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Clinical Paper

Manual vs. integrated automatic load-distributing band CPR with equal survival after out of hospital cardiac arrest. The randomized CIRC trial☆,☆☆

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ABSTRACT

Objective: To compare integrated automated load distributing band CPR (iA-CPR) with high-quality manual CPR (M-CPR) to determine equivalence, superiority, or inferiority in survival to hospital discharge.
Methods: Between March 5, 2009 and January 11, 2011 a randomized, unblinded, controlled group sequential trial of adult out-of-hospital cardiac arrests of presumed cardiac origin was conducted at three US and two European sites. After EMS providers initiated manual compressions patients were randomized to receive either iA-CPR or M-CPR. Patient follow-up was until all patients were discharged alive or died. The primary outcome, survival to hospital discharge, was analyzed adjusting for covariates, (age, witnessed arrest, initial cardiac rhythm, enrollment site) and interim analyses. CPR quality and protocol adherence were monitored (CPR fraction) electronically throughout the trial.
Results: Of 4753 randomized patients, 522 (11.0%) met post enrollment exclusion criteria. Therefore, 2099 (49.6%) received iA-CPR and 2132 (50.4%) M-CPR. Sustained ROSC (emergency department admittance), 24 h survival and hospital discharge (unknown for 12 cases) for iA-CPR compared to M-CPR were 600 (28.6%) vs. 689 (32.3%), 456 (21.8%) vs. 532 (25.0%), 196 (9.4%) vs. 233 (11.0%) patients, respectively. The adjusted odds ratio of survival to hospital discharge for iA-CPR compared to M-CPR, was 1.06 (95% CI 0.83–1.37), meeting the criteria for equivalence. The 20 min CPR fraction was 80.4% for iA-CPR and 80.2% for M-CPR.
Conclusion: Compared to high-quality M-CPR, iA-CPR resulted in statistically equivalent survival to hospital discharge.

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1. Introduction

High-quality chest compressions (i.e., correct depth, rate, full release and high chest compression fraction) are emphasized by The International Liaison Committee on Resuscitation (ILCOR).[1] Mechanical chest compression devices were developed to assist rescuers in giving consistent high-quality compressions.[2–4] A mechanical chest compression device that uses a load distributing band (LDB) has been shown in animal and human studies to improve hemodynamic parameters over manual CPR (M-CPR).[5–8] Studies comparing LDB devices with M-CPR in the setting of out-of-hospital cardiac arrests (OHCA) have produced conflicting results.[9–12] Retrospective studies found improved outcomes,[10–12] but one randomized controlled trial showed worse cerebral performance at hospital discharge in the LDB arm, and consequently the trial was terminated early.[9]

It is important to determine the role of mechanical CPR in prehospital resuscitation, as it could be a powerful adjunct in treating OHCA. It is unlikely that a CPR device will ever fully replace the need for manual compressions. However, if device compressions can be shown to be as safe and effective as manual compressions, then it could be used to assist providers when performing CPR. Therefore, there was a need for another randomized clinical trial comparing manual and integrated mechanical CPR, where a patient receives manual compressions while the mechanical device is deployed.

The randomized Circulation Improving Resuscitation Care (CIRC) Trial objective was to compare automated LDB-CPR integrated with manual CPR (iA-CPR) to high quality manual CPR (M-CPR), to determine equivalence, superiority, or inferiority in survival to hospital discharge after OHCA.

2. Methods

The CIRC methods and design including the statistical analysis plan have been previously published.[13] CIRC was a randomized, controlled group sequential trial of adult OHCA of presumed cardiac origin conducted under exception from informed consent for emergency research and approved by the Institutional Review Boards (three US sites: Fox Valley Region, WI; Hillsborough County, FL; Houston, TX) or Ethics committee (two European sites: Vienna, Austria; Nijmegen, The Netherlands).[13] Sites represented a variety of emergency medical service (EMS) system types in order to enhance external validity. The agencies served between 135,100 and 2,144,500 citizens with response areas between 68 and 888 square miles.

After 4 h of initial training emphasizing the importance of providing high quality CPR, providers were allowed to enroll patients into the trial.[13–15] CPR was performed according to the 2005 Guidelines.[14,15] Respiration, rhythm, and pulse were evaluated every 3 min.

An independent data safety monitoring board (DSMB) monitored the trial, determined whether the pre-defined stopping criteria were met, and reviewed all adverse events. Adverse events were reported based on clinical examination and in some cases autopsies.

