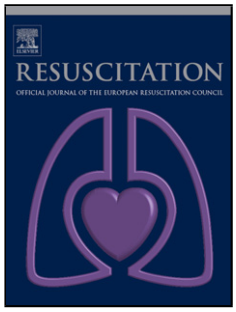

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Relationships between Three Twelve Month Outcomes in Children enrolled in the Therapeutic Hypothermia After Pediatric Cardiac Arrest Trials

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Abstract

Aim. To inform design aspects of future trials by comparing 3 and 12-month neurobehavioural outcomes in children enrolled in Therapeutic Hypothermia After Pediatric Cardiac Arrest Out-of-Hospital and In-Hospital (THAPCA-OH, THAPCA-IH) trials.

Methods. The THAPCA trials evaluated two targeted temperature management interventions (hypothermia, 32.0-34.0^{o}C; normothermia, 36.0-37.5^{o}C). Children, aged 2 days to <18 years, were enrolled from 2009-2015. Three and 12-month post-cardiac arrest (CA) outcomes included the

Vineland Adaptive Behavior Scales, Second Edition (VABS-II) (population mean=100, SD=15) and the Pediatric Cerebral Performance Category (PCPC) scale. Children without significant pre-existing neurodevelopmental deficits were included in primary outcome analyses. Among survivors, favorable 12-month outcome was defined as VABS-II >70.

Results. VABS-II and PCPC were available at 3 and 12 months in 204 of 222 eligible survivors (THAPCA-OH, n=82; THAPCA-IH, n=122). Relative to THAPCA-IH, THAPCA-OH had significantly less pre-CA disability and significantly greater 12-month CA impairment, based on both VABS-II and PCPC. Correlations between 3 and 12-month VABS-II scores were strong for THAPCA-OH (r=0.95) and THAPCA-IH (r=0.72), and lower (p=<0.001) in THAPCA-IH. Between time-points correlations were lower, but still significant in children <1 year at CA (p <.001). In both cohorts, 3-month VABS-II and PCPC categorical outcomes had high sensitivity (> 70%) for predicting favorable 12-month VABS-II outcomes, but specificity was lower for THAPCA-IH (68-89%) relative to THAPCA-OH (>95%). Overall, 12-month diagnostic accuracy was >80% for both VABS-II and PCPC in both cohorts.

Conclusions. In future paediatric cardiac arrest clinical trials that enroll similar cohorts, integration of 3-month neurobehavioral outcome measures should be considered.

Abbreviations:

IH-CA – in-hospital cardiac arrest
OH-CA – out-of-hospital cardiac arrest
VABS-II – Vineland Adaptive Behavior Scales-Second Edition
THAPCA-OH - Therapeutic Hypothermia after Pediatric Cardiac Arrest, Out-of-Hospital
THAPCA-IH – Therapeutic Hypothermia after Pediatric Cardiac Arrest, In-Hospital
PCPC- Pediatric Cerebral Performance Category
POPC - Pediatric Overall Performance Category
SD – standard deviation

Keywords: cardiac arrest; pediatrics; outcome; neurobehavioral

Introduction

Children who survive cardiac arrest (CA) are at substantial risk for poor neurobehavioural outcomes. Identification of therapeutic interventions that will improve long-term outcomes is a high priority for resuscitation research. A substantial challenge in the design of clinical trials in this heterogeneous and medically complex population is the selection of appropriate neurobehavioral outcome measures. Assessment measures must be well-standardized, reproducible, and applicable to the full paediatric age-range (i.e. infancy to young adulthood). Selection of the optimal timing for outcome evaluation must balance considerations regarding challenges inherent in cognitive assessments of young children, and pragmatic considerations in time allocation for implementation and completion of major multicenter clinical trials.

