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Editorial

Top cardiac arrest randomised trials of 2023

Cardiac arrest and resuscitation science is advancing rapidly, with the last decade witnessing a surge in the publication of randomised clinical trials (RCT) that can inform guidelines and clinical practice. Several RCTs focusing on temperature control,[1–3] post-resuscitation physiological targets,[4–6] and treatment of refractory cardiac arrest[7,8] were published in 2021 and in 2022, and mostly of out-of-hospital cardiac arrest (OHCA). This trend of high-quality RCTs continued in 2023.

In this article, we summarise the key findings from four important multicentre RCTs published in 2023: Early Initiation of Extracorporeal Life Support in Refractory OHCA (INCEPTION) trial,[9] Targeted Therapeutic Mild Hypercapnia after Resuscitated Cardiac Arrest (TAME),[10] A Randomized tRial of Expedited transfer to a cardiac arrest center for non-ST elevation OHCA (ARREST),[11] and STEroid for Out-of-Hospital Cardiac Arrest (STEROHCA) trial[12] (Table 1, Fig. 1). Articles were selected based on their large sample size, multicentre design, assessment of significant clinical outcomes, and publication on high-impact medical Journals.

INCEPTION trial

The INCEPTION trial, performed in 10 out of the total 16 cardiothoracic surgery centres in The Netherlands, was the first multicentre RCT of extracorporeal cardiopulmonary resuscitation (ECPR).[9] Notably, it is the only ECPR RCT to date that has completed the planned enrolment. ECPR was compared with conventional cardiopulmonary resuscitation (CPR) in 134 adults with refractory OHCA and an initial shockable rhythm. This RCT found a similar rate of survival with favourable neurological outcome at 30 days for ECPR and conventional CPR (20% versus 16%, p = 0.52).[9] Subsequent Bayesian analyses estimated a 42% probability of a minimal clinically important difference (5% absolute risk reduction),[13] increasing to 61% in a per-protocol analysis that excluded patients not meeting inclusion criteria, amongst which time to cannulation exceeded 60 minutes, and with return of spontaneous circulation (ROSC) before hospital arrival.[14]

ECPR benefit was less evident in INCEPTION than in previous single-centre RCTs,[7,15] Importantly, INCEPTION was a pragmatic study, where clinical practice was not standardized across participating centres whose experience and case volume varied considerably.[16] These factors were particularly evident for delays in establishing ECPR: the time between hospital arrival and cannulation initiation, and between cannulation initiation and extracorporeal flow were 16 and 20 minutes,[9] considerably longer than previous trials, potentially diminishing any beneficial effect of ECPR. Overall, the INCEPTION trial highlights the challenges of implementing this complex intervention that may be effective at a single high performing centre across a whole system.

The International Liaison Committee on Resuscitation (ILCOR) suggests that ECPR may be considered as a rescue therapy for selected OHCA patients when conventional CPR is failing to restore spontaneous circulation in settings in which this can be implemented (weak recommendation, low-certainty evidence).[17] Meta-analyses of RCTs only, including the INCEPTION trial, are in favour of ECPR.[18] However, the heterogeneity in design of these studies and their limitations warrants caution in their interpretation.[19]

TAME trial

Post-resuscitation guidelines recommend normocapnia for comatose adults after OHCA.[20] However, higher partial pressure of arterial carbon dioxide ($PaCO_2$), a major regulator of cerebrovascular tone, may potentially improve cerebral perfusion by increasing cerebral blood flow. Mild hypercapnia after cardiac arrest increased cerebral oxygen saturation, as shown with near-infrared spectroscopy[21], and was associated with better outcomes in two observational studies.[22,23] In a small phase II RCT, mild hypercapnia reduced release of neuron-specific enolase (NSE), a biomarker of neuronal injury.[24] Accordingly, the TAME trial, a multi-centre RCT enrolling 1700 comatose adults resuscitated after OHCA and admitted to 63 intensive care units in 17 countries, tested if mild hypercapnia ($PaCO_2$, 50 to 55 mm Hg [6.7 to 7.3 kPa]) would improve outcomes as compared with normocapnia ($PaCO_2$, 35 to 45 mm Hg [4.7 to 6 kPa]).[10] The TAME trial complements other RCTs investigating physiological targets after resuscitation, such as temperature,[1–3] oxygenation, and blood pressure[4–6] published in the last three years.