2.1. Study design

CIRC consisted of three phases: (1) *the in-field phase*: where all OHCA patients were treated with the LDB device, allowing providers to gain experience with the LDB device; (2) *the run-in phase*: where providers randomized eligible patients and study data were collected to assess protocol compliance and to address the Hawthorne effect of participating in a trial; and (3) *the statistical inclusion phase*: where eligible patients were randomized and all data was collected and used in the statistical analysis. Sites transitioned from one phase to another when they met pre-specified protocol compliance criteria, which included maintaining minimum treatment intervals (e.g., defibrillator electrodes attached within 3 min from power on). This review was not done by study arm and did not consider patient outcome.[13] For more details see web appendix.

2.2. Randomization and masking

EMS providers carried the device to every likely OHCA. Sealed randomization cards were opened after an indication for CPR was found and resuscitation with manual compressions was initiated (web appendix Fig. 1, CPR algorithm). Patients were allocated to the two arms in a 1:1 ratio using randomized permuted blocks of 24 stratified by study site. Patients and their care providers could not be blinded to study arm assignment.

2.3. Inclusion and exclusion

Study inclusion criteria were age $\geq$18 years and OHCA of presumed cardiac origin. Patients were excluded if, presumed to be pregnant, had a Do Not Resuscitate (DNR) order, were presumed too big for the CPR device (estimated weight greater than 300 pounds or chest circumference greater than 51 in.), were a prisoner or ward of the state, had received mechanical chest compressions prior to randomization, or if the randomizing EMS unit arrived more than 16 min after emergency call.[16] In some cases, inclusion and exclusion criteria were determined after patient enrollment by the site investigator as EMS providers were advised not to delay treatment to determine study eligibility. Exclusion for patient size was not permitted after enrollment. See web appendix for description and analysis of post enrollment exclusions.

2.4. Equipment

Each EMS vehicle was equipped with the LDB device (AutoPulse; ZOLL Medical Corporation, Chelmsford, MA), a defibrillator that could be a LIFEPAK® 12 or 15 (Physio-Control, Redmond, WA) or E Series® (ZOLL Medical, Chelmsford, MA), or an Automated External defibrillator (AED) that could be a LIFEPAK® 500 (Physio-Control, Redmond, WA) or AED Pro® (ZOLL Medical, Chelmsford, MA). All devices used internal memory to automatically save treatment information.

2.5. Data collection

Data were collected from EMS and hospital patient care documentation. Electronic defibrillator records [accelerometer or transthoracic impedance (TTI)] were independently analyzed and interpreted by reviewers who were blinded to patient outcome, but not study arm (identifiable TTI waveforms created by the study device). For ambiguous data two reviewers analyzed the data and reached a consensus. Data were managed by a Data Coordinating Center (DCC) at the Medical College of Wisconsin (Milwaukee, WI). Throughout the trial only the statistician [AW] and DCC staff had access to the study database.

2.6. Outcome measures

The primary outcome measure was survival to hospital discharge. Secondary outcome measures were: sustained ROSC, defined as being admitted to the hospital with perfusing blood pressure, survival to 24 h, and modified Rankin Scale (mRS) score (range 0–5, good outcome $\leq$ 3) prior to discharge.[17] It was the research coordinator and site investigator who made the evaluation. Study