Recently, the Therapeutic Hypothermia after Pediatric Cardiac Arrest Out-of-Hospital (THAPCA-OH) and In-Hospital (THAPCA-IH) Trials evaluated two targeted temperature management strategies, hypothermia or normothermia, in children who were comatose after CA resuscitation.[1,2]

The neurobehavioral measure selected for inclusion in the primary outcome was adaptive behavior composite score on the Vineland Adaptive Behavior Scales, Second Edition (VABS-II).[3] The detailed rationale for selection of this measure has been reported.[4] Briefly, the VABS-II is a caregiver-report of functional skills and provides age-corrected standard scores (mean=100, SD=15) in four domains (communication, daily living, socialization, motor skills) and an overall adaptive behavior composite; higher scores denote better functioning. The time-point selected for outcome assessment was 12 months, based on attempting to balance sufficient time for recovery

with need to optimize enrollment and follow-up within the study timeframe. In both trials, a dichotomous approach was selected for the primary outcome. Favorable outcome was defined as one-year survival with VABS-II score >70 (no more than 2SD below the age-corrected standard score); only individuals with pre-CA scores in this range were eligible for the primary outcome. Although the primary outcome was evaluated at 12 months after CA, VABS-II evaluations were also completed at 3 months. The Pediatric Cerebral Performance Scale (PCPC) and the Pediatric Overall Performance Scale (POPC),[5,6] descriptive ordinal function measures of neurological and overall health respectively, were also scored at both time-points, to facilitate comparisons with other paediatric CA outcome studies.

In our initial analyses of THAPCA trial neurobehavioral outcomes in long-term survivors, we noted unexpectedly strong correlations between 3 and 12 month outcomes;[7,8] however, direct comparison of correlations between the THAPCA cohorts and within the youngest age subgroups were not explored. Understanding the relationship between 3 and 12 month outcomes is important for future trial design in these populations. Incorporation of 3 month outcomes could optimize subject retention and follow-up, reduce costs and allow for adaptive trial design strategies (i.e. incorporating initial outcome data to modify treatment and patient allocation options, and to potentially inform early stopping rules for interim efficacy monitoring). The goals of this study are to understand the relationships between 3 and 12-month neurobehavioral outcome measures in both THAPCA cohorts, to evaluate the influence of age on these relationships, to explore agreement between 3 and 12 month classifications of favorable outcomes, and to compare outcome classifications based on VABS-II and PCPC.

Methods

Study population

Children, ages 2 days to 18 years, were enrolled (THAPCA-OH, n=295; THAPCA-IH, n=329). Full inclusion and exclusion criteria, randomization, and enrollment details are published.[9] Two hundred and four of 222 eligible survivors (those without pre-existing neurodevelopmental deficits) had both 3 and 12 month neurobehavioural outcomes.

Assessment Measures

Global Functioning.

PCPC provides a measure of neurological functioning and POPC measures overall health (including neurological functioning).[5,6] These clinician-rated scales, initially described for classification of paediatric intensive care outcomes more broadly, are scored from 1 to 5; 1 represents normal function and 5 represents severe impairment. These scales have been recommended for reporting paediatric CA outcomes.[10] We incorporated analysis of two definitions that have been used to classify favorable neurobehavioural outcome [Favorable I: PCPC=1 (normal) or PCPC=2 (mild disability) as a strict definition of favorable outcome and Favorable II: PCPC=1-3 (normal, mild, or moderate disability)] as a broader definition of favorable outcome.[11-14]

Neurobehavioural Functioning

The VABS-II [3] measures functional skills and provides age-corrected standard scores [mean=100, standard deviation (SD)=15] for overall adaptive behavior composite and four domains (communication, daily living, socialization, motor skills) and v-scores (mean=15, SD=3)

for subdomains. Subdomains include developmentally-sequenced items, starting with skills typical of infancy. The VABS-II parent/caregiver rating form and survey interview versions yield comparable scores.[3]

Procedures

Each THAPCA site's institutional review board approved the study; caregiver informed consent was obtained prior to enrollment. Within 24 hours of enrollment, a primary caregiver completed the VABS-II rating form to determine pre-CA functioning. Site research coordinators reviewed responses and in some cases read items to caregivers and recorded responses, collected demographic and CA-related variables, and also rated pre-CA neurological status (scored with PCPC).

