


BMJ Open Automated mechanical cardiopulmonary resuscitation devices versus manual chest compressions in the treatment of cardiac arrest: protocol of a systematic review and meta-analysis comparing machine to human

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ABSTRACT

Introduction Cardiac arrest is a leading cause of death in industrialised countries. Cardiopulmonary resuscitation (CPR) guidelines follow the principles of closed chest compression as described for the first time in 1960. Mechanical CPR devices are designed to improve chest compression quality, thus considering the improvement of resuscitation outcomes. This protocol outlines a systematic review and meta-analysis methodology to assess trials investigating the therapeutic effect of automated mechanical CPR devices at the rate of return of spontaneous circulation, neurological state and secondary endpoints (including short-term and long-term survival, injuries and surrogate parameters for CPR quality) in comparison with manual chest compressions in adults with cardiac arrest.

Methods and analysis A sensitive search strategy will be employed in established bibliographic databases from inception until the date of search, followed by forward and backward reference searching. We will include randomised and quasi-randomised trials in qualitative analysis thus comparing mechanical to manual CPR. Studies reporting survival outcomes will be included in quantitative analysis. Two reviewers will assess independently publications using a predefined data collection form. Standardised tools will be used for data extraction, risks of bias and quality of evidence. If enough studies are identified for meta-analysis, the measures of association will be calculated by dint of bivariate random-effects models. Statistical heterogeneity will be evaluated by I^2 -statistics and explored through sensitivity analysis. By comprehensive subgroup analysis we intend to identify subpopulations who may benefit from mechanical or manual CPR techniques. The reporting follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Ethics and dissemination No ethical approval will be needed because data from previous studies will be retrieved and analysed. Most resuscitation studies are

Strengths and limitations of this study

- This systematic review and meta-analysis addresses gaps in the current evidence-base on chest compression techniques as part of cardiopulmonary resuscitation by providing a comprehensive assessment of randomised and quasi-randomised clinical trials, and comprehensive subgroup analysis.
- Extensive and differentiated multi-step search strategy including 12 databases without language restrictions.
- Methods follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols guidelines, Meta-Analysis Of Observational Studies in Epidemiology statement and Cochrane Handbook.
- This review is limited to randomised and quasi-randomised clinical trials of heterogeneous design and quality.
- Potential clarification which subpopulations, in which situations, under which circumstances, and at which time may benefit from which chest compression technique, may improve treatment decisions.

conducted under an emergency exception for informed consent. This publication contains data deriving from a dissertation project. We will disseminate the results through publication in a peer-reviewed journal and at scientific conferences.

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INTRODUCTION

For thousands of years, mankind has struggled to ‘re-animate’ people showing no signs of life. A milestone of cardiopulmonary resuscitation (CPR), manual closed-chest cardiac massage, was introduced in 1960.¹ More

recent developments are machines that perform chest compressions mechanically and automatically through inflatable vests, pistons or load distributing bands. But can automated mechanical chest compression devices surpass human performance, and again revolutionise CPR?

Rationale

Mechanical CPR may represent a method of improving compression quality in certain clinical scenarios and for chosen subpopulations. Many patients who suffer sudden cardiac arrest have the potential for recovery with good quality of life, but this recovery hinges on high quality CPR at the time of the event.²⁻⁴

Burden of disease

Sudden cardiac arrest following coronary heart disease is a major cause of death in industrialised nations with an age-related prevalence of 80–150 per 100 000 person years and mortality rates as high as 80%–90%. In about 10% of patients, sudden cardiac arrest following an acute myocardial infarction is the first manifestation of a (previously unknown) coronary heart disease. In younger patients, ion channel disease, hereditary cardiomyopathies and myocarditis are frequent causes of sudden cardiac arrest.²⁻⁹

Reflecting this special group, sudden cardiac arrest is a vast socioeconomic burden, as these patients are at the height of their careers. With the progress of modern medicine, even elderly or handicapped people have the potential to recover from an incident with a good quality of life. Beyond the vast social burden of losing lives, to the pure healthcare-related costs which are estimated US\$33 billion per year in the USA,¹⁰ losses of earnings and productivity have to be added in order to realise the costs across the entire society. Though, the burden of premature death in years of potential life lost is greater for sudden cardiac arrest than for all individual cancers and most other leading causes of death.¹¹

What is known?