At 6 months, targeted mild hypercapnia for 24 hours beginning at randomisation did not improve survival with favourable neurological outcome (43.5% vs 44.6%, relative risk (RR), 0.98; 95% confidence interval (CI), 0.87–1.11; P = 0.76) or mortality (48.2% vs 45.9%, RR, 1.05; 95% CI, 0.94–1.16). Potential adverse effects of mild hypercapnia include the worsening of cerebral oedema and elevation of intracranial pressure;[25] however, data from this study suggest that clinically relevant elevations in intracranial pressure were unlikely. Moreover, mild hypercapnia may have adverse haemodynamic effects, but a sub-study of the TAME trial found no evidence of increased pulmonary vascular resistance or worsened right ventricular function compared with normocapnia.[26] Preliminary data also

Table 1 – Summary of important multicentre randomised trials of cardiac arrest and cardiopulmonary resuscitation published in 2023.

Study	Setting	Population	Intervention	Control	Primary outcome	Secondary outcomes (main)
Suverein 2023 (INCEPTION)[9]	10 cardiosurgical centres in The Netherlands	Witnessed OHCA patients (18–70 years) with an initial shockable rhythm refractory to 15 minutes of advanced life support	Extracorporeal CPR at hospital arrival	Conventional CPR	Survival with a favourable neurological outcome at 30 days 20% vs 16% (OR 1.4; 95% CI, 0.5–3.5)	Survival with favourable neurological outcome at 6 months 20% vs 16% (OR 1.3; 95% CI, 0.5–3.3)
Eastwood 2023 (TAME)[10]	63 intensive care units in 17 countries	Resuscitated comatose OHCA patients (≥18 years) of presumed cardiac or unknown cause	Mild hypercapnia ($PaCO_2$ 50–55 mmHg [6.7 to 7.3 kPa])	Normocapnia ($PaCO_2$ 35–45 mmHg [4.7 to 6 kPa])	Survival with a favourable neurological outcome at 6 months 44% vs 45% (RR 0.98; 95% CI, 0.87–1.11)	Mortality at 6 months 48% vs 46% (RR 1.05; 95% CI, 0.94–1.16) Poor functional outcome at 6 months 53% vs 51% (RR 1.05; 95% CI, 0.95–1.15)
Patterson 2023 (ARREST)[11]	35 acute hospitals, 7 of them cardiac arrest centres, in the Greater London area, UK	Resuscitated OHCA patients (≥18 years) of presumed cardiac cause without ST-segment elevation myocardial infarction	Transport to a cardiac arrest centre	Transport to the closest emergency department	All-cause mortality at 30 days 63% vs 63% (RR 1.00; 95% CI, 0.90–1.11)	Mortality at 3 months 65% vs 64% (RR 1.02; 95% CI, 0.92–1.12) Favourable neurological outcome at 3 months 30% vs 31% (RR 1.01; 95% CI, 0.92–1.11)
Obling 2023 (STEROHCA)[12]	2 cardiac arrest centres in Denmark	Resuscitated comatose OHCA patients (≥18 years) of presumed cardiac cause	Bolus intravenous injection of 250 mg methylprednisolone (2 × 125 mg/2 mL) over 5 min	Placebo (4 mL isotonic NaCl) over 5 min	Daily measurements of IL-6 and NSE from admission until 72 hours - Lower IL-6 values at 24 and 48 hours - No difference in NSE values	Mortality at 180 days 25% vs 36% (HR 0.65; 95% CI, 0.35–1.2)

Abbreviations: OHCA, out-of-hospital cardiac arrest; CPR, cardiopulmonary resuscitation; HR, hazard ratio; IL-6, interleukin-6; NSE, neuron specific enolase; OR, odds ratio; RR, risk ratio.

