Return to Work After Refractory Out-of-Hospital Cardiac Arrest in Patients Managed With or Without Extracorporeal Cardiopulmonary Resuscitation: A Nationwide Register-Based Study

Gregers, Emilie; Kragholm, Kristian; Linde, Louise; Mørk, Sivagowry Rasalingam; Andreasen, Jo Bønding; Terkelsen, Christian Juhl; Lassen, Jens Flensted; Møller, Jacob Eifer; Laugesen, Helle; Smerup, Morten; Kjærgaard, Jesper; Møller-Sørensen, Peter Hasse; Holmvang, Lene; Torp-Pedersen, Christian; Hassager, Christian; Søholm, Helle

Published in:
Journal of the American Heart Association

DOI (link to publication from Publisher):
10.1161/JAHA.123.034024

Publication date:
2024

Document Version
Publisher's PDF, also known as Version of record

Journal of the American Heart Association

ORIGINAL RESEARCH

Return to Work After Refractory Out-of-Hospital Cardiac Arrest in Patients Managed With or Without Extracorporeal Cardiopulmonary Resuscitation: A Nationwide Register-Based Study

Emilie Gregers, MD; Kristian Kragholm, MD, PhD; Louise Linde, MD; Sivagowry Rasalingam Mørk, MD, PhD; Jo Bønding Andreasen, MD, PhD; Christian Juhl Terkelsen, MD, DMSc, PhD; Jens Flensted Lassen, MD, PhD; Jacob Eifer Møller, MD, DMSc, PhD; Helle Laugesen, MD; Morten Smerup, MD, PhD; Jesper Kjærgaard, MD, DMSc, PhD; Peter Hasse Møller-Sørensen, MD, PhD; Lene Holmvang, MD, PhD; Christian Torp-Pedersen, MD, DMSc; Christian Hassager, MD, DMSc*;Helle Søholm, MD, PhD*

BACKGROUND: Extracorporeal cardiopulmonary resuscitation (ECPR) is increasingly used for refractory out-of-hospital cardiac arrest (OHCA). However, survivors managed with ECPR are at risk of poor functional status. The purpose of this study was to investigate return to work (RTW) after refractory OHCA.

METHODS AND RESULTS: Of 44 360 patients with OHCA in the period of 2011 to 2020, this nationwide registry-based study included 805 patients with refractory OHCA in the working age (18–65 years) who were employed before OHCA (2% of the total OHCA cohort). Demographics, prehospital characteristics, status at hospital arrival, employment status, and survival were retrieved through the Danish national registries. Sustainable RTW was defined as RTW for ≥6 months without any long sick leave relapses. Median follow-up time was 4.1 years. ECPR and standard advanced cardiovascular life support were applied in 136 and 669 patients, respectively. RTW 1 year after OHCA was similar (39% versus 54%; P=0.2) and sustainable RTW was high in both survivors managed with ECPR and survivors managed with standard advanced cardiovascular life support (83% versus 85%; P>0.9). Younger age and shorter length of hospitalization were associated with RTW in multivariable Cox analysis, whereas ECPR was not.

CONCLUSIONS: In refractory OHCA-patients employed prior to OHCA, approximately 1 out of 2 patients were employed after 1 year with no difference between patients treated with ECPR or standard advanced cardiovascular life support. Younger age and shorter length of hospitalization were associated with RTW while ECPR was not.

Key Words: extracorporeal cardiopulmonary resuscitation ■ out-of-hospital cardiac arrest ■ return to work

Survival after out-of-hospital cardiac arrest (OHCA) has improved over time but remains low, with 30-day survival ranging from 3% to 20% across different countries and regions worldwide.[1] In the Capital Region of Denmark, a 30-day survival of 42% in patients with OHCA with prehospital return of

Correspondence to: Emilie Gregers, MD, Department of Cardiology, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen O, Denmark.
Email: emilie.gregers@gmail.com

*C. Hassager and H. Søholm are co–last authors.

This manuscript was sent to Kori S. Zachrison, MD, MSc, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.034024

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- One-year return to work after refractory out-of-hospital cardiac arrest was similar between survivors managed with extracorporeal cardiopulmonary resuscitation (ECPR) and survivors managed with standard advanced cardiovascular life support.
- About 50% of survivors managed with ECPR returned to work during follow-up.
- No survivors managed with ECPR were admitted to a permanent nursing home.

What Are the Clinical Implications?

- Despite longer duration of hospitalization and lower return to work in ECPR compared with survivors managed with standard advanced cardiovascular life support, ECPR management may not only yield life but also content in life.

Nonstandard Abbreviations and Acronyms

ARREST	Advanced Reperfusion Strategies for Patients With Out-of-Hospital Cardiac Arrest and Refractory Ventricular Fibrillation
CPC	cerebral performance category
ECPR	extracorporeal cardiopulmonary resuscitation
INCEPTION	Early Initiation of Extracorporeal Life Support in Refractory OHCA
OHCA	out-of-hospital cardiac arrest
ROSC	return of spontaneous circulation
RTW	return to work
sACLS	standard advanced cardiovascular life support

spontaneous circulation (ROSC) and 20% in patients with refractory OHCA brought to a hospital with ongoing cardiopulmonary resuscitation (CPR) have been reported.[2] Because of the worse prognosis of refractory OHCA, extracorporeal CPR (ECPR) as rescue therapy is receiving increased attention. ECPR is a resource-heavy treatment modality with increased risk of periprocedural complications and with uncertain effect on post-OHCA functional status. Considerations for ECPR treatment are therefore reserved for selected patients with refractory OHCA.[3]

Randomized trials on the effect of early ECPR have shown diverging results in terms of survival with favorable neurological outcome, which underlines the necessity for studies investigating functional status after refractory OHCA managed with ECPR.[4–6] Neurological outcome is usually reported in OHCA research as cerebral performance category (CPC), Glasgow Outcome Scale, or the modified Rankin Scale. However, return to work (RTW) as a measure of neurological outcome might better reflect return to pre-OHCA function than the traditional neurological scores. RTW in an unselected cohort of adult survivors of OHCA has been investigated previously and showed that 3 of 4 survivors returned to work after OHCA.[7] To our knowledge, no studies have examined the proportion of patients returning to work after refractory OHCA managed with ECPR.

The aim of this study was therefore to examine RTW and sustainable RTW in survivors of refractory OHCA managed with standard advanced cardiovascular life support (sACLS) or with ECPR and to examine long-term survival.

METHODS

Data from this study are available through Statistics Denmark upon reasonable request.