Three and 12 months following CA, a research assistant (Kennedy-Krieger Institute, Baltimore, MD), trained by a neuropsychologist (BS), conducted a semi-structured telephone interview to assess neurobehavioural function (including VABS-II). PCPC scores were assigned based on consensus between a rehabilitation physician (JC) and neuropsychologist (BS) after review of the medical and functional details gathered by the RA during the telephone interview. Procedures for follow-up data collection for THAPCA were published.[1,2]

Data Analysis

Characteristics between the THAPCA-OH and THAPCA-IH groups were compared using Wilcoxon rank-sum tests or *t* tests for continuous variables and PCPC/POPC categorical variables and Fisher's exact test for other categorical variables. Change in VABS-II scores from 3 to 12

months were calculated and summarized using histograms. Pearson correlation coefficients were used to measure the relationship between VABS-II scores at 3 and 12 months. Magnitudes of correlation were compared using the Fisher *z* transformation.[15] Correlation comparisons were performed in R, version 3.4.3, using the package cocor.[16] All other analyses were performed using SAS software, version 9.4 (SAS Institute).

Results

Sample Characteristics

Table 1 shows the characteristics of the 204 survivors with 3 and 12 month neurobehavioral outcomes. The THAPCA-OH (n=82) and THAPCA-IH (n=122) participants differed significantly in several respects. The THAPCA-OH group was older, more likely to be male, had less pre-CA disability, and were more likely to have CA due to respiratory etiology. The THAPCA-OH group received fewer doses of epinephrine, included more cases with estimated duration of chest compressions in the 15 to 30 minute range, and had shorter durations of hospitalization post-CA.

Table 2 reports the pre-CA, 3, and 12 month PCPC and VABS-II scores separately for the THAPCA-OH and THAPCA-IH groups. Overall, while the OH group had significantly less pre-CA disability than the IH group, 3 and 12 months PCPC and VABS-II scores were significantly worse for THAPCA-OH relative to THAPCA-IH. In the THAPCA-OH group, over half had a PCPC of 4 or 5 at 3 and 12 months (56% and 51%, respectively), whereas about a quarter had scores in this range in THAPCA-IH (24% and 25%). Similarly, at both 3 and 12 months, the THAPCA-OH mean VABS-II score was more than 2 SD lower than the age-expected mean score of 100, whereas the THAPCA-IH mean VABS-II score was about 1 SD lower.

Relationships between Three and Twelve Month Outcomes

Figure 1 displays relationships between 3 and 12 month VABS-II scores for both THAPCA-OH and THAPCA-IH survivors, and includes analyses of correlations between 3 and 12 month scores by age group (at time of CA) categories. Each graph includes four quadrants, which are delineated by the pre-defined favorable score cut-off values of 70 at 3 months (x axis) and 12 months (y axis). There were strong correlations between 3 and 12 month scores for the overall groups in both cohorts (THAPCA-OH, r=0.95; THAPCA-IH, r=0.72, p<0.001) and for all age subsets (<3 year, <2 years, <1 year at CA, r=0.92-0.66, p<0.001). Within each cohort, relative to those > 1 year of age, correlations for those < 1 year were lower, although not significantly different (THAPCA-OH > 1 year at CA, r=0.95 versus < 1 year at CA, r=0.88, p=0.08; THAPCA-IH > 1 year at CA, r=0.81 versus <1 year at CA, r=0.66, p=0.08). When comparing between the THAPCA cohorts, individual score correlations were significantly stronger for the THAPCA-OH for the overall samples (p<0.001) and for all but the youngest age subset (<3 year, p< 0.001; <2 years, p=0.002; <1 year at CA, p=.053); smaller sample sizes may affect power to detect significant between-trial differences within the younger age cohorts).

