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Review

Strategies to improve out-of-hospital cardiac arrest outcomes in the pre-hospital environment – Part B: non-pharmaceutical strategies

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Abstract

Introduction
Out-of-hospital cardiac arrest (OHCA) historically has low survival rates. Higher rates of survival have recently developed in some small geographical areas, which pre-empted an increase in the volume of research in this field. The aim of this paper is to consolidate the findings of the strategies that do not focus on drugs.

Methods
This is a systematic search and review, rather than a systematic review. A search of four databases (MEDLINE, CINAHL, Informit, Scopus) was undertaken in February 2017. Papers published between 2007 and 2017 containing strategies that may be used by paramedics when resuscitating adult patients in OHCA from presumed cardiac aetiology were identified.

Results
Twenty-eight studies were included in the review, comprising six separate strategies. This manuscript reports on the four non-pharmaceutical strategies (use of a modified resuscitation protocol; use of a mechanical chest compression device; intra-thoracic pressure regulation and application of therapeutic hypothermia).

Conclusion
Use of a modified resuscitation protocol to improve the quality of cardiopulmonary resuscitation, was the only strategy showing evidence to warrant a recommendation for immediate implementation. Future studies should focus on strategy specific patient subsets.

Keywords:
heart arrest; emergency medical service; advanced life support

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Introduction

Globally, out-of-hospital cardiac arrest (OHCA) is a substantial problem with historically low survival rates (1). Impressively high rates of survival from OHCA have recently been reported in some small geographical areas, resulting in increased published research in this field. There are now many studies that have investigated specific strategies to improve outcomes, so it is timely this evidence is reviewed and consolidated.

The aim of this review is to identify, describe and synthesise the evidence for each strategy and make recommendations for improved outcomes from OHCA in high income countries with developed out-of-hospital health care. This is the second in a series of two papers arising from a systematic search and review investigating strategies to improve outcomes from OHCA. Part A addressed strategies focussing on pharmaceuticals (2), and this paper (Part B) addresses strategies focusing on non-pharmaceuticals.

Methods

This study is a systematic search and review (3) in which systematic methods were utilised for searching literature, data extraction, and appraising included studies. The focus is the component of emergency medical services (EMS) provided care which includes intra-arrest and immediate post-arrest life support. The full methods (search strategy, inclusion/exclusion criteria, data extraction, PRISMA diagram) and initial results have been reported previously (Part A) (2). Briefly, four databases (MEDLINE, CINAHL, Informit, Scopus) were searched systematically in February 2017. Papers published between 2007 and 2017 describing primary studies of strategies appropriate for use by paramedics when resuscitating adult patients in OHCA from presumed cardiac aetiology were identified.

Forest plots for each of the four strategy groups were constructed using Review Manager (RevMan) (version 5.3, Copenhagen). This was to provide a visual summary of results to assist with interpretation. The outcome was survival to hospital discharge, or survival to 30 days for studies that did not record survival to hospital discharge. An overall effect size was deliberately not calculated, as this was not meta-analyses and was not the intended purpose of the review. An intention to treat approach was used for randomised controlled studies (RCTs) and the equivalent for non-RCTs.

Results

Twenty-eight papers were included in the review, incorporating six groups of strategies. There were four groups of non-pharmaceutical strategies, which incorporated 23 studies (Table 1). Five papers relating to two pharmaceutical strategies have been reported previously in Part A (2).

Table 1. Strategies and number of papers in this review

Strategy	Number of studies
Use of a modified resuscitation protocol*	7
Use of a mechanical chest compression device	7
Intra-thoracic pressure regulation	3
Application of therapeutic hypothermia	6

*This group includes studies in which the modified resuscitation protocol was primarily aimed at improving CPR quality. This strategy was also known as minimally interrupted cardiac resuscitation, cardio-cerebral resuscitation, team-focussed CPR and pit crew approach.

The 23 studies included in this review are summarised in Table 2, grouped by the four strategies. The results of the studies are visually summarised using Forest Plots in Figure 1, also grouped by strategy.