Medical problem

CPR quality is important for resuscitation success. With manual CPR, increasing fatigue of the rescuers and frequent interruptions of compressions have been reported. Both fatigue and interruptions decrease blood flow required for adequate myocardial and brain perfusion which is crucial for return of spontaneous circulation (ROSC) and good neurological outcome. Compared with insufficiently performed chest compressions, chest compressions of good quality and with little interruptions have been shown to improve survival rates.¹²⁻¹⁴

The issues encountered by manual CPR led to the development of mechanical CPR systems which are supposed to improve CPR quality, an essential determinant of survival.^{14 15} Application studies have shown that by using mechanical CPR devices higher arterial carbon dioxide levels, which are an indicative of better tissue perfusion, can be achieved¹⁶⁻¹⁸ as well as better haemodynamic

conditions, thereby leading to improved coronary and cerebral blood flow.^{16 19-21} Furthermore, it has been stated that coronary and brain perfusion are the leading determinants of survival following resuscitation. Based on the premise that automated mechanical CPR provides a sustained quality of chest compressions, better outcomes might be expected from these devices.²²

A search in literature, carried out in a primary evaluation as a supplemental appraisal of a medical thesis, showed numerous studies of heterogeneous design, many of poor quality.^{22 23} Three high-quality, prospective, large, multicentre randomised controlled trials (RCTs) on mechanical CPR (Circulation Improving Resuscitation Care (CIRC),²⁴ LUCAS in Cardiac Arrest (LINC)²⁵ and Pre-Hospital Randomised Assessment of a Mechanical Compression Device in Cardiac Arrest (PARAMEDIC)²⁶) have been published, as well as several publications from retrospective registry analyses.^{22 27-30} They find inconsistent and contradictory results, leaving it unclear if manual or mechanical chest compressions during CPR may improve the outcome of patients suffering from cardiac arrest. Considered more in detail, we neither have evidence if there is a special point of time to instal a mechanical CPR device, nor if there are special situations or subgroups of patients who will particularly benefit from mechanical chest compressions. In particular, we do not know if one compression technique (vertical piston vs semi-circumferential load-distributing band) is superior.^{22 31}

Need for the systematic review

A recently published Cochrane Review shows several weaknesses³¹: most important, the intended subgroup analysis to distinguish vertical chest compressions by a piston from semi-circumferentially constricting compressions by a load-distributing band, and in-hospital from out-of-hospital cardiac arrest, was abandoned due to the variability of included trials. Therefore, this meta-analysis does not consider different treatments, which may have different or even contrary effects on the outcomes, which might increase between-trial heterogeneity unnecessarily.

Beyond the Cochrane review, several other meta-analyses of poor quality have been published. One review was sponsored by the manufacturer of a mechanical CPR device.³² As this study shows a superiority of the device produced by the sponsor of the review to the competitors' device, and to manual CPR, the reader should be aware of conflicts of interest by the authors affiliated with this company. This has been criticised, as 'industry sponsored meta-analyses are more likely to recommend an intervention'.³³ Moreover, this particular study examined ROSC only, but no long-term outcomes, and included both clinical and animal models. Possible conflicts of interest may also be considered if authors conducting the systematic review coauthored a trial which is included in the review, as they have to assess critically their own publications.^{24 26 34 35}

Another review provides an overview of existing systematic reviews and studies and comes to the conclusion that there are more studies needed for a definitive judgement.³⁶ Systematic reviews are at increased risk of selection and attrition bias and confounding when observational studies are included,³⁷ which applies to some reviews.^{22 32 35 38} Further reviews do not distinguish between different chest compression techniques in their meta-analysis, as described earlier,^{31 35 38 39} or only include one particular device.^{40–42} Respectively, others focus only on in-hospital⁴³ or out-of-hospital^{32 34 35 39 41 42} cardiac arrest.