Figure 2 depicts the magnitudes and frequencies of change between 3-month and 12-month VABS-II scores for the THAPCA-OH and THAPCA-IH groups for all ages and separately for the subset of children <3 and <1 years of age. The overall mean VABS-II score change between 3 and 12 months for the overall group was 1.5 (SD=11.9) [THAPCA-OH, mean=1.8, SD=9.3; THAPCA-IH, mean=1.3, SD=13.4, p=0.73)]. In both cohorts, few children improved or declined more than 15 points (i.e. 1 SD of population mean) between 3 and 12 months; for THAPCA-OH, 6/82 (7.3%)

improved more than 15 points and 2 (2.4%) declined more than 15 points, and for THAPCA-IH, corresponding improvements and declines were noted in 17/122 (13.9%) and 13/122 (10.7%) respectively. Young children in the THAPCA-IH groups had the highest rate of greater than 15 point decline (subset <3 years=13/88, 14.8%; subset <1 year=12/71, 16.9%), whereas very few young children in THAPCA-OH had declines of that magnitude (<3 years=1/37, 2.7%; subset <1 year=0/17, 0%).

Relationships between 3 and 12 Month Favorable and Unfavorable Classifications

In the THAPCA trials, 12 month VABS-II scores were used to classify favorable and unfavorable outcomes. Since PCPC scores may also be applied to classify paediatric CA outcomes, we examined the 12 month favorable/unfavorable classifications for both measures. At 12 months post-CA using PCPC Favorable I criteria (PCPC 1-2), 40% (n=33) of the THAPCA-OH group and 52% (n=63) of the THAPCA-IH group had favorable outcomes; applying PCPC Favorable II criteria (PCPC 1-3), 49% (n=40) of the THAPCA-OH group and 75% (n=92) of the THAPCA-IH group had favorable outcomes. Using the pre-defined VABS-II scores of > 70 for classification, 50% (n=41) of the THAPCA-OH group and 77% (n=94) of the THAPCA-IH group had favorable 12 month outcomes.

Table 3 compares the sensitivity, specificity, positive predictive value, negative predictive value, and area under the curve when the 3-month VABS-II, PCPC Favorable I (PCPC 1 or 2) and Favorable II (PCPC 1-3) categorical outcomes are used to predict the primary favorable 12-month VABS-II outcome. When using these 3-month outcomes as predictors in THAPCA-OH, sensitivity (percent of participants with favorable outcome at 12-months who had favorable

outcome at 3-months) was over 70% and specificity (percent of participants with unfavorable outcome at 12-month who had unfavorable outcome at 3-months) was >95% for all three of the 3-month outcome classifications. For THAPCA-IH, sensitivity was similar (>70%), whereas specificity was lower (68-89%). The overall diagnostic accuracy (area under the curve) was at least 80% for all three of the 3-month classification schemas, in both THAPCA-OH and THAPCA-IH groups.

Discussion

This is the first detailed, prospective study examining correlations between relatively early and longer-term neurobehavioural outcomes in two groups of paediatric CA survivors who were comatose following resuscitation. Based on a preceding retrospective study[17] that delineated significant differences between paediatric OH-CA and IH-CA populations with respect to CA etiology, medical co-morbidities, and outcomes, the THAPCA targeted temperature treatment trials were conducted independently in these two groups. Results of the current study confirmed that there were important differences in sample characteristics between the THAPCA-OH and THAPCA-IH cohorts, including both greater pre-CA disability and better outcomes for children in the IH group than in the OH group. Survivors in the THAPCA-OH group were older, more likely to have CA due to respiratory etiology, and to have shorter lengths of hospitalization post-CA. Moreover, we found the relationship between 3 and 12 month outcomes was strong for both trial cohorts and that these relationships differed by age at time of CA, in both groups.