Use of a modified resuscitation protocol

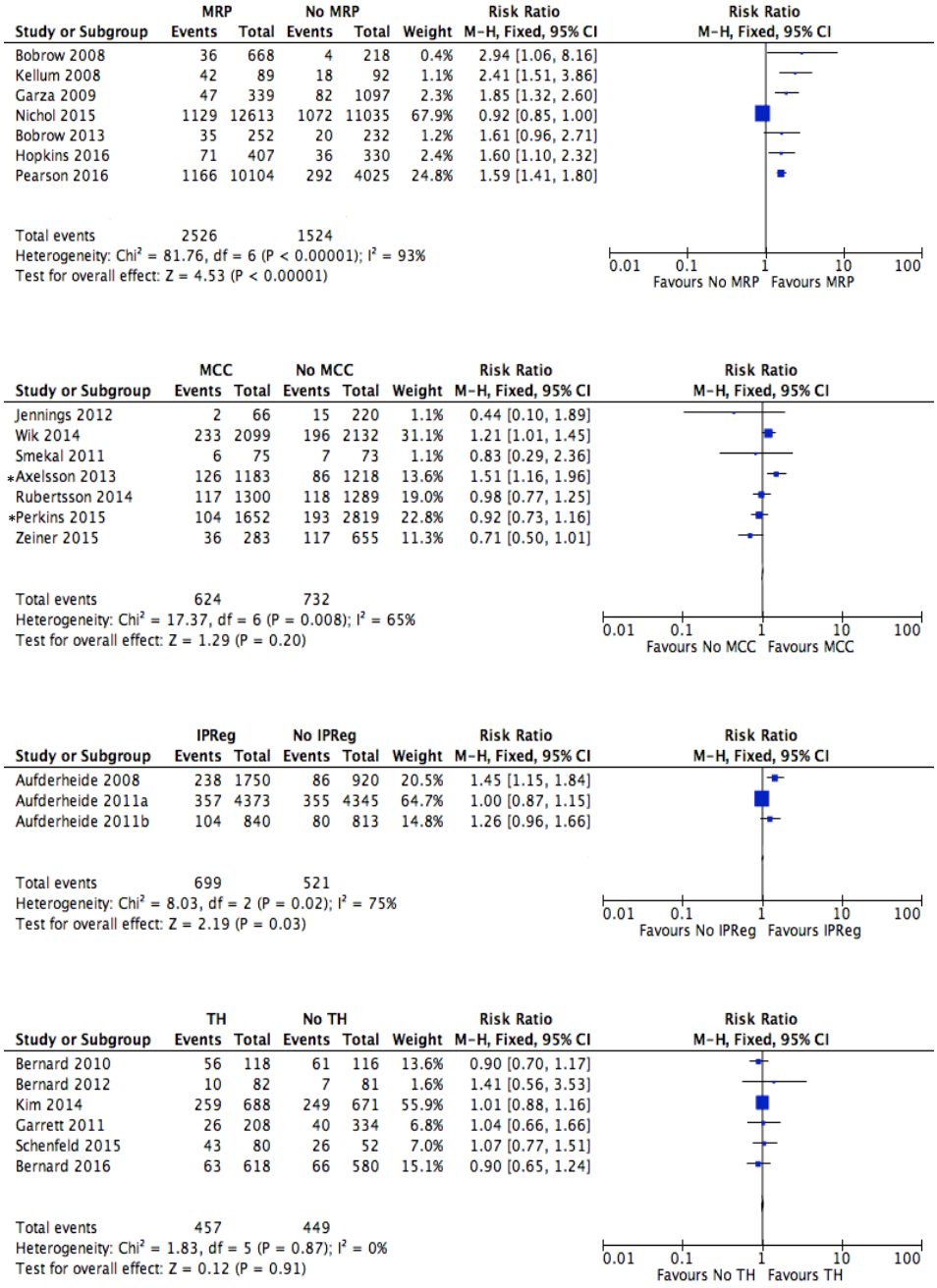
Modified resuscitation protocol (MRP) was investigated in seven studies (4-10), all aimed at actively improving the quality of the resuscitation attempt. Four studies (one large cluster-randomised trial (7) and three before/after study designs (4-6)) focused on reducing interruptions in chest compressions and three studies had a broader scope, involving a pit crew approach to resuscitation (all prospective, before/after designs (8-10)). Collectively, these seven studies suggest a MRP improves survival to hospital discharge (Figure 1).

Some common components of the four modified resuscitation protocols focussing on reducing interruptions in chest compressions (such as emphasis on the quality of chest compressions and delayed definitive airway placement) have already been implemented into current standard practice. However, the deviation from current practice among all four studies was a meaningful reduction in interruptions in chest compressions. This was applied in the RCT (7) by continuous chest compressions alongside concurrent ventilations; using an altered ratio of compressions to ventilations (50:2) in the study by Gaza et al (6); and initiating resuscitation with 200 uninterrupted compressions without ventilations in the remaining two studies (for three cycles in the Kellum et al study (5) and up to 8 minutes in the Bobrow et al study (4)). Reduction in positive pressure ventilations were observed in the three before/after studies (4-6). Bobrow et al used passive oxygen insufflation (4), whereas a change of ventilation pattern (at least in part), without a reduction in ventilations delivered overall, was observed in the RCT (7).

All three before/after studies (4-6) showed results in favour of the modified protocol. The effect size on survival to hospital discharge was more pronounced in the subgroup of witnessed shockable patients in the Bobrow et al (4) and Gaza et al (6) studies. Favourable results in this subgroup were consistent

with the Kellum et al study (5). Significant favourable return of spontaneous circulation (ROSC) rates were shown in the Kansas City study (6) post-protocol implementation for the subset of witnessed shockable, however ROSC rates for all rhythms and witness status were not reported. No significant effects were observed on ROSC and survival to admission rates by Bobrow et al (4) but only 61% of cases treated after training actually met the complete MRP compliance criteria. When protocol compliance analysis was undertaken, ROSC and survival to admission rates became significantly favourable in those who received treatment with MRP compared to those who did not. Survival to hospital discharge rates also improved.

While the results of the three before/after studies are positive, interpretation must be considered within the context of limitations: 1) study design and differences in inclusion/ exclusion criteria; and 2) multiple components within each protocol which may have impacted positively or negatively on patient outcomes. It is impossible to know how much impact was attributable to which change. Compliance analysis was



*The outcome displayed is survival to 30 days
Modified resuscitation protocol (MRP), use of a mechanical chest compression device (MCC), intra-thoracic pressure regulation (IPReg) and application of therapeutic hypothermia (TH).

Figure 1. Forest Plot of survival to hospital discharge after OHCA, by pre-hospital strategy (non-pharmaceutical)

undertaken only in one study (4), we cannot be sure how closely the protocols were followed in the others. Additionally, the training conducted would likely have improved other areas of care, so it is difficult to assess the impact on outcomes. The cluster-randomised trial (7) observed slightly lower rates of survival to hospital discharge with favourable neurological outcomes in the intervention group compared with the control group, but these differences were not significant. The only significant difference in favour of the intervention group was in the outcome of hospital free days (number of days out of hospital up to 30 days post-event). In compliance-only analyses, survival was also lower in the intervention group ($p<0.001$). A large proportion of the compliance only population were excluded as the algorithm used could not differentiate between intervention and control groups, leaving imbalances in characteristics and treatments between groups. This and the multiple other limitations may provide some explanation for the results.

The remaining three studies in this group involved a pit crew approach (8-10). The principles of pit crew approach include many factors already included within current EMS CPR training in Australia, such as attention to correct compression rate, rhythm, depth, recoil, limiting interruptions and rotating compression providers regularly. However, pit crew approach takes these concepts and applies them with a well-practiced choreographed approach. EMS providers have designated roles which are frequently practised within teams, so on treating a real OHCA patient, the process is smooth, organised and strictly structured, optimising efficiency.