STUDY POPULATION

In this nationwide cohort study using a registry-based follow-up design, we included adult patients with refractory OHCA in the period from July 1, 2011, to December 31, 2020. Patients aged >65 years (common age of retirement) and patients not employed the month before OHCA were excluded. The patients were identified through the national Danish Cardiac Arrest Registry, which includes all patients with OHCA with CPR initiated by bystanders or emergency medical services (EMS), excluding patients with obvious signs of death. We defined refractory OHCA as patients with ongoing CPR at hospital arrival. As a rule in Denmark, all patients with OHCA where resuscitation efforts are not deemed futile are transported by ground- or helicopter-based EMS with paramedics accompanied by a physician and receive prehospital and in-hospital sACLS according to current guidelines. Patients were categorized into 2 groups according to the in-hospital management of OHCA: sACLS or ECPR. Patients were categorized in the ECPR group if treatment with venoarterial extracorporeal membrane oxygenation was initiated within the first 24 hours after OHCA. To confirm that indication for extracorporeal membrane oxygenation treatment was ECPR, and not cardiogenic shock after ROSC, hospital records were examined for each identified potential patient managed with ECPR, and patients without ECPR were recategorized as sACLS. All patients without ECPR management

were categorized in the sACLS group. Use of Impella (Abiomed, Danvers, MA, USA) alone was not characterized as ECPR. Initiation of ECPR was done at the clinician's discretion supported by national consensus guideline on the use of ECPR, which was introduced in 2018 as previously described.[8]

In Denmark, patients with refractory OHCA are treated at tertiary heart centers (4 distributed across the country), which all offer ECPR to selected patients. ECPR was gradually introduced in Denmark from 2011 to 2017.

The study was approved by the Danish Patient Safety Authority (3–3013-3109/1). In Denmark, informed consent is not required for registry-based studies. Data access and use on the Statistics Denmark server was approved by the appropriate data-responsible institution, the Capital Region of Denmark (approval number P-2019-400).

Study Design

Information on age, sex, date of OHCA, prehospital parameters (witnessed arrest, bystander interventions, presenting heart rhythm, and EMS response time), and status at hospital arrival (ROSC, ongoing CPR or declared dead) were retrieved from the Danish Cardiac Arrest Registry. EMS response time was only available for OHCAs in 2016 or later. The Danish National Patient Registry[9] was used to retrieve data on procedures during hospitalization (extracorporeal membrane oxygenation, Impella, and intra-aortic balloon pump) using the Danish Medical Coding Classification System and comorbidities before OHCA using the *International Classification of Diseases, Tenth Revision* (*ICD-10*).[10] Information on comorbidities before OHCA was additionally retrieved from the Danish National Prescription Registry.[11] Information on employment status was obtained through the Danish National Labor Market register (the DREAM database) from the time of the OHCA until the end of 2020. The DREAM database has been validated previously with a positive predictive value of 98.2 for determining economic self-support and exclusion from the workforce compared with self-reported information.[12] Patients were classified as employed if they were not on any social benefits (state educational grants, maternity leave pay, and leave-of-absence schemes excluded). Baseline employment status was assessed from a 5-week time span before OHCA defined as either employed or on social benefits. RTW was defined as any employment occurring at any time point from 4 weeks after OHCA and onward throughout the entire follow-up period. Time from OHCA to RTW was calculated. Duration of employment in months was calculated for patients returning to work and sustainable RTW was defined as employment for ≥6 months without a long sick leave relapse (>4 weeks) after RTW. One-year RTW was assessed from a 5-week time span 1 year after OHCA. Additionally, data on industry affiliation before and 1 year after OHCA together with annual personal income the year before and the year after OHCA were drawn to quantify significant job changes. Disability pension before and after OHCA was also assessed. In Denmark, disability pension can be granted to people who, due to physical or psychological disabilities, are unable to hold a job despite possibilities of reduced work time. Data on annual personal income, home care (assistance with cleaning, hygiene, medicine, transfers, etc), and enrollment in a nursing home were obtained through Statistics Denmark. Income data were available only for the period 2010 to 2018 and home care data for the period 2010 to 2019. Information on survival was obtained through the Danish Cause of Death Registry.[13] The last day of follow-up was January 1, 2022 (median, 4.1 years [interquartile range, 1.6–6.1 years]); survival was calculated from the date of the OHCA until this date. The Danish Civil Personal Registration Number, unique to each Danish citizen, was used for linking data across registries.[14]

Study Outcomes

The primary outcome was RTW. Secondary outcomes were long-term survival, sustainable RTW, disability pension, enrollment in a nursing home, and changes in income after OHCA.

Statistical Analysis

Data are presented as median with interquartile range for continuous variables with differences tested by the Mann–Whitney *U* test, and frequencies with percentages for categorical variables with differences tested using χ^2 and Fisher exact test as appropriate.

Cumulative incidence curves with CIs were used to visualize RTW during the first year after OHCA for 30-day survivors managed with ECPR and sACLS, and differences were tested using the log-rank test. Additionally, RTW was tested with death as a competing risk using Gray's test. Kaplan–Meier curves were used to visualize the probability of survival the first year after the OHCA and the probability of sustainable RTW the first 6 months after returning to work. Differences were tested using the log-rank test. Univariable and multivariable Cox regression analyses estimating hazard ratio and 95% CI were performed adjusting for potential confounders after checking for proportional hazards assumption and lack of interactions. A directed acyclic graph was used to create an overview of and identify potential confounders (Figure S1–S2). All available potential confounders were included in univariable Cox regression analyses. Due to cohort size, only a limited number of variables could be included in the multivariable analysis; therefore, only OHCA

management and the variables significantly associated with RTW in univariable analyses were included in the multivariable Cox regression analysis. Adjusted *P* values were calculated using Benjamini and Hochberg false discovery rate correction for multiple testing. A *P* value <0.05 was considered statistically significant in all analyses. Due to Statistics Denmark regulations, results with ≤3 patients are reported as ≤3 only. No power calculations were done due to the retrospective observational nature of the study, with all patients managed with ECPR from 2011 to 2020 in Denmark included in the study. A post hoc power calculation with power of 80% and level of significance 0.05 yielded an effect size of 0.3.

RESULTS

Patients and Characteristics

During the 10-year study period, 44 360 people had an OHCA in Denmark. Of these, 4454 (10%) were adults with refractory OHCA. Of patients with refractory OHCA, 805 (18%) were aged 18 to 65 years and employed before the OHCA and thus included in the study. Of included patients, 669 were managed with sACLS (83%) and 136 (17%) with ECPR (Figure 1). Compared with patients managed with sACLS, patients managed with ECPR were younger (median, 51 versus 53 years), more often had favorable prehospital circumstances (more witnessed arrest, bystander CPR, and presenting with shockable rhythm), more often received renal replacement therapy, and median length of hospitalization was longer (Table 1). The differences disappeared when looking at 30-day survivors only, except for renal replacement therapy and length of hospitalization (Table 2).

Return to Work

For 30-day survivors, 61 patients returned to work (73%; Table 2). We found significantly lower RTW during follow-up in the ECPR group compared with the sACLS group (51% versus 84%; adjusted *P*=0.01). Of note, median follow-up time was shorter in patients managed with ECPR compared with patients managed with sACLS (2.2 years versus 5 years; adjusted *P*=0.02). The cumulative incidence of RTW within the first year was likewise lower in the ECPR group (40%) compared with the sACLS group (73%; *P*=0.002; Figure 2A). This did not change when death was used as a competing risk (40% versus 73%; *P*<0.001). For 30-day survivors, there was no statistically significant difference in RTW at 1-year status (39% versus 54%; adjusted *P*=0.5; Table 2).

The cumulative incidence curve suggests that patients managed with ECPR have more weeks of sick leave before RTW compared with patients managed with sACLS, yet this difference was not statistically significant (adjusted *P*=0.03; Figure 2A and Table 2).

Of patients who returned to work during follow-up, we found that 83% of patients managed with ECPR and 85% of patients managed with sACLS achieved sustainable RTW (*P*>0.9; Figure 2B and Table 2).