Fig. 1 – Infographic of four important randomised clinical trials published in 2023 in the fields of cardiac arrest and cardiopulmonary resuscitation. Abbreviations: OHCA, out-of-hospital cardiac arrest; CPR, cardiopulmonary resuscitation; RCT, randomised clinical trial; $PaCO_2$, partial pressure of carbon dioxide, STEMI, ST-elevation myocardial infarction; IL-6, interleukin-6; NSE, neuron-specific enolase.

indicate that in patients with acute myocardial infarction, mild hypercapnia may protect against myocardial ischemia–reperfusion injury, as it was associated with lower peak and serial high-sensitivity troponin T release following revascularisation.[27]

ARREST trial

The ARREST trial is the first and only multicentre RCT that tested if the direct transport of resuscitated OHCA patients without ST elevation after ROSC to a cardiac arrest centre improves outcomes compared with transportation to the geographically closest emergency department.[11] Among the 862 patients randomised in London, UK, 61% had a cardiac cause and, of them, 40% exhibited coronary artery disease and 20% an acute coronary syndrome. The cause of arrest remained unidentified in 19% of patients. The median time from cardiac arrest to hospital arrival was 84 min (IQR 68–104) in the cardiac arrest centre group and 77 min (IQR 63–96) in the standard care group. While there was no difference in pre-randomisation characteristics, more patients in the cardiac arrest centre group were identified as being in cardiogenic shock, admitted to intensive care unit, received organ support (haemodynamic, ventilatory, and renal), and received coronary angiography, which was also more rapid. This observation may be attributable to higher access to diagnostics and interventions or different clinical practice in cardiac arrest centres.

At 30 days, all-cause mortality in the cardiac arrest centre group and the standard care group was the same (63% vs 63%, RR for survival 1.00 [95% CI, 0.90–1.11], p = 0.96). Also at 3 months, there was no difference in all-cause mortality (65% vs 64%, RR 1.02 [95% CI, 0.92–1.12]) and survival with favourable neurological outcome (30% vs 31%, [RR 1.01; 95% CI, 0.92–1.11]).[11] A possible effect on survival from transport to a cardiac arrest centre was found in patients younger than 57 years and those aged 57–71 years, respectively, experiencing higher and lower survival rates compared with standard care.[11] The trial was powered to detect a 10% absolute risk reduction in mortality with transport to a cardiac arrest centre, which may have been much greater than the potential true effect size. Before the results of this RCT, a meta-analysis with mostly

observational data found that treatment in a cardiac arrest centre was associated with improved survival with favourable neurological outcomes.[28] However, the results of the ARREST trial are consistent with recent RCTs testing advanced post-resuscitation interventions such as immediate coronary angiography in patients without ST elevation.[29–31] The ARREST study also highlights the challenge for on scene clinicians in deciding which patients with a presumed primary cardiac arrest will benefit from cardiac arrest centre care.

STEROHCA trial

The STEROHCA trial, a Danish phase II RCT, tested if the administration of high-dose methylprednisolone to adult OHCA patients with ROSC could reduce inflammatory injury, potentially preventing secondary neurological injury and worsening of post-cardiac arrest syndrome.[29] The primary outcome was the plasma values of IL-6 and NSE from admission until 72 hours.

Among the 158 patients randomised, the early prehospital administration of a 250 mg intravenous bolus of methylprednisolone reduced inflammation compared with placebo. The median time to randomisation was 20 minutes from ROSC. Although baseline IL-6 values were similar between groups, the intervention group exhibited a significant reduction at 24 hours (2.1 pg/mL [95% CI, 1.3–3.2] vs 29.8 pg/mL [95% CI, 18.9–46.8], $p < 0.0001$) and at 48 hours (5.7 pg/mL [95% CI, 3.8–8.4] vs 10.1 pg/mL [95% CI, 6.7–15.1], $p = 0.04$). No difference was observed at 72 hours. Similarly, a significant treatment-by-time interaction for high-sensitive C-reactive protein was found. The observed mitigation of inflammation did not translate into improved blood values of brain injury biomarkers such as NSE and neurofilament light chain. Importantly, the mean NSE values in the study population were low and close to those predicting neurological recovery,[32] suggesting that the degree of brain injury in these patients was lower than in other studies on post-resuscitation care. These results align with those of the 2021 IMICA trial, which showed a reduction in high-sensitive C-reactive protein values but no improvement of neurological outcome after administration of the IL-6 inhibitor tocilizumab.[33]

Although STEROHCA was not powered for mortality, there were more survivors in the intervention group at six months (75% vs 64%; unadjusted hazard ratio 0.65 [95% CI, 0.35–1.2], $p = 0.17$; adjusted hazard ratio 0.35 [95% CI, 0.18–0.67], $p = 0.002$). Importantly, the injection of high-dose methylprednisolone was deemed safe, as demonstrated by a similar incidence of adverse events between groups. Two prior RCTs of cardiac arrest patients who received glucocorticoids along with vasopressin have reported a higher rate of survival and neurological outcome[34,35], and one trial an increased incidence of ROSC.[36] The STEROHCA should help inform a larger multicentre trial of steroids after cardiac arrest.