The inclusion criteria for all three studies was patients who had an OHCA of non-traumatic aetiology and had a resuscitation attempt by EMS. The Pearson and Bobrow studies (8,10) further stipulated presumed cardiac aetiology, while the Hopkins study (9) excluded aetiologies of drowning and strangulation (in addition to trauma). The Hopkins study (9) included patients of all ages versus adults only in the Pearson and Bobrow studies (8,10).

Increased neurologically intact survival to discharge was shown in all three studies in the post-intervention group (8-10). Increased survival to hospital admission in the post-intervention phase was also demonstrated in all three studies, but was non-significant in the Pearson study (10). Additionally, the Hopkins study (9) showed increased field ROSC post-intervention and the Pearson study (10) demonstrated significant results in favour of the intervention in the subgroup of witnessed shockable cases (over all outcomes).

All three studies were retrospective and non-randomised. Individual components of the broader initiative studies (Hopkins and Bobrow (8,9)) cannot be analysed independently, so the true contribution of pit crew approach is uncertain. Additionally, it is difficult if not impossible to ascertain which components (or combination of) are effectively transferable to other areas/organisations. The multiple agency contribution (with unknown consistency) of the study by Pearson (10) brings further limitations.

Overall, these seven studies provide some evidence that use of a modified resuscitation protocol (largely to improve the quality of CPR) will likely improve patient outcomes. The specifics of the strategies applied is inconsistent between studies, so the most effective application is still unclear, although all studies featuring a pit crew approach showed favourable outcomes. The studies with results in favour of the intervention are retrospective in nature and the only prospective randomised study (study without pit crew approach) showed no effect (7). Overall, results surrounding this strategy are promising but require further rigorous research.

Use of a mechanical chest compression device

Seven studies investigated use of a mechanical chest compression device (11-17). Two types of devices were found: 1) A load distributing band (LDB) design (Autopulse®); and 2) an active compression/decompression design (LUCAS). As shown in Figure 1, no consistent results were observed across studies in relation to the effect of mechanical chest compression devices on survival to hospital discharge/30 days.

Two studies involved a LDB device; one RCT (12) and one retrospective matched case-control study (11). The RCT showed no significant difference between groups in survival to hospital discharge with MRS<3, however significant reductions in ROSC to ED and survival to 24 hours were observed (12). Only some covariates were adjusted for in analyses, hence there are potentially other confounders that were not investigated. In the case-control study (11), ROSC to ED was higher in cases than controls but not significantly. Similar results were found within sub-analysis of bystander witnessed cardiac aetiology patients only and when data were stratified by shockable status.

Four studies (three RCTs (13,15,16) and one retrospective case series (14)) investigated the use of a LUCAS device. Two of the RCTs were large randomised trials (LINC (15) and PARAMEDIC (16)) and one was a smaller study (13) which acted as the pilot study for LINC.

There were some differences in the protocols applied with LUCAS in the RCTs. In the LINC study (15), 3-minute cycles of continuous compressions were applied to cases (with a shock delivered to all patients at the 90-second mark on the first round and shock delivered on subsequent rounds if shockable on last analysis), while controls received standard 2 minute cycles at 30:2. In the PARAMEDIC study (16), the same standard 2 minute cycles were applied to cases and controls. Factors such as continuous compressions and defibrillation during CPR are under investigation as strategies to improve outcomes in their own right and as a result, the impact of these cannot be ruled out as contributory to any findings in LINC (rather than solely the LUCAS).

All three studies investigated various length of patient outcome and all applied intention-to-treat (ITT) methodology. The pilot study was used to inform LINC, hence the relatively small sample, which is the likely explanation for the lack of significant results. No significant differences were found between the intervention and non-intervention groups for any outcome in LINC. This was also mostly true in PARAMEDIC, with exceptions of significantly fewer cases with favourable neurological outcome at 3 months (overall) and 30-day survival (shockable subset only). Compliant average causal effect analyses showed similar results.

In LINC (15), the lack of effect may have been due to the treatment differences between the intervention and non-intervention algorithms, which may have had a pronounced effect on survival (27). This is not the case in PARAMEDIC, but the pragmatic methodology likely explains the marginal results in favour of the control group. True adherence to algorithms and CPR quality were not routinely measured in any of the studies and there is some evidence of omission which may also impact observed outcomes.

The final study using LUCAS compared two time periods, before and after the introduction of LUCAS as part of ambulance equipment (14). There were significant increases in survival to admission between periods 1 and 2, however these improvements may be attributable to other factors (eg. implementation of the 2005 resuscitation guidelines and significant changes in witnessed status and proportions of patients receiving post-resuscitation care and bystander CPR). Further analysis indicated that among patients from period 2 only, survival to hospital was significantly lower in patients that had a LUCAS applied (n=705) versus those that did not (n=465). In multivariate analyses, administration of mechanical compressions was inversely associated with survival. This may be because the LUCAS device is only indicated in a high-risk cohort of patients, ie. those where initial manual CPR and defibrillation has been unsuccessful, much the same as adrenaline which was also inversely associated with survival in the same multivariate analysis. Testing strategies on high risk cohorts makes it difficult to provide a large enough sample to provide adequate power and is a problem with research involving many cardiac arrest strategies.

The final study involved both the Autopulse and LUCAS devices (17). Significantly lower rates of 30-day survival with favourable neurological outcome and sustained ROSC were found in the intervention group. A lower rate of survival to 30 days was also found in the intervention group, although non-significant. Additionally, when survival analysis adjusting for relevant variables was undertaken, use of a mechanical chest compression device was significantly associated with death in hospital. There were many limitations in this study most of which would likely yield results in favour of the intervention group, so the significant results against the intervention seem obscure.

Across all seven studies, there is insufficient rigorous evidence to support use of a mechanical chest compression device versus high quality manual CPR. There are some clear practical advantages of mechanical chest compression devices over manual compressions, such as the provision of continuous high-quality CPR without fatigue or inconsistencies which can remain uninterrupted throughout defibrillation and transport. It may be that further, more rigorous research could highlight true benefit to patient outcomes from their use in specific circumstances.