Looking at mean distribution of different types of social benefits during the first year of OHCA in patients without RTW, the mean duration of sick leave benefits the first year was 93% and 65% for patients managed with ECPR and patients managed with sACLS, respectively, while mean duration of unemployment benefits was 4% and 23%, respectively (Figure S2).

Assessing change in individual income from the year before the OHCA to the year after the OHCA for 1-year survivors, we found no difference between patients managed with ECPR and patients managed with sACLS either in total income or when looking at patients with RTW or on social benefits (–17% versus –10%, –11% versus –6%, –17% versus –19%, respectively). Additionally, we found no difference in the number of patients with 1-year RTW who were still affiliated with the same business area as before their OHCA (67% versus 80%; adjusted *P*=0.7; Table 3).

Factors Associated With RTW

In univariable Cox regression analyses of potential factors associated with RTW, we found that ECPR, hospitalization for >3 weeks, and age >35 years were negatively associated with RTW after refractory OHCA (Figure 3). In multivariable Cox regression analysis, we found hospitalization for ≥3 weeks and age >35 years negatively associated with RTW (Figure 4). The concordance for the multivariable Cox regression was 0.72.

Nursing Home and Disability Pension

Few 30-day survivors received home care (≤3 versus 4, *P*>0.9) or were admitted to a permanent nursing home facility, with no difference between patients managed with ECPR and patients managed with sACLS (0 versus ≤3; *P*>0.9). Also, we found no difference in the number of patients receiving home care (≤3 versus 4; *P*>0.9), nor in the number of patients receiving disability pension due to inability to work (20% versus 10%; adjusted *P*=0.5).

Survival

Thirty-day and 1-year survival were significantly higher in the ECPR group compared with the sACLS group (26% versus 8%, and 24% versus 7%, respectively; *P*<0.001; Table 1). The probability of surviving the day of OHCA (day 0) was 70% for patients managed with ECPR and 18% for patients managed with sACLS. More than 90% of 30-day survivors were still alive after

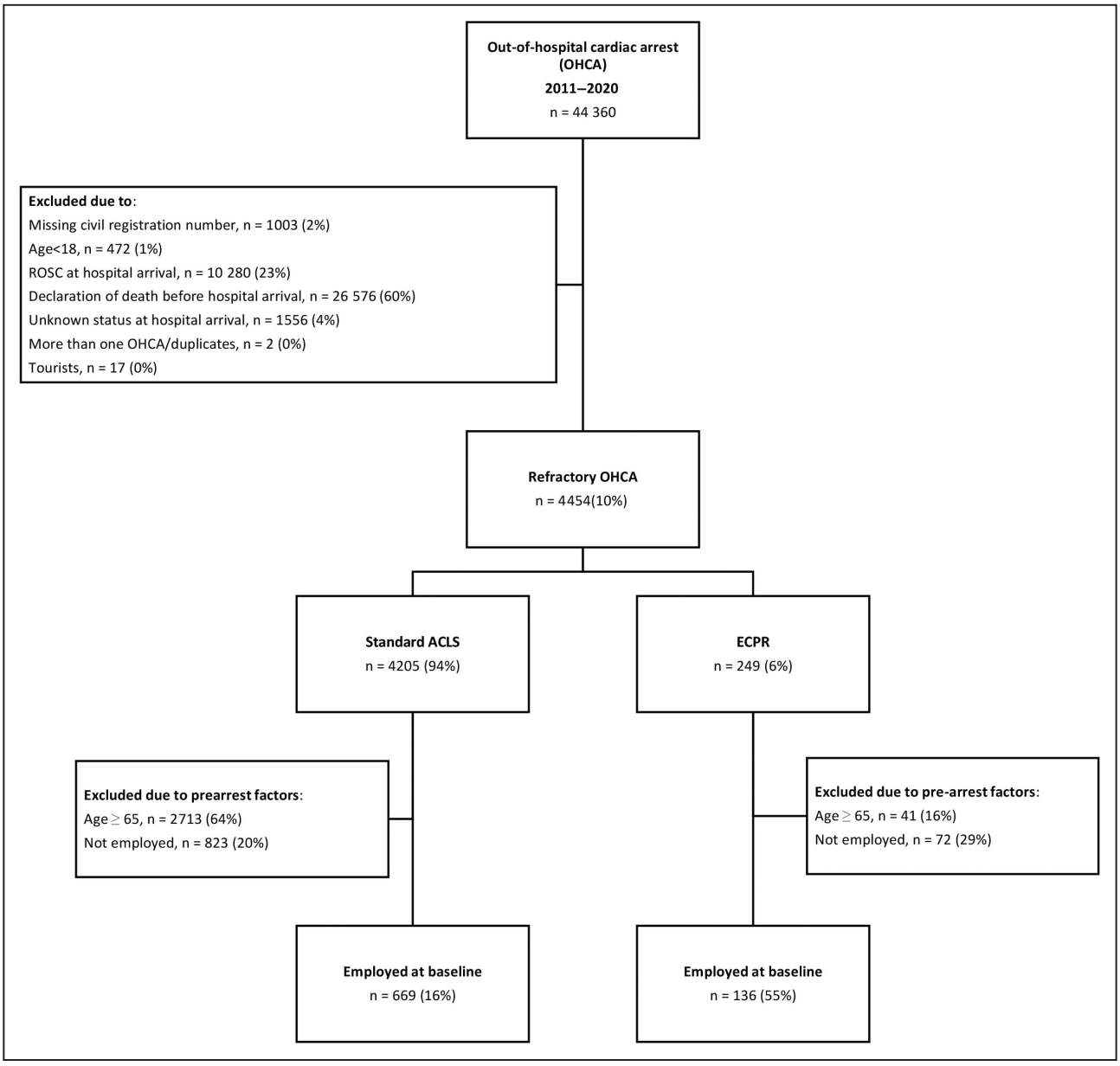

Figure 1. Study inclusion process.
Flowchart of adult patients aged <65 years with refractory OHCA and employed before OHCA included during the 10-year study period (2011–2020). ACLS indicates advanced cardiac life support; OHCA, out-of-hospital cardiac arrest; and ROSC, return of spontaneous circulation.

1 year, with no difference between patients managed with ECPR and patients managed with sACLS (adjusted *P*=0.9; Table 2 and Figure 5).

DISCUSSION

In this nationwide registry-based study examining the functional status in patients with refractory OHCA aged <65 years and employed before OHCA, we found that the likelihood of surviving 30 days was lower in the sACLS group. Yet among 30-day survivors, more patients managed with sACLS than patients managed with ECPR returned to work. Nonetheless, about 50% of survivors managed with ECPR returned to work during follow-up and no differences were found in income change and achievement of sustainable RTW (>6 months) after OHCA. Additionally, no significant differences were seen in disability pension and admission to nursing home when comparing survivors managed with ECPR with survivors managed with sACLS.

