Risk of Mortality Associated With Therapeutic Hypothermia Among Sudden Cardiac Arrest Survivors With Known Heart Failure

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Current guidelines do not inform about use of therapeutic hypothermia among heart failure (HF) patients who suffer from cardiac arrest. We assessed the risk of mortality associated with hypothermia among cardiac arrest survivors with HF. This analysis includes 1,416 comatose patients with cardiac arrest who achieved return of spontaneous circulation on admission and had a left ventricular ejection fraction (LVEF) assessment or HF admission within the previous year. HF was defined as either previous episode of HF or presence of left ventricular ejection fraction <50%. Hazard ratios (HR) and 95% confidence intervals (CI) for association of hypothermia and mortality among patients with and without HF were computed using Cox proportional hazard models adjusted for several risk factors. A propensity score matched analysis was also performed. There were 624 patients (44%) with pre-existing HF and 467 patients (33.0%) received hypothermia. The mortality rate was higher in HF patients treated with hypothermia compared with patients without hypothermia (75.4% vs 53.2%, p <0.0001). Hypothermia was associated with increased mortality among HF patients (HR 1.69; 95% CI 1.27, 2.24, p <0.001) and was not associated with mortality among non-HF patients (HR 1.21; 95% CI 0.93, 1.56, p = 0.15). The association of hypothermia with mortality was higher among HF patients who presented with shockable rhythm compared with nonshockable rhythm (interaction p value = 0.0495). Hypothermia is associated with increased mortality among cardiac arrest survivors with known HF. **(Am J Cardiol 2019;124:751−755)**

Each year around 300,000 people suffer from out of hospital and 200,000 suffer from in-hospital sudden cardiac arrest in the United States.[1−3] As per recent data an estimated 6.5 million Americans adults suffer from heart failure (HF).[4] Because both cardiac arrest and HF are common, it is expected that sudden cardiac arrest occurs among pre-existing HF ranges from 12% to 21% of this specific population.[5] Current 2015 American Heart Association guidelines for postcardiac arrest care recommend therapeutic hypothermia for all comatose patients after return of spontaneous circulation (ROSC). However, guidance regarding specific subgroups that may benefit from therapeutic hypothermia remains lacking. Left ventricular dysfunction in itself is a poor prognostic marker among patients with cardiac arrest but how hypothermia modifies or affects it has not been studied.[6] The present study aims to examine the risk of mortality among patients with known HF who presented with cardiac arrest and were subjected to therapeutic hypothermia in a large cohort of cardiac arrest patients.

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Methods

This is a retrospective cohort study conducted at a large tertiary care hospital with a large catchment area covering Western North Carolina, North Carolina. We performed a retrospective chart review of all the patients who developed cardiac arrest at Wake Forest Baptist Hospital between January 1, 2012 to December 31, 2016 (5 years). We included patients with outside hospital nontraumatic cardiac arrest as well patients with in-hospital arrest. Inclusion criteria included all consecutive adult patients (age ≥18 years), able to survive beyond 24 hours, and able to achieve systolic blood pressure ≥90 mm Hg or mean arterial blood pressure ≥65 mm Hg after fluid resuscitation with or without vasopressors. Patients were excluded if Glasgow coma scale ≥8, >3 estimated hours since cardiac arrest, do-not-resuscitation designation as a code status, nonmechanically ventilated patients, pregnant, active ongoing bleeding, and arrest secondary sepsis. The patient demographics and medical records were extracted from existing electronic medical chart data. These data were approved for use in research by the institutional review board of Wake Forest University with patient consent waived. Initially, 2,122 patients were identified but after exclusions, a total of 1,416 patients were included in the study.

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Baseline demographic data including age, gender, race, height and weight, body mass index, primary rhythm of arrest and duration of cardiopulmonary resuscitation, previous medical illness including diabetes, hypertension, smoking status, end-stage renal disease, previous stroke, hyperlipidemia cerebrovascular accidents were carefully extracted from the chart based on self-report. Admission hemoglobin, creatinine, lactic acid, and arterial pH were obtained from the laboratory values. Emergency medical service documentation and code sheets were reviewed to obtain information about pharmacotherapy, defibrillation, and duration of cardiopulmonary resuscitation. Electrocardiograms were reviewed to assess the initial rhythm and 12-lead electrocardiogram postcardiac arrest was used to assess ST elevation myocardial infarction. The details regarding past medical history were confirmed if they were mentioned in 2 separate clinical encounters documented by a physician.