Intra-thoracic pressure regulation

Three studies (all led by the same author - Aufderheide) involved the use of single or multiple devices to regulate intra-thoracic pressure in the intra-arrest phase of cardiac arrest (18-20). Overall, no consistent trends were observed to suggest regulation of intra-thoracic pressure increases survival to hospital discharge (Figure 1).

Two of the studies were large multicentre RCTs, ROC PRIMED (19) and ResQTrial (20). In ROC PRIMED, there were no significant differences between groups for any outcome measure and the study was terminated early due to interim analysis demonstrating futility. On post-hoc analysis, increased survival to discharge with satisfactory neurological function was observed in the subgroup of patients who were in the second lowest quartile (59.9-71%), when defined by CPR fraction. ROC PRIMED had many limitations, which may have contributed to the lack of significant findings and early termination.

In ResQTrial, there were significant differences in favour of the intervention in survival to hospital discharge with MRS ≤3, survival to 90 days and survival to 1 year, but not in survival to 24 hours. There were some methodological issues with this study including early discontinuation of a third arm investigating the use of an Impedance Threshold Device (ITD) alone (without active compression-decompression cardiopulmonary resuscitation (ACDCPR)). It therefore cannot be established if the results are from either intervention independently or a synergistic effect of the two. This study appears methodologically sound, but the overall impact of the methodological and other limitations on results is largely unknown.

The third study compared two time periods before and after the introduction of the 2005 CPR guidelines, which included the use of an ITD (18). However, a major limitation of this study is that it is the human component of a larger study involving swine and effects cannot be solely attributed to the use of an ITD but may be a combination of interventions and guideline changes. When broken down by initial rhythm, survival to hospital discharge was significant only in cases of VF and was not significant in asystole or PEA.

There is some evidence supporting improvements in short term outcomes when an ITD is used in combination with ACDCPR and perhaps in survival to discharge in patients with an initial

rhythm of ventricular fibrillation (VF) when ITD is used alone. There are profound limitations of the three studies in this review including funding/affiliations from the only current manufacturer of the ITD. To improve the evidence base in order to make a more definitive conclusion, large scale independent blinded RCTs isolating the ITD are required.

Application of therapeutic hypothermia

Six studies investigated therapeutic hypothermia (TH) (21-26), initiated in the post-arrest phase in three of the studies (21-23), in the intra-arrest phase in two (24, 26) and in either phase in one (25). None of these studies reported significant findings in survival to hospital discharge to support or refute therapeutic hypothermia (Figure 1).

All three studies where TH was initiated post-arrest were RCTs and used an IV infusion of cold fluid as the cooling method (21-23). The largest of these (23) used normal saline as the fluid. The patient outcome measures were analysed overall and stratified by initial VF status. Additionally, there were multiple limitations.

The remaining two studies (21,22) in which the strategy was initiated in the post-arrest phase were run concurrently, by the same research team and within the same population. One investigated patients with an initial rhythm of VF and a presumed cardiac aetiology only, for which a rapid infusion of 2 litres of lactated ringers was administered (21); the other included patients with an initial rhythm of asystole or pulseless electrical activity (PEA) of any aetiology and used 2 litres of Hartmann's (22). Therefore, these two studies collaboratively included all OHCA patients in this area for the specified time period, unless the initial rhythm was pulseless VT or other exclusion criteria were met.

The study investigating lactated ringers in VF (21), demonstrated no significant differences between groups in patient outcome measures so was stopped early due to perceived futility. This meant the parallel trial (22) was logistically too difficult to continue so was also stopped. While there were between group differences in favourable outcomes in the subgroup of cardiac aetiology only, these were not significant, however this may be due to limited sample size (and the early termination). There were further limitations to both studies.

Both studies in which TH was initiated in the intra-arrest phase of arrest used an infusion of cold normal saline (up to 2 litres) as the cooling agent; one of which was an RCT (26) and one was a before/after study (24). The RCT included adults of non-traumatic aetiology only, had high quality randomisation techniques and used ITT analysis (26). ROSC was investigated stratified by shockable status and occurred less frequently in the intervention group of those with an initially shockable rhythm, which remained when adjustments were made for fluid volume administered. This study was finished early due to a change in hospital cooling protocols, although significant results would have been unlikely. Additionally, only 10% of all cardiac arrest patients were enrolled, the reasons for which are unknown.

In the before/after study (24), higher rates of prehospital ROSC and survival to hospital admission were observed in cases than controls (only significant in pre-hospital ROSC). A positive linear association was also observed between the amount of cold fluid administered and likelihood of obtaining ROSC, with two significant changes in outcome at 200 mL (vs. ≤50 mL) and 700 mL (vs.≤200 mL). There were various limitations in addition to those associated with the retrospective nature of the study.

The remaining study initiated therapeutic hypothermia in either the intra or post-arrest phase (25). A therapeutic hypothermia protocol was implemented part way through the study period; providing the basis of a before/after study. The primary outcome was time to target temperature following ROSC while the patient specific outcomes were secondary. There were no significant differences between groups in any of the outcomes, which for patient specific outcomes is likely the result of insufficient power. Additionally, there were other limitations to this study.

Overall, there is a lack of strong evidence supporting the implementation of TH in either the intra-arrest or post-arrest phase of out-of-hospital cardiac arrest. The only study (24) showing any significant results in favour of out-of-hospital TH in either phase was a less rigorous study with many inherent limitations. The studies of more rigorous design finished early. In addition, the specifics of the strategy such as cooling method, fluid type and patient selection also require clarification.

Discussion

Four non-pharmaceutical strategies were identified for inclusion in this systematic search and review. The most positive results were observed for use of a modified resuscitation protocol, particularly use of a pit crew approach. The modified resuscitation protocols differed but were common in their primary objective of improving the quality of CPR. Instigation of such protocols aims to support paramedic skills and ensure the delivery of higher quality CPR will not suffer over time, as would be expected if paramedics simply received training with no surrounding governance.