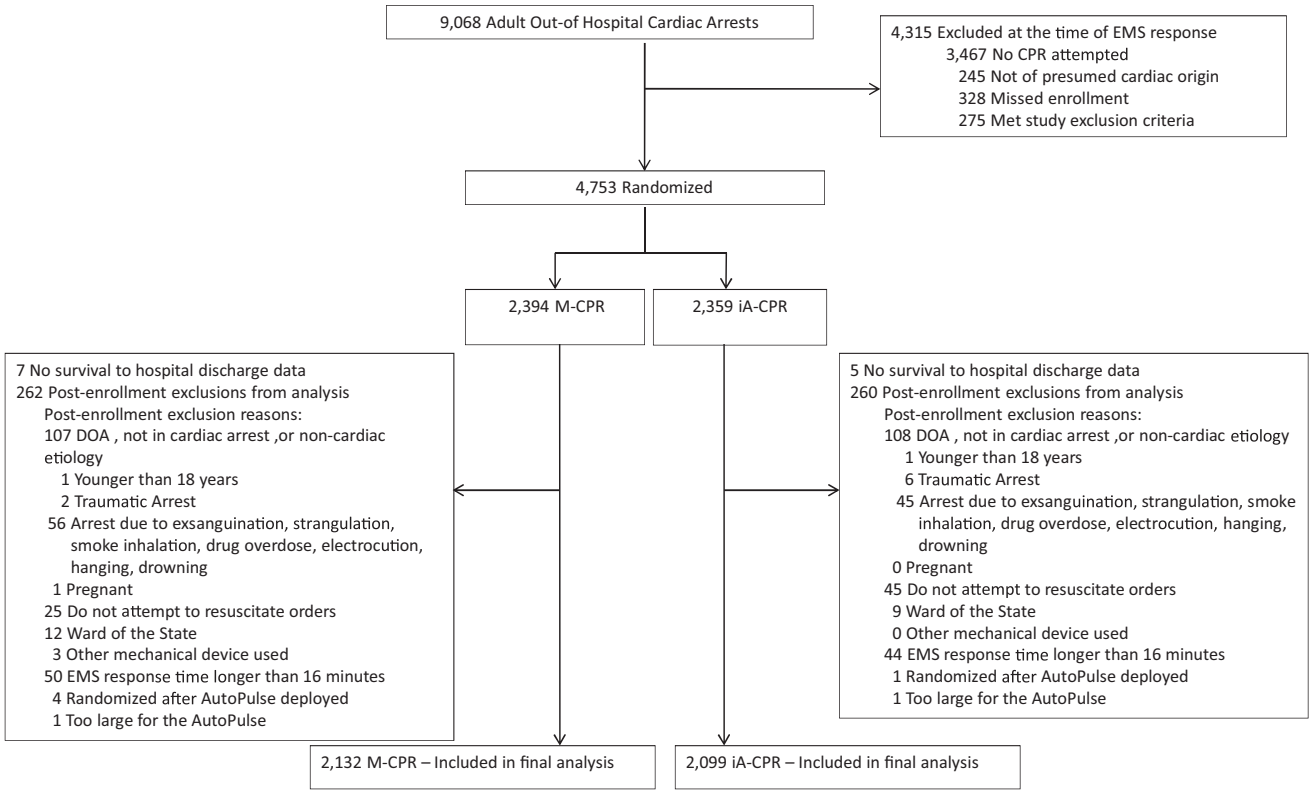

Fig. 1. Distribution of potential study patients. *DOA – Dead on Arrival (*Note*: this occurred when a first responder enrolled the patient and a later arriving unit determined the patient was not viable).

personnel only collected the mRS data on survivors who had consented to continued participation in the trial based on IRB and our interpretation of the Exception from Informed Consent (EFIC) regulation issued by the Food and Drug Administration (FDA). Study personnel who collected the outcome data were not always blinded to study arm.

2.7. Statistical analysis

Statistical analyses of the primary outcome were conducted according to the pre-specified analysis plan.[13] A modified intention-to-treat analysis was conducted, which excluded patients who were retrospectively found to meet exclusion criteria.[13] Primary outcome was analyzed using the Group Sequential Double Triangular (GSDT) Test using the software package PEST 4 (University of Reading, Reading, United Kingdom).[18] CIRC was designed to have a two-sided significance level of 5% and a power of 97.5% to detect a log odds ratio (OR) of 0.37 (i.e., an OR of 1.44). The anticipated survival to hospital discharge in the M-CPR arm was 9%. In the absence of superiority or inferiority, equivalence would be declared if the 95% CI of the log-OR lay fully between −0.37 and 0.37 (i.e., OR between 0.69 and 1.44). The maximum sample size was set at 7390 patients, but the trial could be stopped earlier if pre-defined stopping rules were met. Based on data from the run-in phase variables associated with survival to hospital discharge were selected as covariates: patient age categorized as 18–59, 60–74, and 75 years and over, witnessed arrest, initial cardiac rhythm, and enrollment site.

The first interim analysis was conducted after 748 patients were enrolled. Additional analyses were conducted every two months until a stopping boundary was crossed. Interim and final analyses were based on score statistics for the log-OR adjusting for the pre-identified covariates and multiple interim analyses. The final analysis was an 'overrunning' analysis, to provide a *p*-value, median unbiased estimate, and 95% confidence interval for the log-OR, adjusting for the interim analyses and the four covariates (web appendix Fig. 2).[19,20] One sided *p*-values for testing non-inferiority of each intervention arm were calculated. For statistical analyses details, see methods paper[13] and web appendix.