While both groups had strong correlations between 3 and 12 months VABS-II scores, correlations were stronger for THAPCA-OH than THAPCA-IH cohort. For many IH-CA survivors, medical

comorbidities likely contributed to the larger variances between the two outcome assessments. The THAPCA protocols did not include collection of medical data (other than hospital discharge day and hospital discharge PCPC score) after the initial five-day intervention period. However, the IH-CA cohort included many children with complex pre-CA medical disorders (reflected in their significantly lower pre-CA POPC scores than for the OH-CA cohort) and these cases also had significantly longer post-CA hospital stays. These children were at heightened risk for subsequent illnesses and hospitalizations compared to the OH-CA cohort over the nine month time interval, which may account for the more frequent declines of at least 15 points from 3 to 12 months (illustrated in Figure 2) in the IH group.

The IH-CA survivor cohort was also significantly younger than the OH-CA group (median age at CA: THAPCA-IH=0.5 years, THAPCA-OH=3.4 years). Our data provide evidence that age at CA influenced the relationship between 3 and 12 month post-CA outcomes in both cohorts and the relationships were weakest in the youngest age group. At least two distinct factors could contribute to these trends. Assessment of functioning is particularly challenging in very young children, given their relatively limited behavioral repertoire, and standardized parent-reported function measures of baseline (i.e. pre-CA) function, such as VABS-II, are particularly challenging in hospitalized infants with pre-existing medical illnesses. Importantly, while the correlation between the 3 and 12 month VABS-II was lowest for the youngest children, it remained robust in both cohorts [THAPCA-OH (r=0.88). THAPCA-IH (r=0.66)] in children less than 1 year of age at CA.

The strong relationships between 3 and 12 month VABS-II outcomes in both cohorts have important implications for the design of future clinical trials in similar populations. Incorporation

of 12-month assessments to determine neurobehavioral outcomes adds substantial complexity and cost to the design of paediatric studies (in comparison with corresponding trials in adult CA populations that typically rely on earlier time points to assess outcomes in survivors).[18,19] These relationships also provide robust justification for adaptive trial designs that integrate 3-month outcome measures to modify and refine intervention protocols and/or subject allocation. For example, future hypothermia trials in similar paediatric populations might use adaptive designs with 3-month outcome assessments to investigate optimal durations of target temperature control and/or optimal temperature targets.

Our results also address another pragmatic consideration in study design, reliance on dichotomous vs. continuous outcome measures. For the THAPCA trials, a dichotomous outcome (survival with favorable cut-off VABS-II) was ultimately selected as the primary outcome because of the ease of interpretation.[4] The strong correlations between 3 and 12-month continuous VABS-II scores and adequacy of the 3-month VABS-II cut-off score to classify 12-month favorable outcomes illustrate the utility and complementarity of both dichotomous and continuous outcomes in this population.

In view of the relatively common inclusion of PCPC outcomes in paediatric CA studies, we examined the relationships between 3-month PCPC and 12-month VABS-II classifications in both THAPCA-OH and THAPCA-IH cohorts, and compared trends using both broader (Favorable II, PCPC 1-3) and stricter (Favorable I, PCPC 1-2) definitions of favorable outcomes. Although the two schemes provided slightly different rates of sensitivity and specificity, overall classification accuracy was similar. Importantly, PCPC outcomes can be easily obtained from medical record review, whereas the VABS-II data is obtained either through a lengthy caregiver rating form or a

semi-structured interview completed by a trained interviewer. While the PCPC is a less time intensive measure, use of global categories and lack of age-specific normative data limit its utility as a measure of detailed neurobehavioural outcomes.

Study strengths include the prospective design, large sample size, broad paediatric age range, high follow-up rate, and use of well-validated, detailed outcome measures that assess multiple domains of functioning. Additionally, use of a trained interviewer at a central follow-up center maximized the reliability of VABS-II and PCPC data collected across sites. Our THAPCA cohorts were restricted to a well-characterized and high disability risk group of children who were comatose for several hours after resuscitation (pain localization or responsiveness to commands were THAPCA exclusion criteria).