Quality CPR makes a difference to outcomes (28). As such, recent literature has a heavy focus on the importance of achieving optimal CPR (28-34) and therefore, it is unsurprising that studies identified in this review with protocols promoting and maintaining optimal CPR, showed positive results. There has also been recent focus on optimising the use of factors

promoting the efficiency of teams in clinical circumstances, such as leadership and the use of non-technical skills, to improve outcomes (35, 36). A pivotal study to this concept in the out-of-hospital environment was TOPCAT2 (37), which presented a specialist second-tier response to OHCA to focus on non-technical skills (more specifically leadership, communication and clinical decision making), with goals closely aligned to that of a pit crew approach. A primary objective of a pit crew approach is to promote and support the deliverance of high quality CPR, but there is little evidence specifically investigating further benefits. The Bobrow study (8) measured minimally interrupted cardiac resuscitation protocol (MICR) compliance. There was an increase in compliance in the post-intervention phase, supporting the importance of the delivery of high-quality CPR. Additionally, when calculations including adjustments for MICR protocol compliance were undertaken (so effectively removing the impact of CPR quality from the intervention), the results remained significantly in favour of the intervention, indicating there may be benefit from additional constituents of the intervention. This suggests factors of a pit crew approach (such as highly effective teamwork and impeccable use of non-technical skills) impact positively on the quality of a resuscitation attempt beyond their contribution to the provision of high-quality CPR.

Equivocal results were independently found for use of a mechanical chest compression device and intra-thoracic pressure regulation, meaning that neither can be recommended for routine implementation.

There are four recent systematic reviews/meta-analyses on use of a mechanical chest compression device, three of which (38-40) support the findings presented in this systematic search and review (to not recommend for routine implementation). The other (a meta-analysis) contradicts the findings of this study, concluding that LDB CPR had significantly greater odds of ROSC than manual CPR (1.62; 95% CI: 1.36-1.92; p<0.001).

Use of a mechanical chest compression device does have clear practical advantages in certain subsets of patients, such as those requiring transport. There have been recent international studies investigating the use of a mechanical chest compression device, specifically to facilitate high quality chest compressions during transport in subsets of patients that may benefit from more definitive care, such as interventional cardiology and/or extracorporeal membrane oxygenation (ECMO) (41,42). Some international ambulance services (such as London) already have such procedures in place for transfer to interventional cardiology only, but there are none yet routinely in place for direct transfer specifically to ECMO. The relevant ECMO studies to date have hypothesis generating capability only, but with positive results, hence require more rigorous investigation. Additionally and more recently, use of a mechanical chest compression device as a pre-empt to out-of-hospital initiated ECMO is a further strategy which has been investigated in a hypothesis generating capacity (43), which will likely lead to more rigorous studies.

Three studies in this review investigated a method of regulating intra-thoracic pressure. The theory of intrathoracic pressure regulation to improve outcomes is certainly convincing, but the inherent floors in the three reviewed studies limit interpretability. Therefore, more rigorous evidence, with potential strategy development, is required before a recommendation can confidently be made. An alternative method of intrathoracic pressure regulation is use of a device which regulates pressure. No study using this device (known as CirQlator) (45), fulfilled the inclusion criteria for this review, so it was not discussed. Further investigation of alternative methods to regulate intrathoracic pressure such as this, would contribute to the evidence base of this strategy.

In this review, there was no supportive evidence in favour of the application of out-of-hospital therapeutic hypothermia. For some time, therapeutic hypothermia in the post-cardiac arrest patient has been recognised as a beneficial treatment (as supported by a recent systematic review and meta-analysis (46)) and routinely applied to in-hospital protocols where feasible. The benefits of the out-of-hospital application of this strategy has been under greater question; although out-of-hospital application has been shown to achieve optimal temperature earlier than in-hospital application, longer term benefits have not been proven (47). Additionally, the timing (intra-arrest or post-arrest) and method of out-of-hospital application has also been questioned. The cooling methods in the studies identified by this review are the administration of various types of cold fluid (normal saline, lactated ringers or Hartmann's). However, there are other feasible out-of-hospital cooling methods used either in combination or isolation within published literature that did not meet the inclusion criteria for this review. Examples are external cooling measures such as the application of ice-packs and use of an intra-nasal cooling device known as Rhinochill (48-50). Preferential timing and method are important questions to answer before a recommendation could be made.

Additionally, recent high quality in-hospital studies have suggested that temperature maintenance, rather than reduction is the important factor to achieve preferred patient outcomes (51). Although outside the inclusion boundaries of this review, this brings further question to the value and/or specifics of a out-of-hospital strategy and it seems logical that further out-of-hospital studies be informed by this and further evidence, including in-hospital studies.

The limitations of this search and review have been reported previously (2). Limitations include the exclusion of studies published in a non-English language or in grey literature, the potential that relevant studies were missed (although the methodology was rigorous) and the lack of detailed critical

appraisal for each paper due to the broad objective and design of the review. While Forest plots were used to visually summarise results of included studies, no overall effect was presented. This was deliberate as this was not meta-analyses. The inherent differences between studies would make an overall effect size misleading; nonetheless, this is acknowledged as a limitation. Recommendations arising from this review are summarised in Table 3.

Table 3. Recommendations

1	Where feasible, a modified resuscitation protocol to achieve high quality CPR (preferably with some degree of pit crew approach) be implemented in EMS internationally. Systems in which this is implemented should have established sophisticated data collection methods in place to allow the measurement of impacts over time
2	Further research into the use of a mechanical chest compression device be undertaken with a focus on specific subsets of OHCA patients. The most beneficial approach is likely in collaboration with other strategies, to provide a pathway to more definitive care. With no further research and where feasible, mechanical chest compression devices should be introduced for circumstances where clear practical advantages exist, ie. single paramedic response, prolonged resuscitation and/or requirement of intra-arrest transport
3	Large independent studies of intra-thoracic pressure regulation effectiveness be commenced
4	Further research into out-of-hospital therapeutic hypothermia with particular consideration of timing (intra-arrest versus post-arrest) and method of application
5	Large epidemiological studies be undertaken to inform target populations

Conclusion

There is a shortage of high-quality evidence for strategies that may be used by paramedics to improve outcomes from OHCA. The only strategy group that showed adequate evidence to warrant immediate implementation recommendations was use of a modified resuscitation protocol to improve the quality of CPR (preferably with some degree of pit crew approach).