Some reviewers only search Medline, the most important database, though under-representing publications indexed to other databases. As numerous European journals are indexed to EMBASE, this may have led to selection bias and an over-representation of American trials (or trials published in American journals). As two of the main competitors have been developed in the USA and in Europe, this search strategy may not be representative. Furthermore, we have to consider that there are fundamental differences between the American paramedic-based emergency medical service system and the physician-staffed systems as largely provided in European countries.^{32 36 44}

Adverse effects

Important adverse effects of mechanical CPR systems are injuries caused by chest compression. They comprise bone fractures (eg, ribs, sternum, vertebrae) and organ lacerations (eg, liver, spleen).⁴⁵ Injuries do not seem to be more frequent than those caused by manual chest compressions, but the pattern may differ.^{22 46 47} The installation of the device may delay the further CPR process and therefore delay life-saving measures like defibrillation and supporting measures like airway management or intravenous access.^{27 48–51} And last but not least, as it goes for any technical device, failures may occur.

Objectives

Patients

The objective of this systematic review and meta-analysis is to detect whether adults suffering from cardiac arrest, or specific subpopulations (setting urban vs rural, region, in-hospital vs out-of-hospital, and if applicable initially presented rhythm, aetiology and concomitant treatment) may benefit from the application of automated mechanical CPR devices.

Experimental intervention

Automated mechanical CPR devices deliver chest compressions independently of the user, either through vertical force by a piston, or through semi-circumferentially constricting force by a load-distributing band. So far, it is unknown if one compression technique might be superior. Mechanical CPR devices are also referred to as ‘automated CPR systems’ or ‘external cardiac compressors’.

Until the application of the mechanical CPR device, the patients may have received manual chest compressions as described later. To date, we still do not know if the timing of the application of the devices is of importance.

Control intervention

Conventional manual chest compressions follow valid recommendations. These guidelines are mandatory worldwide and they summarise all the evidence for treatment recommendations and describe the best clinical practice. Furthermore, manual chest compressions are generally available. Hence, manual CPR only is considered as the comparator.

Minimum requirements for conventional manual chest compressions include 100–120 vertical compressions per minute of approximately one-third of the sternum height, performed at the middle of chest (caudal third of sternum, intermammary line) in supine position.⁵²

Outcomes and prioritisation

ROSC is one of our primary outcomes. This common endpoint in resuscitation studies can be easily obtained and does not depend on a clinical follow-up. ROSC, which is measured as binary variable, is defined as any spontaneous pulse ‘detectable by manual palpation of a major artery’ at any time following resuscitation attempts.⁵³

The other primary outcome is the neurological state according to the Glasgow-Pittsburgh cerebral performance category (CPC),⁵⁴ or modified Rankin score (mRS)⁵⁵; the association between CPC and mRS is described elsewhere.⁵⁶ The neurological outcome is evaluated after 30 days, or at hospital discharge. If the CPC scores of 1 and 2 are only reported in a summarised form as an ‘intact’ or ‘good’ neurological outcome, they are treated as a binary event (‘good’ vs ‘poor’).⁵⁴ By way of derogation from our initial study registration, we consider neurologically intact survival as a primary outcome because of the essential importance of this outcome for the individual patients’ further lives.

Secondary outcomes include short-term and long-term survival, resuscitation trauma and CPR quality surrogates (table 1).

CPR quality surrogates may have an impact on patient survival, as fatigue and interruptions decrease the blood flow required for adequate myocardial and brain perfusion, which is crucial for a favourable neurological outcome.^{57 58} Compared with insufficiently performed chest compressions, high fractions of chest compressions have been shown to be associated with improved survival rates.^{14 59–61} Arterial blood pressure is used to describe haemodynamics, as it determines cerebral and coronary perfusion. End-tidal carbon dioxide (etCO₂) is considered a surrogate marker for induced cardiac output.