Per institutional policy, therapeutic hypothermia was employed in patients after cardiac arrest within 6 hours of ROSC for an expected duration of 24 hours. The goal temperature of 32°C to 36°C was attempted using external cooling methods such as cooling blankets and ice packs. In addition, cold intravenous crystalloid was administered in some patients where the target temperature was difficult to achieve with external agents. Core temperature was measured using rectal probe or temperature sensing urethral catheter. The patient was rewarmed passively after 24 hours unless needed earlier due to hemodynamic instability. The patients with HF were selected based on clinical documentation of HF in the previous medical records and echocardiogram evidence of Left ventricular ejection fraction <50%. Medical records were reviewed up to a year before the index event of cardiac arrest. The patient criteria included patients with both systolic and diastolic dysfunction. Patients with both ischemic and/or nonischemic cardiomyopathy were included in this study. The primary outcome measure was the occurrence of all-cause mortality from the date of index admission to the date of death or January 1, 2018 (whichever came first) using web-based electronic death registration system.

Baseline characteristics were compared by the use of therapeutic hypothermia. Statistical significance for categorical variables was tested using the chi-square method and the analysis of variance or Student's *t* test for continuous variables. Cox proportional hazard models were adjusted. Models are provided in tables and Supplementary Appendix using following models. Propensity score matching was performed to identify controls in 1:1 fashion for all the HF cases. The score was constructed using 31 demographic and clinical covariates (Supplementary Appendix). A nearest neighbor, 1:1 matching was adopted. The propensity score match robustness was tested by evaluation of standardized mean differences (bias %) between the unmatched and matched variables with a cut level of 0.1.[7] The matched cohort had 308 HF cases and 308 controls. We were able to achieve balance on all the variables included in the analysis. Analyses were performed using R statistical software (R Foundation, Vienna, Austria; download available at http://www.R-project.org) and Match It package.[8] Statistical significance was defined as $p \leq 0.05$ for main effects and interaction.

Results

Overall, 1,416 comatose patients (mean age 62.5 ± 14.6 years, 60.2% males, 67.2% white, and 29.7% black) achieved ROSC after cardiac arrest. Over a median period of 17.0 days (interquartile range 4.0 to 252.9 days), 467 (33.0%) were treated with therapeutic hypothermia postcardiac arrest. Pre-existing HF was present in 623 (44%). Table 1 demonstrates a higher prevalence of out of hospital cardiac arrest (OHCA), ventricular tachycardia/ventricular fibrillation (VT/VF) arrest, amiodarone use, lidocaine use, ST elevation myocardial infarction (STEMI), prolonged mechanical ventilation, percutaneous interventions, percutaneous left ventricular assist device use, intraaortic balloon pump (IABP) use, temporary pacemaker use among patients who underwent therapeutic hypothermia, whereas pulmonary embolism was more common in patients without therapeutic hypothermia. In addition, there was longer duration of cardiopulmonary resuscitation (CPR) and higher lactic acid levels among patients with hypothermia than nonhypothermia group. The mortality rates among HF patients who were treated with therapeutic hypothermia compared with those who were not treated with hypothermia, were higher (incidence rate = 146.6 vs. 87.6 per 100 person years). Figure 1 shows the Kaplan-Meier curves for HF patients with and without hypothermia and depicts decreased survival among HF patients treated with hypothermia (log rank <0.0001). There is a sharp decline in survival during the first 30 days postcardiac arrest. In adjusted Cox proportional hazard regression models, the use of hypothermia among HF patient was associated with an increased risk of mortality (hazard ratios [HR] 1.69; 95% confidence interval [CI] 1.27, 2.24, $p < 0.0001$), whereas the use of hypothermia was not associated with increased risk of mortality among non-HF patients (HR 1.21; 95% CI 0.93, 1.56, $p = 0.15$). Table 2 shows the association between use of hypothermia with mortality among subgroups: shockable (VT/VF) rhythm and nonshockable (pulseless electrical activity or asystole) rhythms. Among HF patients, the association of mortality with the use of hypothermia was stronger among patients who presented with shockable rhythm versus the patients who presented with nonshockable rhythm (interaction p value = 0.0495). In sensitivity analysis, hypothermia was associated with increased risk of mortality among HF patients (HR = 1.69; 95% CI = 1.26, 2.27, $p = 0.001$) but not among the propensity-matched controls (HR = 1.30; 95% CI = 0.96, 1.75, $p = 0.09$).