Many strategies are likely advantageous for specific subsets of OHCA patients, so it may be beneficial that future research involving specific strategies focus on those subsets.

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Conflict of interest

The authors declare they have no competing interests. Each author of this paper has completed the ICMJE conflict of interest statement.

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Table 2. Evidence table for non-pharmaceutical strategies to improve OHCA outcomes in the out-of-hospital environment

Year and lead author	Strategy details	Study design/ timeframe	Setting/recruiting method and sample size	Main results	Type of association
Use of a modified resuscitation protocol					
2008 Bobrow (4)	Minimally interrupted cardiac resuscitation (MICR)	Before/after study: Before data Jan 2005 – June 2005 After data July 2005 onward (as training implemented at the site) – June 2007 Protocol compliance analysis (PCA) – Those who received MICR Jan 2005 – Nov 2007 (not ITT)	Arizona, US ITT analysis: Before – 668 After – 218 PCA analysis: Before – 1799 After – 661	Before/after analysis: Survival to discharge (primary outcome): 1.8% before vs. 5.4% after (OR=3.0; 95% CI: 1.1-8.9). In witnessed shockable subgroup: (174) 4.7% before vs. 17.6% after (OR=8.6; 95% CI: 1.8-42) ROSC (secondary outcome): 15.6% before vs. 23.1% after (OR=1.3; 95% CI: 0.8-2.0) Survival to admission (secondary outcome): 16.1% before vs. 16.9% after (OR=0.8; 95% CI: 0.5-1.2)	+
2008 Kellum (5)	Cardio-cerebral resuscitation	Before / after study Before: Jan 2001 – Dec 2003 After: mid 2004 – mid 2007	Wisconsin, US Protocol introduced in 2004 staggered approach of four EMS regions ITT analysis: Before – 92 After - 89	Before/after analysis: Survived to discharge (primary outcome): 18/92 (20%) before vs. 42/89 (47%) after (95% CI: 0.1-0.4) Survived neurologically intact (CPC of 1) (secondary outcome): before 14/92 (15%) vs. 35/89 (39%) after (95% CI: 0.1-0.4)	+
2009 Garza (6)	Modified resuscitation protocol (MRP)	Before / after study Before: Jan 2003 - March 2006 After: April 2006 - March 2007	Kansas City, US – uses first responders from the KCMO fire dep ITT analysis: Before - All rhythms 1097; subgroup bystander witnessed shockable (main study) 143 After - All rhythms 339; subgroup bystander witnessed shockable (main study) 57	Before/after analysis: Survival to discharge (primary outcome): 7.5% before vs. 13.9% after p<0.001. In witnessed shockable subgroup 22.4% before vs. 43.9% after (p=0.0024; OR 2.71; 95% CI 1.34-5.49) ROSC (secondary outcome): 37.8% before vs. 59.6% after (p=0.0051; OR 2.44; 95% CI 1.24-4.80)	+
2015 Nichol (7)	Continuous chest compressions	Cluster randomisation with crossover (47 clusters of EMS agencies – twice per year clusters were crossed over to the other strategy) First agency entered run in phase 6 June 2011 – all study sites stopped 28 May 2015	Resus outcomes consortium (ROC) – Network which includes 10 clinical sites in North America, the regional EMS agencies, 8 ROC sites and 114 EMS agencies ITT analysis: Intervention group: 12,613 Non-intervention group (CPR given at ratio 30:2): 11,035 Compliance analysis (referred to as per-protocol population within study): Intervention group: 6529 Non-intervention group: 3678	ITT analysis: Survived to discharge (primary outcome): 9% intervention vs. 9.7% non-intervention (p=0.07) Survived to discharge with favourable neurological outcome (MRS 3) (secondary outcome): 7% intervention vs. 7.7% non-intervention group (p=0.09)	/

Year and lead author	Strategy details	Study design/ timeframe	Setting/recruiting method and sample size	Main results	Type of association
Use of a modified resuscitation protocol					
2013 Bobrow (8)	Multiple interventions – MICR with pit crew model and real-time audio-visual feedback	Before / after observational cohort study Before (phase 1): 7th Oct 2008 – 31st March 2010 After (phase 2): 27th May 2010 – Sep 2011	Mesa, Arizona, US Single fire-based EMS agency Before - 232 After - 252	Survival to hospital discharge (primary outcome): 8.7% before vs. 13.9% after (OR 1.73; 95% CI 0.93 – 3.21) and (AOR 2.72; 95% CI 1.15 – 6.41) Favourable functional outcome at discharge (CPC score of 1 or 2) (secondary outcome): 6.5% before vs. 10.8% after (OR 1.76; 95% CI 0.88 – 3.52) and (AOR 2.69; 95% CI 1.04 – 6.94)	+
2016 Hopkins (9)	Multiple interventions - Various CPR quality improvement initiatives eg. real-time CPR feedback technology, post-incident feedback, rhythm filtering technology, passive O2 option, impedance threshold device (ITD) added in July 2013, simplified medication algorithm, pit crew approach and more appropriate transport destinations	Before / after study Before: 1 Sep 2008 – 30 Sep 2011 After: 1 Oct 2011 – 31 Dec 2014 Strategy implemented in Sep 2011	Salt Lake City, US Internal Utstein style database ITT analysis: Before – 330 After - 407	Neurologically intact (CPC 1 or 2) survivors at discharge (primary outcome): 25/330 = 8% before vs. 65/407 = 16% after. Increase between periods was 8.4% (p=0.0005; 95% CI 3.8 – 13) Field ROSC (secondary outcome): 100/330 = 30% before vs. 179/407 = 44% after (p<0.0001) Survival to hospital admission (secondary outcome): higher in the after group but not significantly	+
2016 Pearson (10)	Team focussed CPR (TFCPR) (also known as high performance CPR/ pit crew approach)	Before / after observational cohort study Jan 2010 – June 2014 State-wide protocol introduced in July 2012 but incorporation of TFCPR began in 2011	North Carolina, US North Carolina EMS agencies reporting to CARES database Before – 4,025 After – 10,104 Total sample for logistic regression is 11,232 (due to other missing variables)	Neurologically intact at discharge (CPC 1 or 2) (primary outcome): 193/4025 = 4.8% before (95% CI 4.2-5.5) vs. 836/10104 = 8.3% after (95% CI 7.7-8.8) (significantly higher) Survival to hospital admission (secondary outcome): 21.1% before vs. 27.2% after (significantly higher by 95% CI) Survival to hospital discharge (secondary outcome): 7.3% before vs. 11.5% after (significantly higher by 95% CI) In witnessed shockable subgroup, all outcomes significantly higher after: Neurologically intact at discharge 16.8% vs. 28.9%; survival to hospital admission 42.7% vs. 54.1%; survival to hospital discharge 22.1% vs. 36.6%	+