Functional Status: Return to Work

We found an overall RTW of 73% in 30-day survivors, which is comparable with previous studies of RTW

Table 1. Clinical Characteristics

	ECPR n=136	sACLS n=669	*P* value[§]
Demographic characteristics			
Age, y, median (quartile 1–quartile 3)	51 (43–57)	53 (44–58)	0.07
Sex (male), n (%)	114 (84)	528 (79)	0.3
Medical history			
No cardiovascular comorbidities, n (%)	109 (80)	483 (72)	0.1
Hypertension, n (%)	21 (15)	140 (21)	0.2
Diabetes, n (%)	9 (7)	66 (10)	0.3
Previous myocardial infarction, n (%)	≤3*	16 (2)	0.4
Peripheral artery disease, n (%)	0 (0)	10 (1)	0.3
Congestive heart failure, n (%)	4 (3)	20 (3)	>0.9
Stroke, n (%)	≤3*	13 (2)	>0.9
Cardiac arrest characteristics			
Witnessed OHCA, n (%)	108 (79)	430 (64)	**0.002**
Bystander CPR, n (%)	102 (75)	447 (67)	0.1
Shockable presenting rhythm, n (%)	81 (60)	246 (37)	**<0.001**
TOR, n (%)[†]	3 (2)	50 (7)	0.06
EMS response time, min, median (quartile 1–quartile 3)[‡]	8.0 (5.0–10.0)	7.0 (5.0–10.0)	0.4
In-hospital characteristics			
Impella, n (%)	26 (19)	3 (0)	**<0.001**
IABP, n (%)	≤3*	5 (1)	0.2
CAG, n (%)	95 (70)	102 (15)	**<0.001**
PCI, n (%)	54 (40)	52 (8)	**<0.001**
Hospitalization, days, median (quartile 1–quartile 3)	1 (0–7)	0 (0–0)	**<0.001**
Survival outcomes			
30-d survival, n (%)	35 (26)	51 (8)	**<0.001**
1-y survival, n (%)	32 (24)	48 (7)	**<0.001**

CAG indicates coronary angiogram; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; EMS, emergency medical services; IABP, intra-aortic balloon pump; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; sACLS, standard advanced cardiac life support; and TOR, termination of resuscitation. Bold indicates significant *p*-values ($p<0.05$).

*Due to Statistics Denmark, regulations n≤3 cannot be specified.

[†]TOR rules fulfilled.

[‡]Available only for OHCAs after 2015.

[§]Adjusted *P* values calculated using Benjamini and Hochberg false discovery rate correction for multiple testing.

Table 2. Thirty-Day Survivor Characteristics and Outcomes

	ECPR n=35	sACLS n=51	*P* value[‖]
Demographics and medical history			
Age, y, median (quartile 1–quartile 3)	50 (46–57)	49 (37–55)	0.6
Sex (male), n (%)	28 (80)	37 (73)	0.7
No cardiovascular comorbidities, n (%)	28 (80)	43 (84)	0.9
Cardiac arrest characteristics			
Witnessed OHCA, n (%)	28 (80)	39 (76)	>0.9
Bystander CPR, n (%)	26 (74)	33 (65)	0.6
Shockable presenting rhythm, n (%)	25 (71)	37 (74)	>0.9
EMS response time, min, median (quartile 1–quartile 3)[†]	8.0 (5.0–10.0)	5.0 (4.0–7.2)	0.4
In-hospital characteristics			
Impella, n (%)	14 (40)	≤3*	**<0.001**
IABP, n (%)	0 (0)	≤3*	0.5
CAG, n (%)	27 (77)	38 (75)	>0.9
PCI, n (%)	18 (51)	21 (41)	0.6
Renal replacement therapy, n (%)	18 (51)	10 (20)	**0.01**
Hospitalization, d, median (quartile 1–quartile 3)	24 (18–44)	16 (11–25)	**0.01**
Outcomes			
1-y survival, n (%)	32 (91)	48 (94)	>0.9
RTW at 1-y follow-up, n (%)	12 (39)	25 (54)	0.5
RTW during follow-up, n (%)	18 (51)	43 (84)	**0.01**
Time to work, wk, median (quartile 1–quartile 3)	26 (16–50)	12 (4–28)	0.3
Sustainable RTW, n (%)	15 (83)	34 (85)	>0.9
Same business area, n (%)[‡]	8 (67)	20 (80)	0.7
Disability pension, n (%)	7 (20)	5 (10)	0.5
Home care, n (%)[§]	≤3*	4 (8)	>0.9
Nursing home, n (%)	0 (0)	≤3*	>0.9
Follow-up time, y, median (quartile 1–quartile 3)	2.2 (1.3, 4.9)	5.0 (2.5, 6.9)	**0.02**

CAG indicates coronary angiogram; CPR, cardiopulmonary resuscitation; ECPR extracorporeal cardiopulmonary resuscitation; EMS, emergency medical services; IABP, intra-aortic balloon pump; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; RTW, return to work; and sACLS standard advanced cardiac life support. Bold indicates significant *p*-values ($p<0.05$).

*Due to Statistics Denmark, regulations n<3 cannot be specified.

[†]Available only for OHCAs after 2015.

[‡]Comparison of business area before OHCA and 1 year after for patients with 1-year RTW.

[§]Only data from 2011 to 2019 available.

[‖]Adjusted *P* values calculated using Benjamini and Hochberg false discovery rate correction for multiple testing.

after OHCA.[7,15] To our knowledge, no previous studies have investigated RTW specifically in a refractory OHCA cohort.

More survivors managed with sACLS compared with survivors managed with ECPR returned to work during follow-up ($P<0.001$); however, median follow-up time was shorter in the ECPR group (2.2 years) compared with the sACLS group (5.0 years). The shorter follow-up is due to the gradual national introduction of

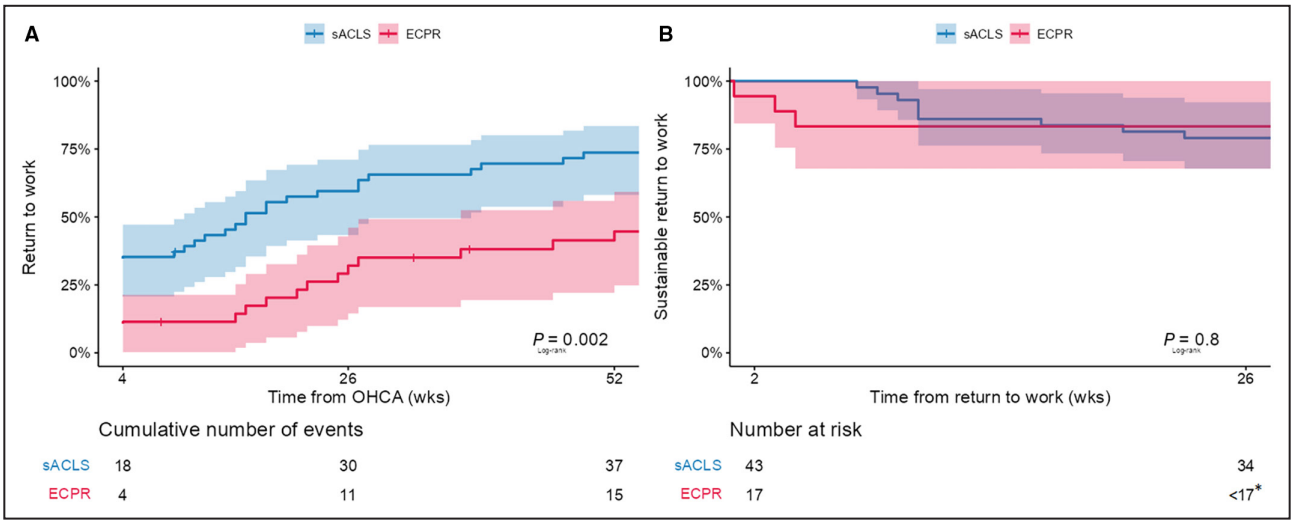

Figure 2. RTW and sustainable RTW after refractory OHCA.
Comparison of refractory OHCA managed with ECPR or sACLS. **A**, Cumulative incidence of RTW 1 year after OHCA for 30-day survivors. **B**, Probability of sustainable RTW the first 6 months after RTW. *Differences in n≤3 cannot be specified due to Statistics Denmark regulations. CPR indicates cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; RTW, return to work; and sACLS, standard advanced cardiovascular life support.