3. Results

During the run-in phase data was collected for 621 patients. The first site began enrollment into the statistical inclusion phase on March 5, 2009. The equivalence stopping boundary was crossed at the 8th interim analysis and the last patient was enrolled on January 11, 2011. During the statistical inclusion phase, 9068 cardiac arrests occurred in the study communities, but 3987 did not meet the study inclusion criteria and 328 patients were missed for enrollment (Fig. 1). Post enrollment, 522 patients were excluded from the study for meeting protocol defined exclusion criteria, but not based on device failure. Table 1 describes the patients included in the trial. The treatment groups are similar with respect to most factors, although there is a higher occurrence of initial VF/VT in the M-CPR group compared to the iA-CPR group (24 vs. 21%; OR 1.18, 95% CI 1.02–1.36, $p = 0.02$).

3.1. Outcome

Of the 4231 patients enrolled in the trial, survival to hospital discharge was not available for 12. Table 2 compares survival rates by demographics and covariates and demonstrates that there are no important differences between treatment groups. Overall, M-CPR demonstrated a numeric increase in survival to hospital discharged compared to iA-CPR (233/2132, 11.0% vs. 196/2099, 9.4%). Modified intention-to-treat analyses are presented in Table 3. After

Table 1
Comparison of the study population by treatment arm.

	M-CPR (n = 2132)	iA-CPR (n = 2099)
Age (mean (standard deviation))	65.6 SD 16.0	65.7 SD 16.4
18–59 years	734 (34%)	706 (34%)
60–74 years	689 (32%)	671 (32%)
75+ years	709 (33%)	722 (34%)
Male gender	1315 (61%)	1295 (61%)
Location of the OHCA		
Public	283 (13%)	293 (14%)
Non-public	1849 (87%)	1806 (86%)
Witnessed		
Bystander witnessed	785 (37%)	785 (37%)
EMS witnessed	233 (11%)	218 (10%)
Not witnessed	1021 (48%)	994 (47%)
Unknown if witnessed	93 (4%)	102 (5%)
Bystander CPR		
Bystander CPR	1035 (49%)	1024 (47%)
No bystander CPR	1014 (48%)	991 (49%)
Unknown if bystander CPR	83 (4%)	84 (4%)
Initial rhythm		
VF/VT	519 (24%)	451 (21%)
Asystole/PEA	1516 (71%)	1572 (75%)
Unknown	97 (5%)	76 (4%)
EMS shocks		
Patients that received at least 1 shock	860 (40%)	798 (38%)
Number of shocks per shocked patient (median, 25th–75th percentile)	3 (1–5)	2 (1–4)
Initial rhythm VF/VT average time from defibrillator on to first shock[a] (min) (median, 25th–75th percentile)	3.5 SD 4.0 (3, 1–4) (n = 510)	4.6 SD 4.8 (4, 2–5) (n = 438)
Initial rhythm VF/VT average time from EMS arrival to first shock[a] (min) (median, 25th–75th percentile)	6.7 SD 6.2 (6, 3–8)	7.5 SD 6.0 (6, 4–9)
Average time from defibrillator on to first recorded compression (s) (median, 25th–75th percentile)	60 SD 137 (33, 6–60)	65 SD 124 (37, 9–67)
Average response interval (min)	6.6 SD 3.0	6.7 SD 2.9
0–5	866 (41%)	811 (39%)
6–10	1017 (48%)	1080 (51%)
11–15	212 (10%)	174 (8%)
>15	18 (1%)	16 (1%)
Unknown	19 (1%)	18 (1%)
First method of prehospital vascular access		
Venous	1547 (73%)	1478 (70%)
Intraosseous	523 (25%)	564 (27%)
None	62 (3%)	57 (3%)
Prehospital drug administration		
Amiodarone	486 (23%)	398 (19%)
Lidocaine	116 (5%)	102 (5%)
Atropine	1670 (78%)	1706 (81%)
Bicarbonate	338 (16%)	292 (14%)
Epinephrine	1946 (91%)	1958 (93%)
Vasopressin	1162 (55%)	1190 (57%)
Hypothermia treatment		
Prehospital hypothermia treatment[b]	311 (15%)	279 (13%)
ED hypothermia treatment[c]	234/689 (34%)	205/600 (34%)
Hospital hypothermia treatment[c]	255/689 (37%)	206/600 (34%)
Percutaneous transluminal coronary angioplasty (PTCA)/percutaneous coronary intervention (PCI)	120/689 (17%)	87/600 (15%)
Average time from arrival to termination/transport (min)[a]	36.1 SD 14.1	37.3 SD 14.3
CPR fraction[d]		
at 5 min	79.0% SD 12.3%	74.7% SD 12.7%
at 10 min	79.7% SD 10.1%	78.5% SD 9.4%
at 20 min	80.2% SD 9.1%	80.4% SD 8.3%
Average compressions in a minute (first 10 min)[d] (median, 25th–75th percentile)	89.2 SD 17.4[f] (89.9, 79.3–100.3)	66.3 SD 10.7[e] (65.9, 61.3–70.2)
Average ventilations in a minute (first 10 min)[d] (median, 25th–75th percentile)	8.8 SD 4.7 (8, 6.2–10.8)	6.8 SD 3.4 (6.3, 4.9–9.8)
Terminated in the field	530 (25%)	509 (24%)