Year and lead author	Strategy details	Study design/ timeframe	Setting/recruiting method and sample size	Main results	Type of association
Use of a mechanical chest compression device					
2012 Jennings (11)	Load distributing band (LDB) (Autopulse®)	Case-control study 1 October 2006 – 30 April 2010	Victoria, Australia Cases - 66 Controls (manual CPR) - 220	Survival to hospital (primary outcome): 17/66 (26%) cases vs. 43/220 (20%) controls (AOR 1.69; 95% CI 0.79-3.63). In shockable subgroup: 50% cases vs. 33% controls (p=0.2). In non-shockable subgroup: 19% cases vs. 12% controls (p=0.28). In bystander witnessed cardiac aetiology subgroup: 14/48 (29%) cases vs. 21/116 (18%) controls (AOR 1.80; 95% CI 0.78-4.11) Survival to discharge (secondary outcome): 2/66 (3%) cases v 15/220 (7%) controls (p=0.38).	/
2014 Wik (12) CIRC	Load distributing band LDB (Autopulse®)	Sequential multicentre RCT March 2009 – Jan 2011	Three US and two EU sites Intervention group: 2099 Non-intervention group (manual CPR) - 2132	Survival to hospital discharge (primary outcome): 9.4% intervention vs. 11% non-intervention (AOR 0.89; 95% CI 0.72-1.1) ROSC to ED (secondary outcome): 28.6% intervention vs. 32.3% non-intervention (AOR 0.84; 95% CI 0.73-0.96) 24hr survival (secondary outcome): 21.8% intervention vs. 25% non-intervention (AOR 0.86; 95% CI 0.74-0.998) Discharged with a MRS□3 (secondary outcome): OR 0.8; 95% CI 0.47-1.37	/
2011 Smekal (13) LINC pilot	Active compression-decompression CPR (ACDCPR) (LUCAS)	RCT pilot study Feb 2005 – April 2007	Sweden ITT analysis: Intervention group - 75 Non-intervention group (manual CPR) - 73	ROSC with BP above 80/50 for at least 5 mins (primary outcome): 23/75 intervention vs. 19/73 non-intervention group (p=0.59) ROSC (secondary outcome): 30/75 intervention vs. 23/73 non-intervention (p=0.3) Hospitalised alive >4h (secondary outcome): 18/75 intervention group vs. 15/73 non-intervention group (p=0.69) Discharged alive (secondary outcome): 6/75 intervention vs. 7/73 non-intervention (p=0.78)	/
2013 Axelsson (14)	ACDCPR (LUCAS)	Before / after study Before (period 1): Jan 1998 – May 2003 After (period 2): Nov 2007 – Dec 2011 Interim period not used due to another study and transition of the OHCA registry.	Gothenburg, Sweden Swedish OHCA registry ITT analysis: Before - 1218 After - 1183 Compliance analysis (main analysis, period 2 only): Intervention – 705 (60%) Non-intervention - 465 (39%) Unknown – 13 (1%)	ITT analysis: Survival to hospital admission (primary outcome): 25.4% before vs. 31.9% after (p<0.0001); survival to 1 month (secondary outcome): 7.1% before vs. 10.7% after (p<0.002) Compliance analysis: intervention vs. non-intervention admitted alive to hospital 28.6% vs. 36.1% (p=0.008) and survival to 1 month 5.6% vs. 17.6% (p<0.0001) respectively	Period 1 v period 2: + Period 2 only: /