ECPR (2010–2017).[8] It is unknown whether low flow time is associated with RTW, as low flow time was not available in our registries. Moreover, it is difficult in registers to differentiate between patients managed with sACLS who did not receive ECPR due to ROSC shortly after hospital arrival and patients managed with sACLS where ECPR was withheld due to the sum of unfavorable OHCA circumstances. However, another study on the Danish ECPR cohort, focusing on the selection of patients and reasons for withholding ECPR, found that 5% of patients managed with sACLS did not receive ECPR due to ROSC at arrival to the catheterization laboratory or shortly after. Moreover, they found a shorter low flow time in patients managed with sACLS compared with patients managed with ECPR (70 versus 100 minutes), which supports that shorter low flow time may account for the higher RTW in survivors managed with sACLS compared with survivors managed with ECPR.[16] We did find hospitalization of ≥3 weeks negatively associated with RTW, indicating that longer hospitalization reflects larger functional loss and might reflect a combination of the severity of OHCA, in terms of prolonged full body ischemia, and the muscle wasting due to prolonged inactivity. Despite differences in RTW, we found no difference in income change between patients managed with ECPR and patients managed with sACLS. Also, we did not find any difference in the number of patients still affiliated with the same business area at 1 year follow-up as before the OHCA. Both factors indicate that the number of patients with significant job changes were similar between groups.

Irrespective of OHCA management, we found that >80% of patients returning to work achieved sustainable RTW. This is slightly higher than previously reported by Kragholm et al, who found that 75% of OHCA survivors with RTW achieved sustainable RTW. However, the difference may be due to Kragholm et al defining patients with short periods of sick leave as not achieving sustainable RTW.[7]

To our knowledge, the percentage of OHCA survivors granted disability pension has not been reported previously. We found that 20% of survivors managed

Table 3. Income Data

	ECPR		sACLS		
	No.	Median (quartile 1–quartile 3)	No.	Median (quartile 1–quartile 3)	*P* value
Overall	17	−17% (−33 to 4%)	37	−10% (−25 to −2%)	0.5
Returned to work	10	−11% (−36 to 4%)	31	−6% (−24 to 4%)	0.6
On social benefits	7	−17% (−28 to 0%)	6	−19% (−24 to −17%)	>0.9

Change in income (%) between the year before cardiac arrest and the year after for 1-year survivors. Available only for patients with cardiac arrest in the period 2011 to 2018. ECPR indicates extracorporeal cardiopulmonary resuscitation; and sACLS, standard advanced cardiac life support.

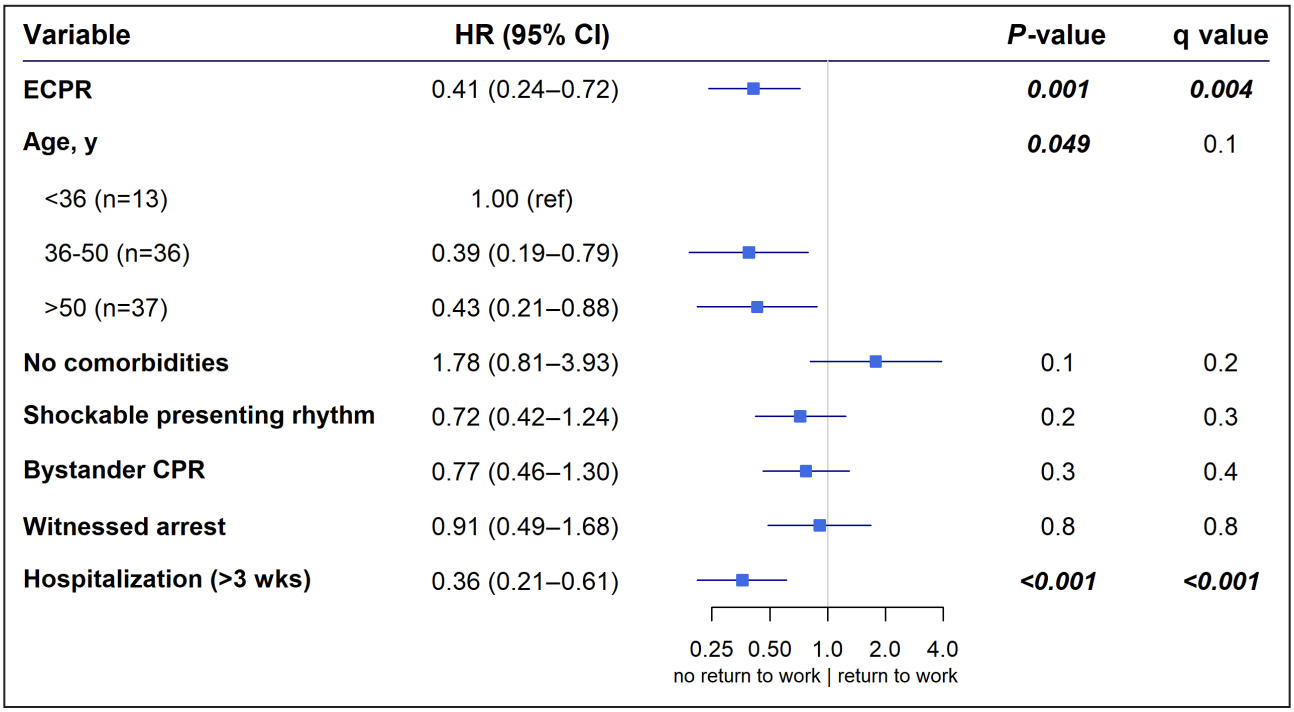

Figure 3. **Univariable Cox regression analyses of return to work in refractory out-of-hospital cardiac arrest patients.** Forest plot of factors potentially associated with return to work with HR and 95% CI. CPR indicates cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; and HR, hazard ratio. Q value indicates adjusted *P* value calculated using Benjamini and Hochberg false discovery rate correction for multiple testing.