CRediT authorship contribution statement

Tommaso Scquizzato: Writing – review & editing, Writing – original draft, Conceptualization. **Claudio Sandroni:** Writing – review & editing, Writing – original draft, Conceptualization. **Jasmeet Soar:** Writing – review & editing, Writing – original draft, Conceptualization. **Jerry P. Nolan:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: TS is the Social Media Editor of Resuscitation, CS is a member of the Editorial Board of Resuscitation, JS is an Editor of Resuscitation, and JPN is the Editor-In-Chief of Resuscitation.

REFERENCES

1. Dankiewicz J, Cronberg T, Lilja G, et al. Hypothermia versus normothermia after out-of-hospital cardiac arrest. N Engl J Med 2021;384:2283–94.
2. Wolfrum S, Roedl K, Hanebutte A, et al. Temperature control after in-hospital cardiac arrest: A randomized clinical trial. Circulation 2022;146:1357–66.
3. Le May M, Osborne C, Russo J, et al. Effect of moderate vs mild therapeutic hypothermia on mortality and neurologic outcomes in comatose survivors of out-of-hospital cardiac arrest: The CAPITAL CHILL randomized clinical trial. JAMA 2021;326:1494–503.
4. Schmidt H, Kjaergaard J, Hassager C, et al. Oxygen targets in comatose survivors of cardiac arrest. N Engl J Med 2022;387:1467–76.
5. Kjaergaard J, Møller JE, Schmidt H, et al. Blood-pressure targets in comatose survivors of cardiac arrest. N Engl J Med 2022;387:1456–66.
6. Bernard SA, Bray JE, Smith K, et al. Effect of lower vs higher oxygen saturation targets on survival to hospital discharge among patients resuscitated after out-of-hospital cardiac arrest: The EXACT randomized clinical trial: The EXACT randomized clinical trial. JAMA 2022;328:1818–26.
7. Belohlavek J, Smalcova J, Rob D, et al. 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: A randomized clinical trial. JAMA 2022;327:737–47.
8. Cheskes S, Verbeek PR, Drennan IR, et al. Defibrillation strategies for refractory ventricular fibrillation. N Engl J Med 2022;387:1947–56.
9. Suverein MM, Delnoij TSR, Lorusso R, et al. Early extracorporeal CPR for refractory out-of-hospital cardiac arrest. N Engl J Med 2023;388:299–309.
10. Eastwood G, Nichol AD, Hodgson C, et al. Mild hypercapnia or normocapnia after out-of-hospital cardiac arrest. N Engl J Med 2023;389:45–57.
11. Patterson T, Perkins GD, Perkins A, et al. Expedited transfer to a cardiac arrest centre for non-ST-elevation out-of-hospital cardiac arrest (ARREST): a UK prospective, multicentre, parallel, randomised clinical trial. Lancet 2023;402:1329–37.
12. Obling LER, Beske RP, Meyer MAS, et al. Prehospital high-dose methylprednisolone in resuscitated out-of-hospital cardiac arrest patients (STEROHCA): a randomized clinical trial. Intensive Care Med 2023. https://doi.org/10.1007/s00134-023-07247-w.
13. Heuts S, van de Koolwijk AF, Gabrio A, et al. A Bayesian re-analysis of the INCEPTION-trial. Eur Heart J Acute Cardiovasc Care 2023. https://doi.org/10.1093/ehjacc/zuad130.
14. Ubben JFH, Suverein MM, Delnoij TSR, et al. Early extracorporeal CPR for refractory out-of-hospital cardiac arrest - A pre-planned per-protocol analysis of the INCEPTION-trial. Resuscitation 2023 110033.
15. Yannopoulos D, Bartos J, Raveendran G, 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;396:1807–16.
16. Ubben JFH, Heuts S, Delnoij TSR, et al. Extracorporeal cardiopulmonary resuscitation for refractory OHCA: lessons from three randomized controlled trials-the trialists' view. Eur Heart J Acute Cardiovasc Care 2023;12:540–7.
17. Berg KM, Bray JE, Ng K-C, et al. international consensus on cardiopulmonary resuscitation and emergency cardiovascular care Science With Treatment Recommendations: Summary from the basic life support; Advanced life support; Pediatric life support; Neonatal life support; Education, implementation, and teams. And first aid task forces. Resuscitation 2023;2023 109992.