SD represents standard deviation.

[a] For time analyses we excluded any time difference that was negative or greater than 60 min.

[b] Denominator is all patients included in the statistical inclusion phase.

[c] Denominator is the number of patients with ROSC.

[d] Prehospital electronic defibrillator data (ECG and TTI and accelerometer) available for 96% of all patients.

[e] The LDB CPR device was programmed to provide compressions at a rate of 80 per minute.

[f] EMS providers were trained to provide compressions at a rate of 100 per minute.

Table 2
Evaluation of potential covariates for survival to hospital discharge by treatment arms.

	M-CPR *n*	Survived to hospital discharge *n* (%, 95% CI)	iA-CPR *n*	Survived to hospital discharge *n* (%, 95% CI)	Total *n*	Survived to hospital discharge *n* (%, 95% CI)
Analysis population	2125	233 (11.0, 9.7–12.4)	2094	196 (9.4, 8.2–10.7)	4219	429 (10.2, 9.3–11.1)
Age[a]						
18–59 years	734	92 (12.5, 10.3–15.1)	703	88 (12.5, 10.3–15.2)	1437	180 (12.5, 10.9–14.3)
60–74 years	686	91 (13.3, 10.9–16.0)	670	65 (9.7, 7.7–12.2)	1356	156 (11.5, 9.9–13.3)
75+ years	705	50 (7.1, 5.4–9.2)	721	43 (6.0, 4.5–7.9)	1426	93 (6.5, 5.4–7.9)
Gender						
Male	1309	152 (11.6, 10.0–13.5)	1293	123 (9.5, 8.0–11.2)	2602	275 (10.6, 9.4–11.8)
Female	816	81 (9.9, 8.1–12.2)	801	73 (9.1, 7.3–11.3)	1617	154 (9.5, 8.2–11.1)
Initial rhythm[a]						
VF/VT	515	126 (24.5, 20.9–28.4)	449	118 (26.3, 22.4–30.5)	964	244 (25.3, 22.7–28.2)
A/PEA	1513	89 (5.9, 4.8–7.2)	1571	69 (4.4, 3.5–5.5)	3084	158 (5.1, 4.4–6.0)
Unknown	97	18 (18.6, 12.0–27.5)	74	9 (12.2, 6.5–21.8)	171	27 (15.8, 11.1–22.0)
Witnessed[a]						
Bystander witnessed	781	134 (17.2, 14.7–20.0)	783	122 (15.6, 13.2–18.3)	1564	256 (16.4, 14.6–18.3)
EMS witnessed	232	42 (18.1, 13.7–23.6)	216	32 (14.8, 10.7–20.2)	448	74 (16.5, 13.4–20.2)
Not witnessed	1019	50 (4.9, 3.7–6.4)	993	36 (3.6, 2.6–5.0)	2012	86 (4.3, 3.5–5.3)
Unknown if witnessed	93	7 (7.5, 3.6–15.0)	102	6 (5.9, 2.7–12.5)	195	13 (6.7, 3.9–11.1)
Bystander CPR						
Bystander CPR	1031	112 (10.9, 9.1–12.9)	1022	99 (9.7, 8.0–11.7)	2053	211 (10.3, 9.0–11.7)
No Bystander CPR	1011	113 (11.2, 9.4–13.3)	988	93 (9.4, 7.7–11.4)	1999	206 (10.3, 9.0–11.7)
Unknown if bystander CPR	83	8 (9.6, 4.9–18.1)	84	4 (4.8, 1.8–12.0)	167	12 (7.2, 4.1–12.2)
Response interval						
0–5 min	863	105 (12.2,10.1–14.5)	807	83 (10.3, 8.4–12.6)	1670	188 (11.3, 9.8–12.9)
6–10 min	1015	102 (10.0, 8.3–12.1)	1077	89 (8.3, 6.8–10.1)	2092	191 (9.1, 8.0–10.4)
11–15 min	210	21 (10.0, 6.6–14.9)	173	15 (8.7, 5.3–13.9)	383	36 (9.4, 6.9–12.8)
>15 min	18	2 (11.1, 2.8–35.2)	16	2 (12.5, 3.1–38.6)	34	4 (11.8, 4.5–27.5)
Unknown	19	3 (15.8, 5.2–39.2)	21	7 (33.3, 16.8–55.3)	40	10 (25.0, 14.0–40.5)
Site[a,b]						
Site A[c]		(7.4)		(11.9)		(9.4)
Site B[d]		(12.8)		(11.6)		(12.2)
Site C[c]		(17.5)		(17.7)		(17.6)
Site D[d]		(8.7)		(5.1)		(6.9)
Site E[d]		(11.0)		(9.4)		(10.2)