This study should be interpreted in the context of several limitations. While these results can inform the design of future clinical trials, we emphasize that their application to clinical prognostication for individual patients may not be warranted. The factors that contribute both to substantial improvements and declines in function between 3 and 12 months in some cases remain uncertain. Moreover, the children who were enrolled in the THAPCA trials were CA survivors who were comatose after resuscitations and at the highest risk for neurobehavioural morbidity. Thus, results cannot be generalized to all paediatric CA survivors. In addition, it is possible that the full extent of deficits in young children may not become evident until school age and correlations between relatively early and long-term outcome measures could decline with longer follow-up. Given the large number of sites and complex infrastructure needed to for the THAPCA trials, collecting outcomes beyond the 12-month time point was not feasible. In terms of the

potential utility of the PCPC as an outcome measure in future trials, it should be noted that for purposes of THAPCA, the caregiver responses provided during the VABS-II interview were used to rate PCPC scores, which may have inflated the predictive accuracy of this measure. This scoring method may limit generalizability of our data to registry-based and observation studies where multiple raters with highly variable training collect these outcome measures.

Conclusion

In this population of children who incurred OH-CA or IH-CA and were comatose after resuscitation, we found significant correlations between 3 and 12-month assessments, even in the youngest children. Favorable neurobehavioral outcome based on 3-month VABS-II and PCPC were accurate classifiers for 12 month outcomes in both cohorts. Results illustrate the potential utility of incorporating 3 month neurobehavioral outcome assessment into the design of paediatric cardiac arrest clinical trials

Contributors' Statements:
Beth Slomine: Dr. Slomine contributed substantially to study design and data interpretation, oversaw neurobehavioural data collection, drafted the manuscript, and approved the final manuscript as submitted.

Faye Silverstein: Dr. Silverstein contributed to study design and data interpretation, reviewed and revised the manuscript, and approved the final manuscript as submitted.

James Christensen: Dr. Christensen contributed to the study design, acquisition of data, and interpretation, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Kent Page: Mr. Page conducted all statistical analyses, contributed to data interpretation, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Richard Holubkov: Dr. Holubkov contributed to study design, oversaw all statistical analyses, contributed to data interpretation, reviewed and revised the manuscript, and approved the final manuscript as submitted.

J. Michael Dean: Dr. Dean participated in the study conceptualization and design, oversaw all data collection, and served as principal investigator for the THAPCA data coordinating center, critically reviewed the manuscript, and approved the final manuscript as submitted.

Frank Moler: Dr. Moler conceptualized and designed the study and served as principal investigator for the THAPCA trials, reviewed and revised the manuscript, and approved the final manuscript as submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Legends to Figures

Figure 1: Correlations between 3 and 12 month outcomes for Out-of-Hospital (OH) and In-Hospital (IH) cardiac arrest groups

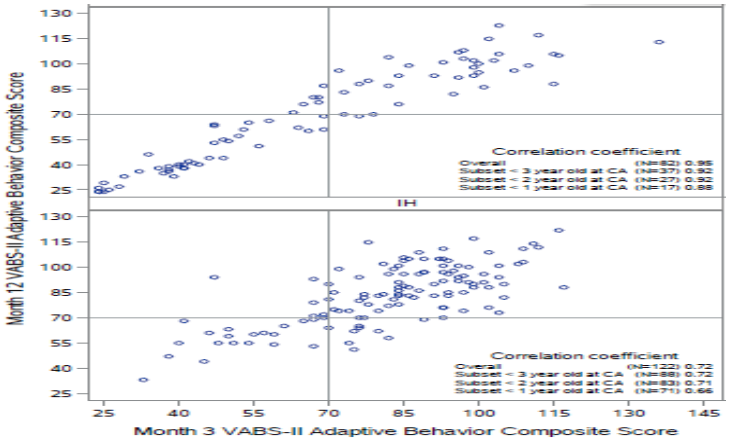
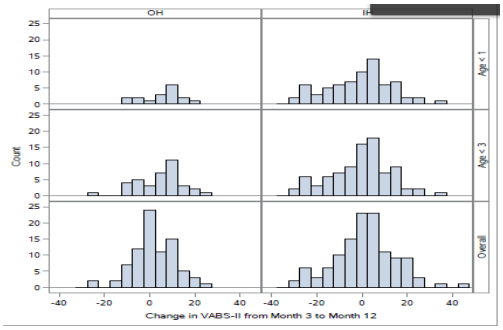