Discussion

To the best of our knowledge, this is the first study to examine the association of mortality with the use of therapeutic hypothermia among patients with pre-existing HF. We demonstrated that this risk was independent of several confounders and found hypothermia had a neutral effect among patients without HF. We also found that the association of mortality with use of hypothermia was stronger among the cardiac arrest patients who presented with shockable rhythm versus the nonshockable rhythm.

Registry data from Get with the Guidelines for out-of-hospital cardiac arrest[9] and in-hospital cardiac arrest[10]

Table 1
Baseline characteristics by hypothermia status

Patient characteristics	Hypothermia		p value
	No (n = 949)	Yes (n = 467)	
Age (years)	62.9±14.6	61.8±14.4	0.18
Men	562 (59.2%)	290 (62.1%)	0.16
White	630 (66.4%)	321 (68.7%)	
Black	293 (30.9%)	128 (27.4%)	
Hispanic	17 (1.8%)	5 (1.1%)	
Hemoglobin ≤10 g/dl	299 (31.5%)	135 (29.4%)	0.42
Prior coronary artery disease	512 (54.0%)	268 (58.3%)	0.13
Hypertension	575 (60.6%)	272 (59.1%)	0.60
Hyperlipidemia	384 (40.5%)	192 (41.7%)	0.65
Diabetes mellitus	258 (27.2%)	119 (25.9%)	0.60
End stage renal disease	295 (31.1%)	150 (32.6%)	0.54
Moderate to severe valvular disease	93 (9.8%)	36 (7.8%)	0.22
Prior cerebrovascular accident	105 (11.1%)	43 (9.4%)	0.32
Current or former smoker	370 (39.0%)	182 (39.0%)	0.67
Prior congestive heart failure	412 (43.4%)	211 (45.2%)	0.53
Out of hospital cardiac arrest	551 (58.1%)	396 (84.8%)	<0.001
Ventricular fibrillation/ tachycardia	243 (25.6%)	242 (51.9%)	<0.0001
Pulseless electrical activity	568 (59.9%)	166 (35.6%)	<0.0001
Asystole	132 (13.9%)	58 (12.4%)	0.46
Duration of cardiopulmonary resuscitation (minutes)	12.5±9.5	19.0±12.7	<0.0001
Body mass index (kg/m^2)	30.5±14.9	31.0±8.5	0.52
Defibrillation	269 (28.4%)	245 (52.7%)	<0.0001
pH	7.26±0.12	7.26±0.11	0.28
Serum creatinine (mg/dl)	2.65±2.58	2.62±2.54	0.79
Hemoglobin (g/dl)	11.1±2.6	12.2±2.5	<0.0001
Lactic acid (mg/dl)	5.0±4.4	5.7±4.2	0.004
Lidocaine infusion	47 (5.0%)	75 (16.1%)	<0.0001
Amiodarone infusion	237 (25.0%)	205 (43.9%)	<0.0001
Epinephrine Injection	878 (92.8%)	446 (95.9%)	0.03
Vasopressor infusion	416 (44.0%)	215 (46.2%)	0.48
Milrinone infusion	31 (3.3%)	16 (3.4%)	0.88
Epinephrine infusion	204 (21.6%)	100 (21.4%)	0.93
Dobutamine infusion	237 (25.1%)	138 (29.7%)	0.07
Heparin infusion	165 (17.4%)	109 (23.4%)	0.008
Antibiotic use	316 (33.5%)	180 (38.7%)	0.06
Prior antiplatelet use	524 (56.0%)	238 (53.5%)	0.38
ST elevation MI	125 (13.2%)	102 (21.8%)	<0.0001
Non-ST elevation MI	194 (20.5%)	99 (21.2%)	0.77
Pulmonary embolism	212 (22.5%)	73 (15.8%)	0.003
Mechanical ventilation ≥48 hours	878 (92.5%)	452 (96.8%)	0.001
Cardiac catheterization	129 (13.6%)	77 (16.5%)	0.16
Percutaneous intervention	111 (11.7%)	78 (16.7%)	0.01
Extra-cardiac membrane oxygenation	16 (1.7%)	14 (3.0%)	0.12
Impella use	17 (1.8%)	19 (4.1%)	0.01
Intra-aortic balloon pump use	316 (33.3%)	204 (43.7%)	<0.0001
Temporary pacemaker use	67 (7.1%)	148 (31.8%)	<0.0001