[a] Included as covariates in the statistical model.
[b] Sample size not provided to prevent identification of site.
[c] Range is provided as: total sample size < 500.
[d] Range is provided as: total sample size > 500.

adjusting for covariates and multiple interim looks, the OR of survival to hospital discharge for iA-CPR compared to M-CPR was 1.06 (95% CI 0.83–1.37). This 95% CI was fully within the pre-defined equivalence region. A sensitivity analysis of all randomized patients including all post enrollment exclusions and counting patients who were lost to follow-up as dead, showed no change in the adjusted OR (1.06 95% CI: 0.83–1.36; $n = 4753$). See also web appendix. Only covariate adjusted analyses of ROSC and 24 h survival have been undertaken, because of the lack of appropriate methodology for adjusting secondary endpoints for interim analyses. These show similar results to those from the covariate-only adjusted analysis of survival to hospital discharge.

3.2. Neurological outcome

mRS scores were available for 310 of 429 patients who survived to hospital discharge (iA-CPR arm 70%, M-CPR arm 74%). The primary reason for not obtaining mRS was because the survivors were discharged before consent could be obtained. The difference in the proportion of patients discharged with a mRS score of 3 or less between iA-CPR and M-CPR was not statistically significant (adjusted OR 0.80, 95% CI 0.47–1.37) (Table 3). Among the survivors in the iA-CPR arm compared to the M-CPR arm, 42% (82/196) vs. 41% (96/233) were discharged home, 10% (20/196) vs. 10% (24/233) to a rehabilitation center, 9% (17/196) vs. 19% (45/233) to a nursing

Table 3
Comparison of outcome by treatment arm.

Outcomes	M-CPR ($n = 2132$)	iA-CPR ($n = 2099$)	Covariate adjusted odds ratio (95% CI)	Covariate and interim analyses adjusted odds ratio (95% CI)[b]
Survival to Hospital Discharge	233 (11.0%) (7 cases unknown)	196 (9.4%) (5 cases unknown)	0.89 (0.72–1.10)	1.06 (0.83–1.37)[a]
Survival to 24 h	532 (25.0%) v	456 (21.8%) (10 cases unknown)	0.86 (0.74–0.998)[b]	
Sustained ROSC	689 (32.3%)	600 (28.6%)	0.84 (0.73–0.96)[b]	
Discharge mRS	($n = 233$)	($n = 196$)		
Score of 0–3	112 (48.1%)	87 (44.4%)	0.80 (0.47–1.37)[b]	
Score of 4–5	61 (26.2%)	50 (25.5%)		
Unknown score	60 (25.8%)	59 (30.1%)		

[a] Adjusted for covariates and interim analyses.
[b] Secondary outcomes can only be adjusted for the covariates, not the interim analyses.

Table 4
Injuries sustained by patients during the trial.

Injury[a]	M-CPR Arm $n=2132$	iA-CPR Arm $n=2099$
Number of patients with a reported injury	225 (11%)	242 (12%)
Injuries reported		
Flail chest[b]	1	0
Hemothorax	1	1
Large vessel injury[b]	0	0
Liver injury	0	1
Mediastinal injuries	1	1
Myocardial laceration[b]	1	0
Pneumothorax	20	33
Pulmonary edema	176	159
Rib Fractures	31	69
Spine fracture	2	4
Spleen injury	0	0
Sternum fracture	4	1
Subcutaneous emphysema	6	21
Tympanic membrane rupture	0	0

[a] Listed injuries are not mutually exclusive (one patient can have multiple injuries) and neither diagnostic exams nor autopsy were required as part of the protocol. Injuries were identified using clinical record review.
[b] Required to be submitted to the medical monitor for review.

home or assisted living, 6% (12/196) vs. 3% (6/233) transferred to another acute care facility, and 33% (65/196) vs. 27% (62/233) were discharged to an unknown location, respectively.