18. Scquizzato T, Bonaccorso A, Swol J, et al. Refractory out-of-hospital cardiac arrest and extracorporeal cardiopulmonary resuscitation: A meta-analysis of randomized trials. Artif Organs 2023;47:806–16.
19. Cheema HA, Shafiee A, Jafarabady K, et al. Extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest: A meta-analysis of randomized controlled trials. Pacing Clin Electrophysiol 2023;46:1246–50.
20. Nolan JP, Sandroni C, Böttiger BW, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines 2021: Post-resuscitation care. Resuscitation 2021;161:220–69.
21. Eastwood GM, Tanaka A, Bellomo R. Cerebral oxygenation in mechanically ventilated early cardiac arrest survivors: The impact of hypercapnia. Resuscitation 2016;102:11–6.
22. Schneider AG, Eastwood GM, Bellomo R, et al. Arterial carbon dioxide tension and outcome in patients admitted to the intensive care unit after cardiac arrest. Resuscitation 2013;84:927–34.
23. Vaahersalo J, Bendel S, Reinikainen M, et al. Arterial blood gas tensions after resuscitation from out-of-hospital cardiac arrest: associations with long-term neurologic outcome. Crit Care Med 2014;42:1463–70.
24. Eastwood GM, Schneider AG, Suzuki S, et al. Targeted therapeutic mild hypercapnia after cardiac arrest: A phase II multi-centre randomised controlled trial (the CCC trial). Resuscitation 2016;104:83–90.
25. Perkins GD, Callaway CW, Haywood K, et al. Brain injury after cardiac arrest. Lancet 2021;398:1269–78.
26. Melberg MB, Flaa A, Andersen GØ, et al. Cardiovascular changes induced by targeted mild hypercapnia after out of hospital cardiac arrest. A sub-study of the TAME cardiac arrest trial. Resuscitation 2023 109970.
27. Melberg M, Flaa A, Andersen GØ, et al. 460 Targeted therapeutic mild hypercapnia after acute myocardial infarction and out-of-hospital cardiac arrest may have cardioprotective effects. A sub-study of the TAME cardiac arrest trial. Resuscitation 2023;192:S7.
28. Yeung J, Matsuyama T, Bray J, Reynolds J, Skrifvars MB. Does care at a cardiac arrest centre improve outcome after out-of-hospital cardiac arrest? - A systematic review. Resuscitation 2019;137:102–15.
29. Lemkes JS, Janssens GN, van der Hoeven NW, et al. Coronary angiography after cardiac arrest without ST-segment elevation. N Engl J Med 2019;380:1397–407.
30. Hauw-Berlemont C, Lamhaut L, Diehl J-L, et al. Emergency vs Delayed Coronary Angiogram in survivors of out-of-Hospital Cardiac Arrest: Results of the randomized, multicentric EMERGE trial. JAMA Cardiol 2022;7:700–7.
31. Desch S, Freund A, Akin I, et al. Angiography after out-of-hospital cardiac arrest without ST-segment elevation. N Engl J Med 2021;385:2544–53.
32. Sandroni C, D'Arrigo S, Cacciola S, et al. Prediction of good neurological outcome in comatose survivors of cardiac arrest: a systematic review. Intensive Care Med 2022;48:389–413.
33. Meyer MAS, Wiberg S, Grand J, et al. Treatment effects of interleukin-6 receptor antibodies for modulating the systemic inflammatory response after out-of-hospital cardiac arrest (the IMICA trial): A double-blinded, placebo-controlled, single-center, randomized, clinical trial: A double-blinded, placebo-controlled, single-center, randomized, clinical trial. Circulation 2021;143:1841–51.
34. Mentzelopoulos SD, Zakynthinos SG, Tzoufi M, et al. Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. Arch Intern Med 2009;169:15–24.
35. Mentzelopoulos SD, Malachias S, Chamos C, et al. Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest: a randomized clinical trial. JAMA 2013;310:270–9.
36. Andersen LW, Isbye D, Kjærgaard J, et al. Effect of vasopressin and methylprednisolone vs placebo on return of spontaneous circulation in patients with in-hospital cardiac arrest: A randomized clinical trial: A randomized clinical trial. JAMA 2021;326:1586–94.

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