MI = myocardial infarction.
Vasopressors included phenylephrine, norepinephrine, dopamine, and vasopressin.

suggest prevalence estimates of 18% and 22% of HF among cardiac arrest survivors. An increase in survival of these patients has been observed over the last decade.[11] These registry data failed to comment on use of therapeutic hypothermia among HF patients. Moreover, the current American Heart Association guidelines[12] do not inform on subgroups of patients who may or may not benefit from therapeutic hypothermia. These guidelines are based on 1 RCT of 275 European witnessed out-of-hospital cardiac arrest patients who were randomized to receive therapeutic hypothermia versus normothermia after reaching hospital,[13] and 1 quasi-randomized trial of 77 comatose Australian cardiac arrest patients who randomized OHCA patients while in the ambulance.[14] Both studies only included patients if they had a shockable rhythm present on first medical contact. A pooled analysis of both trials demonstrated improved survival with pooled RR for 6-month mortality of 0.75 (95% CI, 0.61 to 0.92), which was mainly driven by the first trial. However, these findings were challenged by a 2013 trial of 939 comatose adult OHCA survivors.[15] The mortality risk was not different among the survivors of cardiac arrest, in hypothermia and nonhypothermia group Among cardiac arrest survivors with initial nonshockable rhythm, only 1 retrospective cohort study of 374 patients who demonstrated benefit of mild hypothermia in terms of mortality (adjusted OR 0.56; 95% CI 0.34 to 0.93).[16] Similarly, only 1 retrospective cohort study of 8,316 in-hospital cardiac arrest patients with any initial nonshockable rhythm showed no difference in mortality at hospital discharge (adjusted OR 1.11; 95% CI 0.81 to 1.54), whereas the Penn Alliance for Therapeutic Hypothermia Registry from 6 centers showed benefit of therapeutic hypothermia among 519 in and OHCA survivors.[17] The appraisal of evidence led to strong recommendation for use of therapeutic hypothermia for patients with initial shockable rhythm for comatose out-of-hospital cardiac arrest patients with ROSC and weak recommendations for its use among patients with either nonshockable rhythm except unwitnessed asystole and in-hospital cardiac arrest by Advanced Life Support Task Force.[18] A randomized clinical trial to assess use of therapeutic hypothermia among nonshockable rhythm cardiac arrest patients is underway.[19] The data are even more unclear among patients with in-hospital cardiac arrest with the largest study from the Get with the Guidelines Registry showing lower likelihood of survival among 1,568 propensity-matched survivors with therapeutic hypothermia versus 3,714 in nonhypothermia group (27.4% vs 29.2%; relative risk 0.88; 95% CI 0.80 to 0.97).[20] Due to unclear evidence, current utilization of therapeutic hypothermia remains low and haphazard especially among patients with initial nonshockable rhythm.[21,22] In the Penn Alliance for Therapeutic Hypothermia Registry, a US-based multicenter registry of 167 patients, therapeutic hypothermia was only provided to 24% of postcardiac arrest patients. One-third of our cohort (33%) received hypothermia treatment, which is likely a reflection of contemporary practice pattern. Our observation that therapeutic hypothermia is associated with increased risk of mortality could be explained by several mechanisms. We know that hypothermia leads to increase in systemic vascular resistance due to peripheral vasoconstriction that occurs due to increase in sympathetic tone.[23] Elevated sympathetic tone has deleterious effects on HF patients and could tip the already compromised hemodynamics in these patients toward tissue hypoxia. Moreover, hypothermia increases the susceptibility to develop coagulopathy,[24] microvascular dysfunction,[25] and increased risk