Figure 2: Change in the Vineland Scales of Adaptive Behavior, Second Edition (VABS-II) between 3 and 12 months across age subgroups for Out-of-Hospital (OH) and In-Hospital (IH) cardiac arrest groups



Tables

Table 1: Characteristics of Cardiac Arrest Survivors				
		Study		
	Overall (N = 204)	OH (N = 82)	IH (N = 122)	P-value
Age at Randomization (years): Median [Q1, Q3]	1.6 [0.3, 7.3]	3.4 [1.5, 12.0]	0.5 [0.2, 3.7]	<.001[1]
Male	126 (62%)	59 (72%)	67 (55%)	0.019[2]
Race				0.980[2]
American Indian or Alaska Native	3 (1%)	1 (1%)	2 (2%)	
Asian	6 (3%)	2 (2%)	4 (3%)	
Black or African American	55 (27%)	20 (24%)	35 (29%)	
White	117 (57%)	50 (61%)	67 (55%)	
Other	8 (4%)	3 (4%)	5 (4%)	
Unknown	15 (7%)	6 (7%)	9 (7%)	
Ethnicity				1.000[2]
Hispanic or Latino	43 (21%)	17 (21%)	26 (21%)	
Not Hispanic or Latino	153 (75%)	62 (76%)	91 (75%)	
Stated as Unknown	8 (4%)	3 (4%)	5 (4%)	
Caregivers highest education received				0.554[2]
Some high school or less	38 (19%)	17 (21%)	21 (17%)	
High school graduate or GED	55 (27%)	21 (26%)	34 (28%)	
Vocational school or some college	52 (25%)	18 (22%)	34 (28%)	
College degree	37 (18%)	14 (17%)	23 (19%)	
Graduate or doctoral degree	22 (11%)	12 (15%)	10 (8%)	
Pre-cardiac arrest PCPC				<.001[1]
Normal = 1	156 (76%)	74 (90%)	82 (67%)	
Mild disability = 2	32 (16%)	5 (6%)	27 (22%)	
Moderate disability = 3	15 (7%)	3 (4%)	12 (10%)	
Severe disability = 4	1 (0%)	0 (0%)	1 (1%)	
Pre-cardiac arrest POPC				<.001[1]
Good = 1	119 (58%)	66 (80%)	53 (43%)	
Mild disability = 2	58 (28%)	10 (12%)	48 (39%)	

Table 1: Characteristics of Cardiac Arrest Survivors				
		Study		
	Overall (N = 204)	OH (N = 82)	IH (N = 122)	P-value
Moderate disability = 3	24 (12%)	6 (7%)	18 (15%)	
Severe disability = 4	3 (1%)	0 (0%)	3 (2%)	
Pre-cardiac arrest VABS Adaptive Behavior Composite Score: Mean (SD)	98.0 (15.88)	101.4 (15.73)	95.8 (15.66)	0.015[3]
Primary etiology of cardiac arrest				<.001[2]
Cardiovascular event	72 (35%)	13 (16%)	59 (48%)	
Neurological event	2 (1%)	0 (0%)	2 (2%)	
Congenital heart disease event	20 (10%)	2 (2%)	18 (15%)	
Respiratory event	96 (47%)	58 (71%)	38 (31%)	
Drug overdose	3 (1%)	2 (2%)	1 (1%)	
Electrolyte imbalance	1 (0%)	1 (1%)	0 (0%)	
Other	3 (1%)	1 (1%)	2 (2%)	
Unknown	7 (3%)	5 (6%)	2 (2%)	
Total number of doses of epinephrine administered by EMS and at hospital: Median [Q1, Q3]	3.0 [1.0, 4.5]	2.0 [1.0, 4.0]	3.0 [2.0, 6.0]	<.001[1]
Estimated duration of chest compressions				<.001[2]
Unable to determine	4 (2%)	3 (4%)	1 (1%)	
Less than or equal to 15 minutes	87 (43%)	27 (33%)	60 (49%)	
More than 15 to less than or equal to 30 minutes	51 (25%)	36 (44%)	15 (12%)	
More than 30 minutes	62 (30%)	16 (20%)	46 (38%)	
Treatment Assigned				0.390[2]
Hypothermia	114 (56%)	49 (60%)	65 (53%)	
Normothermia	90 (44%)	33 (40%)	57 (47%)	
Post-cardiac arrest length of stay (days): Median [Q1, Q3]	30.0 [18.0, 62.0]	27.0 [14.0, 48.0]	36.0 [20.0, 65.0]	0.007[1]