Year and lead author	Strategy details	Study design/ timeframe	Setting/recruiting method and sample size	Main results	Type of association
2014 Rubertsson (15) LINC	ACDCPR (LUCAS)	Multicentre RCT Jan 2008 – Aug 2012	Sweden, Netherlands and the UK Intervention group - 1300 Non-intervention group (manual CPR) - 1289	4-hour survival (primary outcome): 23.6% intervention vs. 23.7% non-intervention Survival to ICU discharge with CPC 1 or 2 (secondary outcome): 7.5% intervention vs. 6.4% non-intervention Hospital discharge with CPC 1 or 2 (secondary outcome): 8.3% intervention vs. 7.8% non-intervention 1-month survival (secondary outcome): 8.1% intervention vs. 7.3% non-intervention 6-month survival (secondary outcome): 8.5% intervention vs. 7.6% non-intervention No significant difference between groups in any outcome	/
2015 Perkins (16) PARAMEDIC	ACDCPR (LUCAS2)	Cluster randomised (by vehicle) trial 15 April 2010 – 10 June 2013	Four UK ambulance services Data collected by individual ambulance services and submitted to central trial database Intervention group - 1652 Non-intervention group (manual CPR) – 2819	Survival at 30 days post arrest (primary outcome): 104/1652 = 6% intervention vs. 193/2819 = 7% non-intervention (non-significant in OR and AOR) ROSC, survival to admission and survival at 3 months (secondary outcomes) were very similar between groups Favourable neurological outcome at 3 months (CPC 1 or 2) (secondary outcome) lower in intervention group (AOR 0.72; 95% CI 0.52-0.99)	/
2015 Zeiner (17)	LDB (Autopulse®) or ACDCPR (LUCAS)	Non-randomised trial July 2013 – Aug 2014	Vienna, Austria Intervention group - 283 Non-intervention group (manual CPR) - 655	30-day survival with favourable neuro outcome (primary outcome): 56.8% intervention vs. 78.6% non-intervention group (p=0.009) Sustained ROSC (secondary outcome): 22.9% intervention vs. 30.7% non-intervention (p=0.017) Survival to discharge (secondary outcome): 12.7% intervention vs. 17.8% non-intervention (p=0.052)	/
Intra-thoracic pressure regulation					
2008 Aufderheide (18)	2005 American Heart Association CPR guidelines including ITD	Before / after study Dates of data collection not stated	Six EMS systems in the US Before - 1750 After - 920	Survival to hospital discharge (primary outcome): 9.3% before vs. 13.6% after (p=0.0008; OR 1.54; 95% CI 1.19-1.99). In VF subgroup, 18% before vs. 28.5% after (p=0.0008). No significant differences between groups in non-shockable subgroups	+
2011a Aufderheide (19) ROC Primed	ITD	Double blind RCT June 2007 – Nov 2009	10 sites in the US and Canada Intervention group - 4373 Non-intervention group (sham ITD) - 4345	No significant differences between groups in survival to discharge with MRS≤3 (primary outcome), ROSC on ED arrival, survival to admission, survival to discharge (secondary outcomes) Early termination	/
2011b Aufderheide (20) ResQtrial	ITD and ACDCPR	RCT Run in phase Oct 2005 – April 2009 Enrolled study March 2006 – July 2009	46 EMS agencies in US Intervention group: 840 Non-intervention group: 813	Survival to hospital discharge with MRS≤3 (primary outcome): p=0.019; OR 1.58; 95% CI 1.07-2.36 Survival to 90 days (secondary outcome): 10% intervention vs. 7% non-intervention (p=0.029) Survival to 1 year (secondary outcome): 9% intervention vs. 6% non-intervention (p=0.03)	+

Year and lead author	Strategy details	Study design/timeframe	Setting/recruiting method and sample size	Main results	Type of association
Application of therapeutic hypothermia					
2010 Bernard (21)	Rapid infusion of 2L ice cold lactated ringers post-arrest (VF only)	RCT Oct 2005 – Nov 2007	Victoria, Australia Intervention group - 118 Non-intervention group - 116	Hospital discharge home or to a rehabilitation facility (primary outcome): 47.5% intervention vs. 52.6% non-intervention (p=0.433). All other outcomes non-significant Early termination - futility	/
2012 Bernard (22)	Rapid infusion of up to 2L ice cold Hartmann's post-arrest (asystole or PEA only)	RCT October 2005 – November 2007	Victoria, Australia Intervention group - 82 Non-intervention group - 81	Hospital discharge home or to a rehabilitation facility (primary outcome): 12% intervention vs. 9% non-intervention (p=0.5). In those with cardiac aetiology subgroup, 17% intervention vs. 7% non-intervention (p=0.146) Early termination – logistics	/
2014 Kim (23)	Rapid infusion of 2L cold fluid 4^0C immediately post-arrest	RCT 15 Dec 2007 – 7 Dec 2012 (follow up until May 2013)	Seattle, Washington, US Intervention group – 688 (292 VF; 396 non-VF) Non-intervention group - 671 (291 VF; 380 non-VF)	Survival to hospital discharge (primary outcome): In VF 62.7% intervention vs. 64.3% non-intervention (p=0.69). In non-VF 19.2% intervention vs. 16.3% non-intervention (p=0.3) Neurological status of full recovery or mild impairment (secondary outcome): In VF 57.5% intervention vs. 61.9% non-intervention p=0.69. In non-VF 14.4% intervention vs. 13.4% non-intervention (p=0.3)	/
2011 Garrett (24)	Infusion of up to 2L cold saline intra-arrest (as soon as IV/IO access gained)	Before / after study Before: Oct 2008 – March 2009 After: April 2009 - Sep 2009 (pre-hospital TH protocol initiated in April 2009)	Large metropolitan area, US Before - 334 After - 208	Pre-hospital ROSC (primary outcome): 26.9% before vs. 36.5% after (p=0.018; AOR 1.83; 95% CI 1.19-2.81) (independent of fluid volume). In non-shockable subset 19.3% before vs. 29.9% after (OR 1.78; 95% CI 1.13-2.81). In shockable or witnessed shockable subsets, pre-hospital ROSC was higher in the after group, but not significantly. Survival to admission (secondary outcome): 28.4% before vs. 23.4% after (AOR 1.5; 95% CI 0.96-2.36) Survival to discharge: 12.5% before vs. 12% after (AOR 1.03; 95% CI 0.54-1.98)	+
2015 Schenfeld (25)	Rapid infusion of up to 2L (repeats of 500 mL bolus) cold saline as early as possible (intra/post-arrest)	Before/after study: (introduction of a new protocol) Before: Nov 2007 – March 2009 After: April 2009 – Nov 2011 (pre-hospital TH protocol initiated in April 2009)	Existing QA database used as source – all patients treated in the therapeutic hypothermia clinical pathway of Carolinas Medical Centre (US) Before - 52 After - 80	Time to target temp following ROSC (primary outcome): No difference between groups Hospital survival, good neurological outcome (CPC 1 or 2) or survival at 1 year (secondary outcomes): No differences between groups	/
2016 Bernard (26) RINSE	Rapid infusion of up to 2L (30mls per kg) cold saline intra-arrest	Multicentre RCT Dec 2010 – Dec 2014	Melbourne, Adelaide and Perth, Australia Intervention group - 618 Non-intervention group - 580	Survival to discharge (primary outcome): 10.2% intervention vs. 11.4% non-intervention (p=0.51). No differences between groups when stratified by shockable status ROSC (secondary outcome): In shockable subgroup, 41.2% intervention vs. 50.6% non-intervention (p=0.03)	/

Type of association: + intervention confers benefit; / intervention does not confer benefit