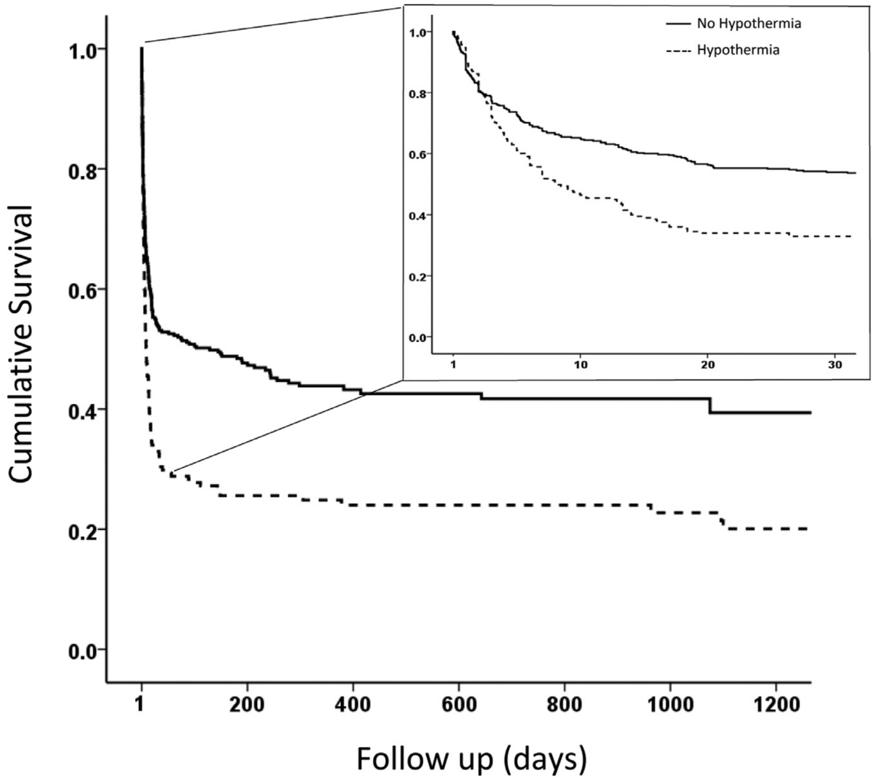

Figure 1. Kaplan-Meier curves for cardiac arrest and pre-existing heart failure patients with and without hypothermia.

of infections,[26] which could themselves lead to increase in mortality.

There are several implications of this study. First, this is the first study that suggests a possible harmful effect of therapeutic hypothermia among HF patients which begs the need for future studies that should evaluate the cardiac safety of therapeutic hypothermia among various cardiac arrest subgroups. Second, if we presume that the harmful effects of therapeutic hypothermia are due to changes in hemodynamics, then probably a more invasive assessment of hemodynamics (e.g., using Swan Ganz catheter) among HF patients. The 2005 publication of evaluation study of HF and pulmonary artery catheterization (ESCAPE) trial that showed no benefit of hemodynamic monitoring in terms of mortality or hospitalization among hospitalized acute HF patients has led to precipitous decline in the use of pulmonary artery catheter.[27] The prevalence of use of invasive monitoring was <5% among our cohort. We hypothesize that because hypothermia could change the hemodynamics, a thorough invasive assessment could aid in clinical decision-making and management among HF patients. These need to be further studied.

Limitations of this study include nonrandomized design and an indication bias could be of concern in such cohort. Although we used a propensity-matched analysis to balance on several confounders and achieved adequate matching,

Table 2
Unadjusted and adjusted risk of mortality associated with hypothermia

	Unadjusted	p	Model 1*	p	Model 2†	p	Propensity score matched	p
Known HF								
Yes	1.66 (1.35, 2.04)	<0.0001	1.77 (1.43, 2.18)	<0.0001	1.69 (1.27, 2.24)	<0.0001	1.69 (1.26, 2.27)	0.001
No	1.21 (1.00, 1.47)	0.045	1.23 (1.02, 1.48)	0.04	1.21 (0.93, 1.56)	0.15	1.30 (0.96, 1.75)	0.09
Interaction p-value	0.015		0.008		0.006			
Known HF with PEA/asystole	1.65 (1.25, 2.16)	<0.0001	1.68 (1.28, 2.21)	<0.0001	1.63 (1.10, 2.41)	0.02		
Known HF with VT/VF	2.61 (1.81, 3.77)	<0.0001	3.02 (2.06, 4.42)	<0.0001	1.99 (1.18, 3.38)	0.01		

* Model 1: age, gender. and race.