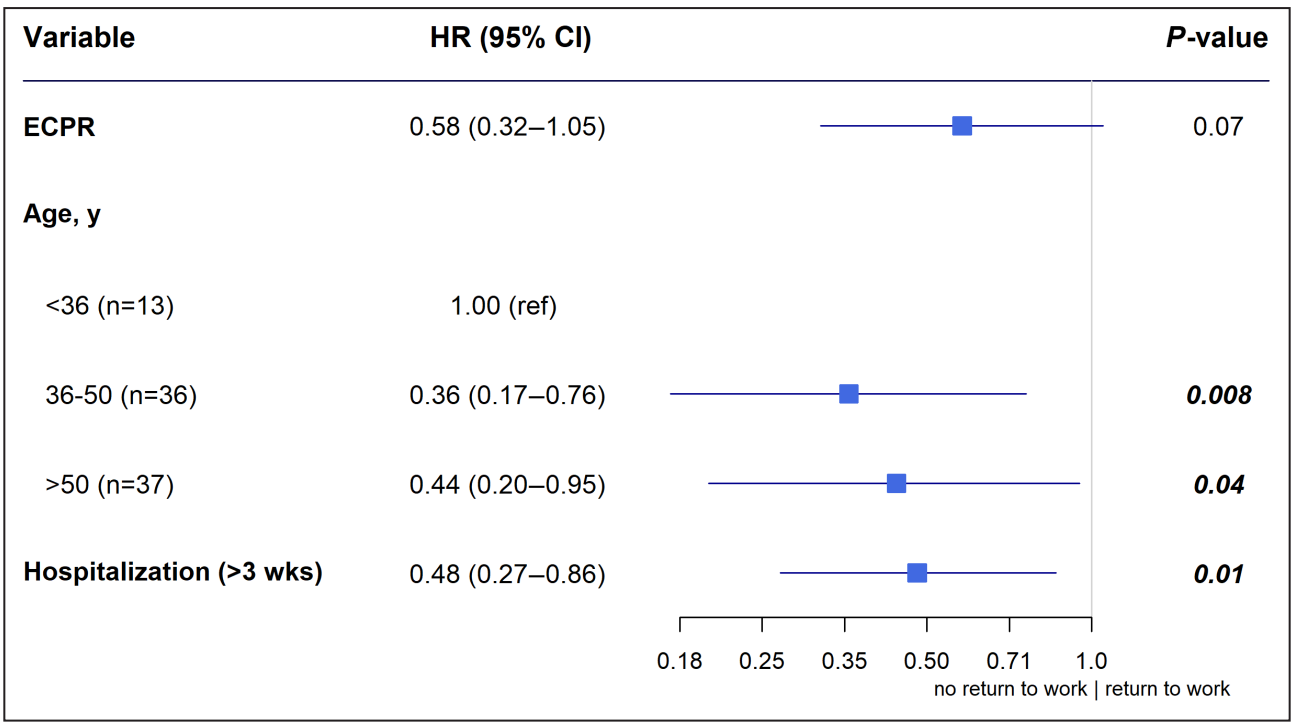

Figure 4. **Multivariable Cox regression analysis of return to work in refractory out-of-hospital cardiac arrest patients.** Forest plot of factors potentially associated with return to work with HR and 95% CI. ECPR indicates extracorporeal cardiopulmonary resuscitation; and HR, hazard ratio.

with ECPR and 10% of survivors managed with sACLS were granted disability pension during follow-up with no significant difference between groups. Disability pension may reflect a permanent unfavorable neurological outcome in OHCA survivors.

Our results show that about 50% of survivors managed with ECPR in our cohort returned to work, suggesting return to prearrest function, while 20% received disability pension, suggesting permanent limitations in function compared with prearrest function. Despite permanent limitations in 20% of survivors managed with ECPR, ≤3 survivors received home care, and none were admitted to a permanent nursing home facility. The functional status of patients managed with ECPR and patients managed with sACLS with no RTW yet without disability pension is not available. However, patients without RTW during the first year were on prolonged sick leave most of the year (mean 93% and 65% of the year for patients managed with ECPR and patients managed with sACLS, respectively). During the first year, survivors managed with sACLS were unemployed a mean of 23% of the year. Patients with neither RTW nor disability pension probably represent a group of patients with limitations in function that may still be reversible to some degree.

Two randomized studies have previously reported neurological outcome after ECPR. Both the ARREST (Advanced Reperfusion Strategies for Patients With Out-of-Hospital Cardiac Arrest and Refractory Ventricular Fibrillation) trial, where patients were randomized to early ECPR or sACLS, and the INCEPTION (Early Initiation of Extracorporeal Life Support in Refractory OHCA) trial, where patients were randomized to ECPR or sACLS, found that all survivors managed with ECPR had a favorable neurological status at 6 months after OHCA.[4,6] The studies measured neurological status using CPC and the modified Rankin Scale. Likewise, in a Danish cohort of patients with refractory OHCA of cardiovascular pathogenesis managed with ECPR, we previously found that 90% of survivors had a favorable neurological status (CPC 1 or 2) at hospital discharge.[17] When comparing previous reports of favorable neurological status measured as CPC and modified Rankin Scale with our results of functional status measured as RTW, it implies that neurological status as assessed by CPC and modified Rankin Scale may not fully reflect recovery of prearrest function.

Whether ECPR is superior to sACLS is still debatable. A meta-analysis by Scquizzato et al[18] suggests increased survival with favorable neurological outcome after refractory OHCA managed with ECPR compared with sACLS. The meta-analysis included 3 randomized studies investigating early ECPR for refractory OHCA and 1 randomized study investigating feasibility of expedited prehospital transportation to ECPR. The primary outcome of the feasibility study was transportation to an ECPR-capable facility within 30 minutes for individuals randomized to expedited transportation. No patients survived with a favorable neurological outcome, and the group concluded that most subjects did not meet eligibility criteria for ECPR.[19] Of the 3 randomized studies investigating early ECPR for refractory OHCA, the ARREST trial found ECPR superior to sACLS, while the INCEPTION trial and Prague study found ECPR nonsuperior to sACLS.[4–6] The conflicting results likely reflect trial design differences and low number of participants.

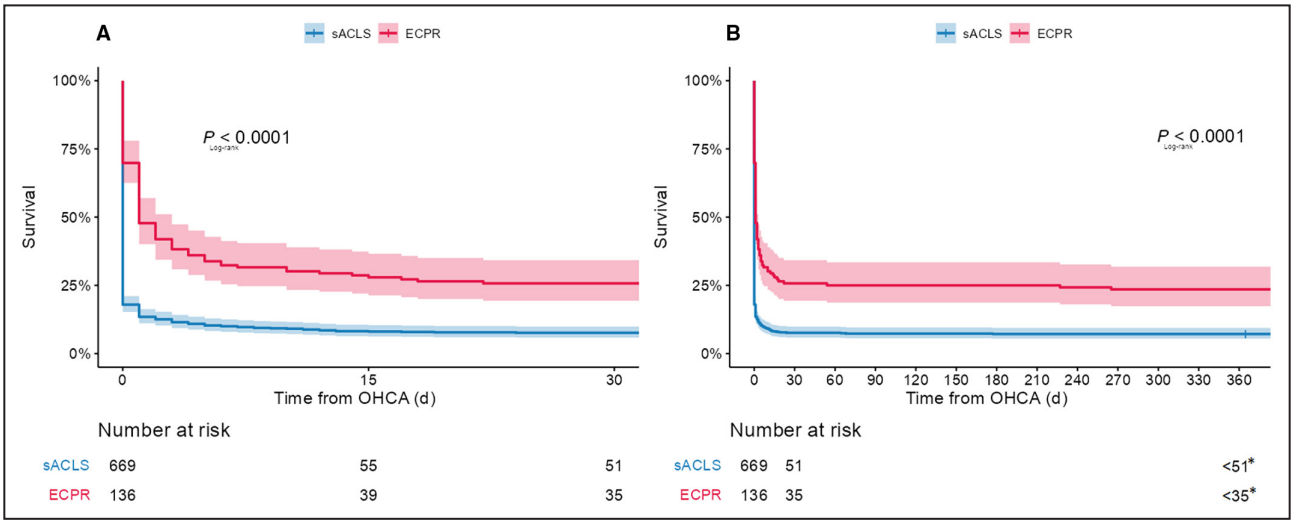

Figure 5. Survival after refractory OHCA.
Kaplan–Meier curves comparing survival between patients (aged <65 years and in employment before OHCA) managed with sACLS to patients managed with ECPR. **A**, Thirty-day survival. **B**, One-year survival. *Differences in n≤3 cannot be specified due to Statistics Denmark regulations. ECPR indicates extracorporeal cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; and sACLS, standard advanced cardiovascular life support.