3.3. Injuries

The distribution of patients with injuries based on clinical record review was not significantly different between groups [iA-CPR 242 (12%), M-CPR 225 (11%), OR 1.10, 95% CI 0.91–1.34, $p=0.31$] (Table 4). However, some injuries were more prevalent in one group than the other. For example, there were more rib fractures, subcutaneous emphysema reported in the iA-CPR group compared to the M-CPR group (Table 4). During the inclusion phase, the medical monitor received 12 reports (0.5%) of unexpected serious events (1 M-CPR, 11 iA-CPR). All reported injuries were consistent with previously reported studies of CPR.[21,22] The DSMB reviewed all medical adverse event reports and determined that no new risks were identified and no safety concerns with the trial.

4. Discussion

The CIRC study demonstrated that iA-CPR is equivalent to high-quality M-CPR for survival to hospital discharge from OHCA of presumed cardiac origin. Neurologic outcome did not differ between strategies. There were slight differences between the unadjusted and adjusted OR for survival to hospital discharge. Adjustment for the interim analyses changed the OR from a small negative effect to a small positive effect. The reason for this is that the study was stopped when the iA-CPR arm had just reached a low point relative to M-CPR. Not performing the adjustment is like allowing the leading sport team to select when to stop a game: they will select a point in time when they are winning. An adjustment is needed to reflect the true effect. Further, although the OR point estimate changes from slightly negative to slightly positive, the actual difference between the adjusted and unadjusted ORs is small, and the 95% confidence intervals from both overlap considerably, contain unity and lie within the equivalence range. Because of the likely correlation between ROSC, survival to 24 h and survival to hospital discharge, it might be expected that an appropriate adjustment to the former two outcomes for the interim analyses might lead to similar conclusions to that for the latter.

Our findings differ from a previous trial that was terminated early when worse neurologic outcome (M-CPR 7.5% vs. LDB-CPR 3.1%), was found in the device arm.[9] CIRC found no statistical difference in neurologic outcome. However, comparison of these trials is difficult since there were differences in both their study designs and their CPR fractions (manual arm 60% and 59% in the device arm[9] compared to 79% and 75% in CIRC for the first 5 min, respectively). The CIRC study focused on ensuring high-quality chest compressions through a 4-h training program and continuous monitoring and reporting of compliance with both M-CPR and device deployment/operational goals. More and more services emphasize the importance of ongoing performance monitoring for out-of-hospital CPR quality and we recommend that EMS agencies should monitor their performance, whether they use a device or not. The CIRC findings are similar to those of the LUCAS in Cardiac Arrest (LINC) trial, which reported a neutral result when comparing manual and LUCAS device CPR.[23] The LUCAS device does not use LDB technology which may limit the comparability between the two trials. In addition, there were several differences in study design including the inclusion and exclusion criteria. However, both studies have established a platform for clinicians to decide about the possible benefit/harm of a mechanical chest compression device for CPR in clinical practice.

While many previous studies have been unable to monitor CPR quality, CIRC analyzed CPR fraction for 96% of the enrolled cases. The high rate of provider feedback likely contributed to the high CPR quality observed in CIRC. Our CPR fraction is higher than has been reported in previous trials and may impact generalizability.[9,22,24] Previous cardiac arrest trials report CPR fractions below 80% with some reporting fractions as low as 48%.[2,9,22–27] A notable exception is the LINC trial, which reported mechanical CPR fraction of 84% in the mechanical and 78% in the manual group based on 10% of their sample.[23] It is difficult to determine what the results of the CIRC trial would have been if the CPR fraction had been lower and perhaps closer to what would be seen under real-world conditions. Further, generalizing CIRC findings to other types of mechanical CPR devices may not be possible because compressions created by a LDB device employ a mechanism for creating blood flow that differs from sternal compression devices.[7]

Neurologic outcomes were missing for 28% of the cases in the CIRC trial (iA-CPR 30%, M-CPR 26%), which is similar (14–25%) to what has been reported in previous trials.[28] In CIRC it was primarily due to patients being discharged (alive) prior to consenting to continued participation in the trial. It is important to note that not obtaining consent was likely not related to the patient's neurologic condition, but the ability of the research coordinator to arrive at the hospital and locate the patient before they were discharged alive. Therefore, it was unlikely to have introduced any bias into our results since missing consent occurred nearly equally in both groups.

