular trachycardia.
[d] PEA: pulseless electrical activity.
[e] Includes national health insurance, automobile insurance, and occupation compensation insurance.
[f] OHCA: out-of-hospital cardiac arrest.
[g] ED: emergency department.
[h] For measures of time intervals, mean differences are reported in the OR column.
[i] EMS: emergency medical service.
[j] Includes no EMS and ED CPR (n=17).

Table 4. Neurological outcome by age, gender, and cardiac rhythm.

Characteristic	Good recovery (N=1235)		Poor recovery (N=7251)		Crude OR (95% CI)[a]
Gender, n (%)					
Men	973	(9.3)	4683	(82.8)	2.04 (1,76, 2.35)
Women	262	(17.2)	2568	(90.7)	Referent
Age, n (%)					
<45 years old	298	(24.1)	941	(75.9)	4.01 (3.35, 4.80)
45-65 years old	670	(18.6)	2933	(81.4)	2.89 (2.49, 3.36)
>65 years old	267	(7.3)	3377	(92.7)	Referent
Initial ECG[b], N (%)					
VF/VT[c]	544	(36.7)	938	(63.3)	5.25 (4.59, 6.01)
PEA[d]	76	(9.2)	747	(90.8)	0.92 (0.72, 1.18)
Asystole	615	(9.9)	5566	(90.1)	Referent

[a] Odds ratio (OR) and 95% confidence interval (CI) compares the odds of having good neurological recovery between gender, age groups, and cardiac rhythm groups.
[b] ECG: electriocardiographic rhythm
[c] VF: ventricular fibrillation, VT: ventricular trachycardia
[d] PEA: pulseless electrical activity

Table 5. Multivariate association of hypothermia treatment and good neurological recovery.

Characteristic	β estimate[a]	Standard error	p-value
Hypothermia * Gender .	0.2014	0.2399	0.4011
Hypothermia * Age			
<45 years old	0.6576	0.2866	0.0217
45-65 years old	0.3457	0.2557	0.1765
Hypothermia * ECG[b]	0.1330	0.2050	0.5164
Insurance			
health insurance[c]	0.5443	0.1904	0.0043
medical aid class 1 and 2	0.3927	0.2348	0.0944
no insurance	-0.1560	0.8459	0.8537
Bystander CPR	0.0638	0.1058	0.5465
Presence of witness	0.6064	0.0918	<0.0001
ED[d] level			
level 1	0.6542	0.1475	<0.0001
level 2	0.3320	0.1295	0.0104
EMS[e] and ED CPR			
EMS and ED CPR	-0.0322	0.1612	0.8416
EMS CPR only	2.2495	0.1682	<0.0001
EMS defibrillation	0.5622	0.0884	<0.0001
Reperfusion therapy	0.9121	0.0998	<0.0001

[a] Estimated coefficients for a multivariate regression of neurologic recovery on therapeutic hypothermia treatment, controlling for covariates and interactions.
[b] ECG: electriocardiographic rhythm
[c] Includes national health insurance, automobile insurance, and occupation compensation insurance.
[d] ED: emergency department.
[e] EMS: emergency medical service.

Table 6. Adjusted odds ratio for good neurological recovery by therapeutic hypothermia treatment, stratified by gender, age and cardiac rhythm (shockable/nonshockable rhythms).

	Women			Men		
Age	n	Crude OR (95% CI)[a]	Adjusted OR (95% CI)	n	Crude OR (95% CI)	Adjusted OR (95% CI)
<45						
Shockable[b]	69	4.38 (1.39, 13.74)	1.64 (0.92, 2.93)	222	1.73 (0.97, 3.10)	2.01 (1.26, 3.18)
Nonshockable[c]	324	2.34 (1.08, 5.05)	1.44 (0.85, 2.44)	624	1.67 (1.01, 2.75)	1.76 (1.14, 2.70)
45-65						
Shockable	112	0.63 (0.21, 1.88)	1.20 (0.70, 2.08)	626	1.57 (1.06, 2.32)	1.47 (1.01, 2.14)
Nonshockable	808	1.44 (0.69, 3.03)	1.05 (0.64, 1.72)	2057	1.53 (1.09, 2.14)	1.28 (0.92, 1.80)
>65						
Shockable	139	3.27 (1.00, 10.73)	0.85 (0.46, 1.57)	314	2.37 (1.25, 4.48)	1.04 (0.63, 1.71)
Nonshockable	1378	0.90 (0.36, 2.30)	0.74 (0.42, 1.31)	1813	0.66 (0.34, 1.28)	0.90 (0.57, 1.46)

[a] OR: odds ratio. 95% CI: 95% confidence interval.
[b] Shockable rhythms include ventricular fibrillation (VF) and ventricular trachycardia (VT).
[c] Nonshockable rhythms include pulseless electrical activity (PEA) and asystole.

Table 7. Adjusted odds ratio for good neurological recovery by therapeutic hypothermia treatment, stratified by gender, age and cardiac rhythm (VF.VT/PEA/asystole).

	Women				Men			
	n (good CPC[a])				n (good CPC)			
Age	TH	No TH	Crude OR (95% CI)[b]	Adjusted OR (95% CI)	TH	No TH	Crude OR (95% CI)	Adjusted OR (95% CI)
<45								
VF/VT[c]	18 (12)	51 (16)	4.38 (1.39, 13.74)	1.65 (0.92, 2.95)	66 (39)	156 (71)	1.73 (0.97, 3.10)	2.00 (1.26, 3.19)
PEA[d]	10 (2)	30 (0)	17.94 (0.78, 410.42)	2.95 (1.44, 6.02)	19 (5)	52 (6)	2.74 (0.72, 10.34)	3.56 (1.87, 6.80)
Asystole	42 (9)	242 (28)	2.08 (0.90, 4.81)	1.15 (0.66, 2.00)	78 (21)	475 (89)	1.60 (0.92, 2.77)	1.39 (0.88, 2.20)
45-65								
VF/VT	20 (5)	92 (32)	0.63 (0.21, 1.88)	1.19 (0.69, 2.07)	127 (69)	499 (215)	1.57 (1.06, 2.32)	1.43 (0.98, 2.09)
PEA	16 (4)	68 (6)	3.44 (0.84, 14.08)	2.13 (1.07, 4.24)	49 (12)	182 (17)	3.15 (1.39, 7.15)	2.58 (1.43, 4.64)
Asystole	65 (5)	659 (52)	0.97 (0.37, 2.53)	0.83 (0.50, 1.39)	220 (38)	1606 (215)	1.35 (0.93, 1.97)	1.00 (0.70, 1.45)
>65								
VF/VT	16 (5)	123 (15)	3.27 (1.00, 10.73)	0.84 (0.45, 1.55)	56 (19)	258 (46)	2.37 (1.25, 4.48)	1.03 (0.62, 1.70)
PEA	25 (1)	147 (9)	0.64 (0.08, 5.27)	1.49 (0.72, 3.11)	44 (5)	181 (9)	2.45 (0.78, 7.72)	1.81 (0.93, 3.51)
Asystole	81 (4)	1125 (57)	0.97 (0.34, 2.75)	0.58 (0.32, 1.05)	188 (5)	1400 (92)	0.39 (0.16, 0.97)	0.70 (0.43, 1.16)

[a] Good CPC includes cerebral performance category scores of 1 and 2.
[b] OR: odds ratio. 95% CI: 95% confidence interval.
[c] VF=ventricular fibrillation, VT=ventricular trachycardia.
[d] PEA=pulseless electrical activity.