While the effect of early ECPR may still be questioned, it is important to notice that in our ECPR program where ECPR is used as a last resort and median low flow time is well above 1 hour,[16] we still found that about 50% of survivors managed with ECPR had preserved prearrest function and returned to work after OHCA. ECPR was negatively associated with RTW in univariable analysis but not in multivariable analysis. This difference indicates that the lower RTW observed in survivors managed with ECPR was driven by the severity of OHCA (in terms of prolonged low flow time), reflected in the length of hospitalization, rather than the management with ECPR. Moreover, a recent qualitative follow-up study of survivors managed with ECPR found high quality of life and preserved cognitive function in long-term survivors managed with ECPR, suggesting that management with ECPR in selected refractory cases of OHCA is reasonable.[20] The importance of selection is highlighted by results of a study on cardiac arrest survivors that found considerably impaired quality of life, with higher age associated with worse outcome.[21] The contrary results likely reflect the strict selection process characterizing ECPR cohorts, which is even more pronounced in our study where only patients employed before the OHCA and aged <65 years were included. The strict selection occurring in our study is also reflected in the higher 30-day survival in patients managed with ECPR compared with patients managed with sACLS (24% versus 7%). We found a 1-year survival of >90% in 30-day survivors irrespective of management with ECPR or sACLS. This result is higher than previously reported in survivors managed with ECPR and in a meta-analysis of long-term survival after OHCA where 1-year survival in Europe was reported as 79%.[22,23] Our high 1-year survival may be explained by the patient selection for the current study (aged 18–65 years and employed before arrest). Interestingly, despite lower 1-year survival in patients discharged alive from the hospital, Alexy et al found a higher survival to discharge than in the current study.[23] This, again, may reflect differences in patient selection.

Strengths and Limitations

The strength of this study is the registry-based follow-up, which diminishes loss to follow-up. Moreover, the number of missing in most variables is limited (≤5% in all variables except EMS response time, where data are available only after 2015, and home care, where data are available only until 2019). The study is limited by the observational design, which means that results reflect associations and not causalities. Unfortunately, low flow time and arterial blood gases are not available in the Cardiac Arrest Registry. It would be interesting to investigate the effect of these parameters on RTW after OHCA in future studies. Changes in income were available only for OHCAs occurring before 2018 and the relatively low number of patients included in these analyses may influence the results. Patients with ongoing CPR at hospital arrival were categorized as refractory OHCA. We have no information on the underlying reasons for initiating or withholding ECPR. In Denmark, ECPR is used as a last resort management in refractory OHCA, and it can be speculated that patients managed with sACLS can be subcategorized into (1) cases with minimal survival chance where all treatment is withheld shortly after hospital arrival and (2) patients achieving ROSC shortly after hospital arrival before ECPR can be initiated. This assumption is supported by a previous Danish study that found the most frequent reasons for withholding ECPR to be long prehospital low flow time, metabolic derangement, and low end-tidal CO_2 and underlines the survival bias of the current study.[16] It should be noted that the outcomes of this study (survival excluded) only reflect the status of 30-day survivors, as immortal time bias otherwise would be an issue.

Due to the low number of patients available for RTW analyses (30-day survivors), only a limited number of statistical analyses could be performed and only a limited number of confounders could be included in the multivariable Cox regression analysis.

CONCLUSIONS

In a cohort of patients with refractory OHCA aged <65 years and in employment before OHCA, we found that despite lower return to work at any time during follow-up for 30-day survivors managed with ECPR compared with sACLS, about 50% of survivors managed with ECPR returned to work and no between-group difference was present at 1-year status. Additionally, >80% achieved sustainable RTW (>6 months) with no difference between the groups. In multivariable Cox analysis, younger age and shorter length of hospitalization were associated with RTW and thereby presumably return to pre-OHCA function in 30-day survivors while ECPR management was not associated with RTW.

ARTICLE INFORMATION

Received December 25, 2023; accepted February 19, 2024.

Affiliations

Department of Cardiology, Rigshospitalet, Copenhagen, Denmark (E.G., J.E.M., J.K., L.H., C.H., H.S.); Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark (K.K.); Department of Clinical Medicine, Aalborg University, Aalborg, Denmark (K.K.); Department of Cardiology, Odense University Hospital, Odense, Denmark (L.L., J.F.L., J.E.M.); Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark (S.R.M., C.J.T.); Department of Anaesthesiology, Aalborg University Hospital, Aalborg, Denmark (J.B.A., H.L.); Department of Clinical Medicine, Aarhus University,

Aarhus, Denmark (C.J.T.); Department of Clinical Medicine, University of Southern Denmark, Copenhagen, Denmark (J.F.L., J.E.M.); Department of Cardiothoracic Surgery, Rigshospitalet, Copenhagen, Denmark (M.S.); Department of Clinical Medicine, Copenhagen University, Copenhagen, Denmark (M.S., L.H., C.H.); Department of Cardiothoracic Anaesthesiology, Rigshospitalet, Copenhagen, Denmark (P.H.M.); Department of Cardiology, North Zealand Hospital, Hillerød, Denmark (C.T.); Department of Public Health, Copenhagen University, Copenhagen, Denmark (C.T.); and Department of Cardiology (H.S.), Zealand University Hospital Roskilde, Roskilde, Denmark.

Sources of Funding

This project was supported by the common foundation of Rigshospitalet and Odense University Hospital (Grant Number 83-A3759) and by the Beckett Foundation (Grant Number 23–2-10 125).

Disclosures

Dr Møller reports personal fees and grants from Orion Pharma, Novartis, Astra Zeneca, Abbott, and Abiomed and served on the scientific advisory board for Boehringer Ingelheim outside the submitted work. Dr Hassager reports grants from the Lundbeck Foundation and speaker's honoraria from Abiomed, outside the submitted work. Dr Kjaergaard reports nonfinancial participation in the advisory board for the CoCa (Calcium for Out-of-Hospital Cardiac Arrest) trial and is supported by the Novo Nordisk Foundation outside the submitted work. Dr Terkelsen is supported by an unrestricted research grant from the Danish Heart Foundation. Dr Søholm is supported by the Novo Nordisk Foundation outside the submitted work. The remaining authors have no disclosures to report.