Table 1: Characteristics of Cardiac Arrest Survivors				
		Study		
	Overall (N = 204)	OH (N = 82)	IH (N = 122)	P-value

[1] P-value is based on the Wilcoxon rank-sum test.
[2] Fisher's exact test.
[3] Two-sided t-test with unpooled variance.

Table 2: Pre-Cardiac Arrest Functioning and Outcomes of Cardiac Arrest Survivors

		Study		
	Overall (N = 204)	OH (N = 82)	IH (N = 122)	P-value
Pre-cardiac arrest PCPC				<.001[1]
Normal = 1	156 (76%)	74 (90%)	82 (67%)	
Mild disability = 2	32 (16%)	5 (6%)	27 (22%)	
Moderate disability = 3	15 (7%)	3 (4%)	12 (10%)	
Severe disability = 4	1 (0%)	0 (0%)	1 (1%)	
Month 3 PCPC				<.001[1]
Normal = 1	55 (27%)	19 (23%)	36 (30%)	
Mild disability = 2	43 (21%)	10 (12%)	33 (27%)	
Moderate disability = 3	31 (15%)	7 (9%)	24 (20%)	
Severe disability = 4	56 (27%)	31 (38%)	25 (20%)	
Coma or vegetative state = 5	19 (9%)	15 (18%)	4 (3%)	
Month 12 PCPC				0.007[1]
Normal = 1	60 (29%)	23 (28%)	37 (30%)	
Mild disability = 2	36 (18%)	10 (12%)	26 (21%)	
Moderate disability = 3	36 (18%)	7 (9%)	29 (24%)	
Severe disability = 4	59 (29%)	31 (38%)	28 (23%)	
Coma or vegetative state = 5	13 (6%)	11 (13%)	2 (2%)	
Pre-cardiac arrest VABS-II Adaptive Behavior Composite Score: Mean (SD)	98.0 (15.88)	101.4 (15.73)	95.8 (15.66)	0.015[2]
Month 3 VABS-II Adaptive Behavior Composite Score: Mean (SD)	76.2 (23.79)	67.5 (28.58)	82.1 (17.81)	<.001[2]
Month 12 VABS-II Adaptive Behavior Composite Score: Mean (SD)	77.7 (23.59)	69.3 (28.30)	83.3 (17.84)	<.001[2]

[1] P-value is based on the Wilcoxon rank-sum test.
[2] Two-sided t-test with unpooled variance.

Table 3: Predicting Favorable Outcome at 12-Months (VABS-II $\geq$ 70)

	Three Month Favorable Outcome Classifications		
	VABS-II > 70	PCPC 1-2 (Normal or Mild Disability)	PCPC 1-3 (Normal, Mild, or Moderate Disability)
THAPCA-OH			
Sensitivity	85%	71%	83%
Specificity	98%	100%	95%
AUC	92%	85%	89%
PPV	97%	100%	94%
NPV	87%	77%	85%
THAPCA-IH			
Sensitivity	94%	70%	90%
Specificity	68%	89%	71%
AUC	81%	80%	81%
PPV	91%	96%	91%
NPV	76%	47%	69%

AUC = area under the curve; PPV = positive predictive value; NPV = negative predictive value