Primary and secondary outcomes are reported according to the ‘Utstein Style’, a protocol for uniform reporting of resuscitation outcomes,⁵³ and the ‘Core Outcome Set for Cardiac Arrest’,⁶² based in parts of previous reviews.

Table 1 Secondary outcomes

Domain	Secondary outcome
Short-term survival	<ul style="list-style-type: none"> ▶ Alive at hospital admission. ▶ Alive ≤30 days after incident. ▶ Alive at hospital discharge.
Long-term survival	<ul style="list-style-type: none"> ▶ Alive 3, 6 and 12 months after incident. ▶ Health-related quality of life⁶² at each time point. ▶ Neurological state^{54–56} at each time point.
Resuscitation trauma	<ul style="list-style-type: none"> ▶ Frequency of injuries and trauma caused by chest compressions (including skin lesions, skeletal fractures, pulmonary lesions, pneumothorax, haemothorax, haemoperitoneum, organ lacerations).
CPR quality surrogates	<ul style="list-style-type: none"> ▶ Guideline compliance (including chest compression depth, frequency, rate, ratio). ▶ No-flow (hands-off) time and ratio. ▶ Arterial blood pressure during chest compressions. ▶ End-tidal carbon dioxide partial pressure with ongoing CPR.

CPR, cardiopulmonary resuscitation.

Review questions

The review of studies is designed to address the following questions:

- ▶ Is a specific CPR technique, manual or mechanical (by band or piston as subgroups) associated with an improved primary or secondary outcome, as stated earlier?
- ▶ May automated mechanical CPR devices improve the process, quality and safety of CPR?
- ▶ What are possible scopes of application for automated mechanical CPR devices? This question seeks to ascertain which patient subgroups in which situations, under which circumstances, and at which time may benefit from automated mechanical CPR.

METHODS AND ANALYSIS

We registered this study at the International Prospective Register of Systematic Reviews. The reporting of this protocol accords to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement.⁶³ The PRISMA-P checklist is provided as an online supplemental file 1. We will follow both Cochrane Handbook⁶⁴ and Meta-Analysis Of Observational Studies in Epidemiology statement.⁶⁵

Eligibility criteria

Study characteristics

Eligible for inclusion will be RCTs and quasi-RCTs comparing mechanical to manual chest compressions in cardiac arrest if at least one primary endpoint or other survival outcome is available. In this context, state (published, accepted for publication or preprint) and mode of publication (full article or conference abstract) will be irrelevant. Studies will only be eligible for inclusion if the data for the control group is published.

Population characteristics and setting

We will only include studies in adult patients (≥18 years of age), as most mechanical CPR devices are not approved for children. We will consider events as ‘in-hospital’ if the

cardiac arrest occurs to a hospitalised patient and if the Medical Emergency Team of the institution is activated. Events treated by official Emergency Medical Services outside hospital buildings will be considered as ‘out-of-hospital’. Both settings, in-hospital and out-of-hospital cardiac arrest, will be eligible for inclusion.

Device characteristics

All mechanical CPR devices that deliver automated chest compressions will be included in the systematic review to gain comprehensive insight into the topic and to avoid selection bias. We identified available devices by a preliminary study^{22 23} and subsequent search via the internet. The devices may compress the chest independently of the user, either through vertical force (applied by a piston) or semi-circumferentially constricting force (applied by a load-distributing band). However, we will conduct subgroup analysis for each compression technique. Technical characteristics differ for each device (table 2).²²

Before the first application of the automated CPR device, patients may receive manual chest compressions as described earlier.

Exclusion criteria

Case series, case–control studies or historically controlled studies will be excluded, as well as studies involving traumatic cardiac arrest, as treatment priorities fundamentally differ from non-traumatic entities. We expect this study population to represent patients suffering from sudden cardiac arrest, which is predominantly a cardiac aetiology.