Supplemental Material

Figures S1–S2

REFERENCES

1. Kiguchi T, Okubo M, Nishiyama C, Maconochie I, Ong MEH, Kern KB, Wyckoff MH, McNally B, Christensen EF, Tjelmeland I, et al. Out-of-hospital cardiac arrest across the world: first report from the international liaison committee on resuscitation (ILCOR). *Resuscitation*. 2020;152:39–49. doi: 10.1016/j.resuscitation.2020.02.044
2. Gregers E, Kjærgaard J, Lippert F, Thomsen JH, Køber L, Wanscher M, Hassager C, Søholm H. Refractory out-of-hospital cardiac arrest with ongoing cardiopulmonary resuscitation at hospital arrival - survival and neurological outcome without extracorporeal cardiopulmonary resuscitation. *Crit Care*. 2018;22:242. doi: 10.1186/s13054-018-2176-9
3. Richardson ASC, Tonna JE, Nanjayya V, Nixon P, Abrams DC, Raman L, Bernard S, Finney SJ, Grunau B, Youngquist ST, et al. Extracorporeal cardiopulmonary resuscitation in adults. Interim guideline consensus statement from the extracorporeal life support organization. *ASAIO J*. 2021;67:221–228. doi: 10.1097/MAT.0000000000001344
4. Yannopoulos D, Bartos J, Raveendran G, Walser E, Connett J, Murray TA, Collins G, Zhang L, Kalra R, Kosmopoulos M, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial. *Lancet*. 2020;396:1807–1816. doi: 10.1016/S0140-6736(20)32338-2
5. Belohlavek J, Smalcova J, Rob D, Franek O, Smid O, Pokorna M, Horák J, Mrazek V, Kovarnik T, Zemanek D, et al. Prague OHCA study group. Effect of intra-arrest transport, extracorporeal cardiopulmonary resuscitation, and immediate invasive assessment and treatment on functional neurologic outcome in refractory out-of-hospital cardiac arrest: a randomized clinical trial. *JAMA*. 2022;327:737–747. doi: 10.1001/jama.2022.1025
6. Suverein MM, Delnoij TSR, Lorusso R, Brandon Bravo Bruinsma GJ, Otterspoor L, Elzo Kraemer CV, Vlaar APJ, van der Heijden JJ, Scholten E, den Uil C, et al. Early extracorporeal CPR for refractory out-of-hospital cardiac arrest. *N Engl J Med*. 2023;388:299–309. doi: 10.1056/NEJMoa2204511
7. Kragholm K, Wissenberg M, Mortensen RN, Fonager K, Jensen SE, Rajan S, Lippert FK, Christensen EF, Hansen PA, Lang-Jensen T, et al. Return to work in out-of-hospital cardiac arrest survivors: a nationwide register-based follow-up study. *Circulation*. 2015;131:1682–1690. doi: 10.1161/CIRCULATIONAHA.114.011366
8. Mørk SR, Stengaard C, Linde L, Møller JE, Jensen LO, Schmidt H, Riber LP, Andreasen JB, Thomassen SA, Laugesen H, et al. Mechanical circulatory support for refractory out-of-hospital cardiac arrest: a Danish nationwide multicenter study. *Crit Care*. 2021;25:174. doi: 10.1186/s13054-021-03606-5
9. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39:30–33. doi: 10.1177/1403494811401482
10. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open*. 2016;6:e012832. doi: 10.1136/bmjopen-2016-012832
11. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;39:38–41. doi: 10.1177/1403494810394717
12. Hjollund NH, Larsen FB, Andersen JH. Register-based follow-up of social benefits and other transfer payments: accuracy and degree of completeness in a Danish interdepartmental administrative database compared with a population-based survey. *Scand J Public Health*. 2007;35:497–502. doi: 10.1080/14034940701271882
13. Helweg-Larsen K. The Danish register of causes of death. *Scand J Public Health*. 2011;39:26–29. doi: 10.1177/1403494811399958
14. Schmidt M, Pedersen L, Sørensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol*. 2014;29:541–549. doi: 10.1007/s10654-014-9930-3
15. Kearney J, Dyson K, Andrew E, Bernard S, Smith K. Factors associated with return to work among survivors of out-of-hospital cardiac arrest. *Resuscitation*. 2020;146:203–212. doi: 10.1016/j.resuscitation.2019.09.006
16. Linde L, Mørk SR, Gregers E, Andreasen JB, Lassen JF, Ravn HB, Schmidt H, Riber LP, Thomassen SA, Laugesen H, et al. Selection of patients for mechanical circulatory support for refractory out-of-hospital cardiac arrest. *Heart*. 2023;109:216–222. doi: 10.1136/heartjnl-2022-321405
17. Gregers E, Mørk SR, Linde L, Andreasen JB, Smerup M, Kjærgaard J, Møller-Sørensen PH, Holmvang L, Christensen S, Terkelsen CJ, et al. Extracorporeal cardiopulmonary resuscitation: a national study on the association between favourable neurological status and biomarkers of hypoperfusion, inflammation, and organ injury. *Eur Heart J Acute Cardiovasc Care*. 2022;11:808–817. doi: 10.1093/ehjacc/zuac135
18. Scquizzato T, Bonaccorso A, Swol J, Gamberini L, Scandroglio AM, Landoni G, Zangrillo A. Refractory out-of-hospital cardiac arrest and extracorporeal cardiopulmonary resuscitation: a meta-analysis of randomized trials. *Artif Organs*. 2023;47:806–816. doi: 10.1111/aor.14516
19. Hsu CH, Meurer WJ, Domeier R, Fowler J, Whitmore SP, Bassin BS, Gunnerson KJ, Haft JW, Lynch WR, Nallamothu BK, et al. Extracorporeal cardiopulmonary resuscitation for refractory out-of-hospital cardiac arrest (EROCA): results of a randomized feasibility trial of expedited out-of-hospital transport. *Ann Emerg Med*. 2021;78:92–101. doi: 10.1016/j.annemergmed.2020.11.011
20. Rasalingam Mørk S, Qvist Kristensen L, Christensen S, Tang M, Juhl Terkelsen C, Eiskjær H. Long-term survival, functional capacity and quality of life after refractory out-of-hospital cardiac arrest treated with mechanical circulatory support. *Resusc Plus*. 2023;14:100387. doi: 10.1016/j.resplu.2023.100387
21. Schnaubelt S, Mayr FB, Losert H, Domanovits H, Sulzgruber P, Holzer M, Sterz F, Uray T. Very long-term survivors of in-hospital and out-of-hospital cardiac arrest show considerable impairment of daily life. *Resuscitation*. 2022;173:192–200. doi: 10.1016/j.resuscitation.2022.01.023
22. Chin YH, Yaow CYL, Teoh SE, Foo MZQ, Luo N, Graves N, Ong MEH, Ho AFW. Long-term outcomes after out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Resuscitation*. 2022;171:15–29. doi: 10.1016/j.resuscitation.2021.12.026
23. Alexy T, Kalra R, Kosmopoulos M, Bartos JA, Elliott A, Gutierrez Bernal A, Martin CM, John R, Shaffer AW, Raveendran G, et al. Initial hospital length of stay and long-term survival of patients successfully resuscitated using extracorporeal cardiopulmonary resuscitation for refractory out-of-hospital cardiac arrest. *Eur Heart J Acute Cardiovasc Care*. 2023;12:175–183. doi: 10.1093/ehjacc/zuac141