No previously published studies that utilized an LDB device identified any safety concerns related to the device.[9,11] There was a low rate of serious and unexpected adverse events reported (12 of 4231), but they did not occur equally in both arms. The incidence of CPR related injuries identified during the trial were similar between the two groups. However, in the iA-CPR group there were more rib fractures and subcutaneous emphysema. Interpretation of this difference is hampered by the fact that in CIRC the iA-CPR group received both manual and mechanical chest compressions, making it difficult to determine the source of the injury. Further, the data on injuries was only captured if it was documented in the medical record; therefore, this data was not systematically collected and may suffer from bias. A recently published autopsy study from one of the CIRC sites illustrated that injury rates are similar between M-CPR and LDB CPR, but they result in different injury patterns.[29] The LINC study reported similar rates of serious adverse events (LUCAS

0.54% vs. Manual 0.23%) compared to our reported events (iA-CPR 0.52% vs. M-CPR 0.05%).[23]

Demonstrating that iA-CPR is clinically similar to high quality M-CPR is important because there are situations where the use of iA-CPR may improve efficiency or provider safety. It is unlikely that device CPR will ever fully replace the need for manual compressions. However, if device compressions can be shown to be as safe and effective as manual compressions, then it could be used to assist providers when performing CPR. Although not evaluated during the CIRC trial, the LDB device may improve efficiency by eliminating the effects of provider fatigue and allowing compressions to be provided in spaces and situations where a human could not provide effective compressions. But this must be evaluated operationally against the potential challenges of deploying the device in such situations. Previous studies have described the use of the LDB device during percutaneous coronary intervention[30] and helicopter transport.[31] We may speculate that use of iA-CPR during transport may facilitate effective compressions and improve provider safety.[32] Further, there is potentially a benefit of iA-CPR from a human resource efficiency perspective, as a crew member who would otherwise be dedicated to perform compressions would be available for other tasks.

The statistical design of the CIRC trial is unfamiliar to many in this field. It is therefore tempting to focus on the raw percentages for survival and neurologic outcomes (unadjusted data). This might be interpreted to imply that since there was a non-significant positive effect of high quality M-CPR compared to iA-CPR, regular use of a mechanical device during resuscitation is not indicated. However, substituting the raw numbers for the adjusted values is problematic. The confidence interval even for the unadjusted survival to discharge and neurologic status includes unity, indicating that there was no statistically significant difference between the interventions. Further, any attempt to read meaning into the raw outcome data should be accompanied by a look at confounding or explanatory data. For example, there was a noticeable difference in the rate of VF/VT between the study arms, which has a direct influence on survival and therefore required adjusting for it.[33–35] We believe this difference was likely due to chance.

The CIRC trial had several limitations. First, due to the nature of the device it was impossible to blind the patients, their providers, or the outcome assessors. Secondly, it was impossible to standardize hospital based post resuscitation care and we were not able to control hospital treatment. Patients were frequently discharged alive before consent to continue participating could be obtained, limiting the amount of mRS data we were allowed to collect. Thirdly, post enrollment exclusions were done. Fourthly, we collected survival to hospital discharge data but did not obtain longer-term outcomes. Finally, we were unable to review compression depth as an indicator of compression quality.

In conclusion, compared to high-quality M-CPR, iA-CPR resulted in statistically equivalent survival to hospital discharge after out of hospital cardiac arrest of presumed cardiac origin.

Authors' contribution

LW oversaw development of the protocol and was responsible for the overall conduct of the trial. All authors contributed to protocol development. FS, RM, MB, PG, ML, DT, MW, DP, and CS oversaw data collection at each of the trial sites. JO oversaw the analysis of all electronic ECG files. AW, an academic statistician at Lancaster University, was responsible for the group sequential design and for conducting the primary and secondary statistical analyses. LW drafted the manuscript and all co-authors reviewed and edited the final manuscript before submission. EBL had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest statement

UH is an employee of ZOLL which manufactures and sells the LDB device (AutoPulse). All other authors' institutions received funding from ZOLL for their participation in the trial. The authors have no other relevant financial conflicts of interest to report.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2014.03.005.

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