† Model 2: model 1 variables, initial rhythm at the time of arrest, defibrillation, ST elevation myocardial infarction, non-ST elevation myocardial infarction, history of medical co-morbidities (hypertension, diabetes, end-stage renal disease, valvular disease, coronary artery disease, hyperlipidemia, smoking), pharmacotherapies (lidocaine, amiodarone, epinephrine, vasopressor, dobutamine, milrinone, antibiotics, paralytic use), mechanical ventilation use ≥48 hours, temporary pacemaker placement, mechanical circulatory support (IABP, extracorporeal membrane oxygenation (ECMO), Impella), out of hospital cardiac arrest, duration of CPR, and pulmonary embolism.

there is a chance for unmeasured residual confounding. In addition, this is a single tertiary care center study with a large catchment area in the Western North Carolina; however, a multicenter study could provide more in depth understanding of the practice patterns. Larger studies lack the specific details as available in this chart review.

In conclusion, this is the first and largest retrospective study to demonstrate a harmful impact of hypothermia on patients with known HF among cardiac arrest survivors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2019.05.055.

1. Kumar G, Nanchal R. Trends in survival after in-hospital cardiac arrest. *N Engl J Med* 2013:368–680.
2. Merchant RM, Yang L, Becker LB, Berg RA, Nadkarni V, Nichol G, Carr BG, Mitra N, Bradley SM, Abella BS, Groeneveld PW. Incidence of treated cardiac arrest in hospitalized patients in the United States. *Crit Care Med* 2011;39:2401–2406.
3. Wong MK, Morrison LJ, Qiu F, Austin PC, Cheskes S, Dorian P, Scales DC, Tu JV, Verbeek PR, Wijeysundera HC, Ko DT. Trends in short- and long-term survival among out-of-hospital cardiac arrest patients alive at hospital arrival. *Circulation* 2014;130:1883–1890.
4. Benjamin EJ, Virani SS, Callaway CW, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, Matchar DB, Matsushita K, Mussolino ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA, Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL, Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. *Circulation* 2018;137:e67–e492.
5. Bradley SM, Kaboli P, Kamphuis LA, Chan PS, Iwashyna TJ, Nallamothu BK. Temporal trends and hospital-level variation of inhospital cardiac arrest incidence and outcomes in the veterans health administration. *Am Heart J* 2017;193:117–123.
6. Gonzalez MM, Berg RA, Nadkarni VM, Vianna CB, Kern KB, Timerman S, Ramires JA. Left ventricular systolic function and outcome after in-hospital cardiac arrest. *Circulation* 2008;117:1864–1872.
7. Stuart EA, Lee BK, Leacy FP. Prognostic score-based balance measures can be a useful diagnostic for propensity score methods in comparative effectiveness research. *J Clin Epidemiol* 2013;66:S84–S90.
8. Ho DE, Imai K, King G, Stuart EA. Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. *Polit Anal* 2007;15:199–236.
9. Ofoma UR, Basnet S, Berger A, Kirchner HL, Girotra S. Trends in survival after in-hospital cardiac arrest during nights and weekends. *J Am Coll Cardiol* 2018;71:402–411.
10. Qazi AH, Kennedy K, Bradley SM, Chan PS. Impact of timing of cardiac arrest during hospitalization on survival outcomes and subsequent length of stay. *Resuscitation* 2017;121:117–122.
11. Shen L, Jhund PS, Petrie MC, Claggett BL, Barlera S, Cleland JGF, Dargie HJ, Granger CB, Kjekshus J, Kober L, Latini R, Maggioni AP, Packer M, Pitt B, Solomon SD, Swedberg K, Tavazzi L, Wikstrand J, Zannad F, Zile MR, McMurray JJV. Declining risk of sudden death in heart failure. *N Engl J Med* 2017;377:41–51.
12. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, Gabrielli A, Silvers SM, Zaritsky AL, Merchant R, Vanden Hoek TL, Kronick SL. Part 9: post-cardiac arrest care: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010;122:S768–S786.
13. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346:549–556.
14. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;346:557–563.
15. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T, Stammet P, Wanscher M, Wise MP, Aneman A, Al-Subaie N, Boesgaard S, Bro-Jeppesen J, Brunetti I, Bugge JF, Hingston CD, Juffermans NP, Koopmans M, Kober L, Langorgen J, Lilja G, Moller JE, Rundgren M, Rylander C, Smid O, Werer C, Winkel P, Friberg H. Targeted temperature management at 33 degrees c versus 36 degrees C after cardiac arrest. *N Engl J Med* 2013;369:2197–2206.
16. Testori C, Sterz F, Behringer W, Haugk M, Uray T, Zeiner A, Janata A, Arrich J, Holzer M, Losert H. Mild therapeutic hypothermia is associated with favourable outcome in patients after cardiac arrest with non-shockable rhythms. *Resuscitation* 2011;82:1162–1167.
17. Perman SM, Grossestreuer AV, Wiebe DJ, Carr BG, Abella BS, Gaieski DF. The utility of therapeutic hypothermia for post-cardiac arrest syndrome patients with an initial nonshockable rhythm. *Circulation* 2015;132:2146–2151.
18. Donnino MW, Andersen LW, Berg KM, Reynolds JC, Nolan JP, Morley PT, Lang E, Cocchi MN, Xanthos T, Callaway CW, Soar J. Temperature management after cardiac arrest: An advisory statement by the advanced life support task force of the international liaison committee on resuscitation and the American Heart Association emergency cardiovascular care committee and the council on cardiopulmonary, critical care, perioperative and resuscitation. *Circulation* 2015;132:2448–2456.
19. Lascarrou JB, Meziani F, Le Gouge A, Boulain T, Bousser J, Belliard G, Asfar P, Frat JP, Dequin PF, Gouello JP, Delahaye A, Hssain AA, Chakarian JC, Pichon N, Desachy A, Bellec F, Thevenin D, Quenot JP, Sirodot M, Labadie F, Plantefeve G, Vivier D, Girardie P, Giraudeau B, Reignier J. Therapeutic hypothermia after nonshockable cardiac arrest: the hyperion multicenter, randomized, controlled, assessor-blinded, superiority trial. *Scand J Trauma Resusc, Emerg Med* 2015;23:23–26.
20. Chan PS, Berg RA, Tang Y, Curtis LH, Spertus JA. Association between therapeutic hypothermia and survival after in-hospital cardiac arrest. *JAMA* 2016;316:1375–1382.
21. Jena AB, Romley JA, Newton-Cheh C, Noseworthy P. Therapeutic hypothermia for cardiac arrest: real-world utilization trends and hospital mortality. *J Hosp Med* 2012;7:684–689.
22. Dresden SM, O'Connor LM, Pearce CG, Courtney DM, Powell ES. National trends in the use of postcardiac arrest therapeutic hypothermia and hospital factors influencing its use. *Ther Hypothermia Temp Manag* 2015;5:48–54.
23. Lantry J, Dezman Z, Hirshon JM. Pathophysiology, management and complications of hypothermia. *Br J Hosp Med* 2012;73:31–37.
24. Varon J, Acosta P. Coagulopathy during therapeutic hypothermia: where are the data? *Resuscitation* 2009;80:726–727.
25. Chun-Lin H, Jie W, Xiao-Xing L, Xing L, Yu-Jie L, Hong Z, Xiao-Li J, Gui-Fu W. Effects of therapeutic hypothermia on coagulopathy and microcirculation after cardiopulmonary resuscitation in rabbits. *Am J Emerg Med* 2011;29:1103–1110.
26. Johansen ME, Jensen JU, Bestle MH, Ostrowski SR, Thormar K, Christensen H, Pedersen HP, Poulsen L, Mohr T, Kjaer J, Cozzi-Lepri A, Moller K, Tonnesen E, Lundgren JD, Johansson PI. Mild induced hypothermia: effects on sepsis-related coagulopathy—results from a randomized controlled trial. *Thromb Res* 2015;135:175–182.
27. Binanay C, Califf RM, Hasselblad V, O'Connor CM, Shah MR, Sopko G, Stevenson LW, Francis GS, Leier CV, Miller LW. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA* 2005;294:1625–1633.