We will not apply any restrictions on manufacturer, model, technique or publication language.

Information sources

We will consider relevant bibliographic databases, as listed in box 1, from inception until the date of search and document the date of our last access on the search engine.

Table 2 Specifications of automated mechanical CPR devices

Device	AutoPulse	LUCAS 3	LifeStat1008	Corpuls CPR	LifeLine ARM	Easy Pulse	MCC Mini Chest Compressor	X-CPR 2
Manufacturer	Zoll Medical, Chelmsford, USA (prior: Revivant)	Stryker, Kalamazoo, USA (prior: Physio-Control, Jolife)	Michigan Instruments, Grand Rapids, USA	GS Elektromedizinische Geräte G. Stemple, Kaufering, Germany	Defibtech, Guilford, USA	Schiller, Baar, Switzerland	Resuscitation International, Scottsdale, USA	CU Medical Systems, Wonju, Korea (prior: Healthwell Medical)
Technique	Semi-circumferentially constricting load distributing band, electric driven	Piston, electric driven	Piston and ventilator, pneumatic driven	Piston, electric driven	Piston, electric driven	Piston, electric driven, non-constricting band	Piston, pneumatic driven, non-constricting band	Piston with semi-circumferentially constricting thoracic strap, electric driven
Compression depth	20% of thorax diameter +0.6/−1.3cm	5.3±0.2cm (4.0–5.3cm for sternum height <18.5cm)	0.0–8.0cm (adjustable)	2.0–6.0cm (adjustable)	5.3±0.3cm	4.0–5.2cm (adjusted for chest circumference or width)	3.8 or 5.1cm (selectable)	(No information provided)
Compression rate	80±5/min	102±2/min	100±6/min	80–120/min (adjustable)	101±1/min	100/min	110±22/min	(No information provided)
Compression/ventilation ratio (c/v)	30:2, 15:2, or continuous compression (selectable)	30:2 or continuous compression (selectable)	30:2 or continuous compression (selectable)	30:2, 15:2, or continuous compression (selectable)	30:2 or continuous compression (selectable), updates possible	30:2 or continuous compression (6selectable)	Continuous compression	(No information provided)
Patient specifications	chest circumference 76–130cm chest width 25–38cm weight ≤136kg	Sternum height 17–30cm chest width ≤45cm	Sternum height 11–37cm chest width ≤56cm	Sternum height 34cm chest width ≤48cm	Sternum height 17–30cm chest width ≤46cm	Chest circumference 76–135cm chest width 22–40cm	Chest circumference 78–130cm	(No information provided)
Device size	83×45×8cm+load-distributing band and battery	58×33×26cm (stowed) 56×52×24cm (assembled)	57×46×19cm (assembled)	45×43×9cm+board (different sizes)	51×51×25cm (stowed) 60×53×23cm (assembled)	18×22×15cm	20×16×15cm+band	(No information provided)
Device weight	11.6kg including battery	8.0kg including battery plus straps	8.9kg plus gas supply	5.5kg including battery plus board (1.7–2.1kg)	7.1kg including battery	3.5kg plus belt with slider (0.3kg)	2.0kg plus gas supply	(No information provided)
Average consumption	Battery run-time~30min	Battery run-time~45min, external power supply	≤45L/min compressed gas	Battery run-time~90min, rechargeable during use	Battery run-time~60min	Battery run-time~45min, external power supply	60±5L/min compressed gas	(No information provided)

Continued

Table 2 Continued

Device	AutoPulse	LUCAS 3	LifeStat1008	Corpuls CPR	LifeLine ARM	Easy Pulse	MCC Mini Chest Compressor	X-CPR 2
Features	Event recorder	Report generator	n/a	Memory card interface	n/a	Computer interface	n/a	n/a
Forerunner models	Vest CPR: inflatable vest, pneumatic driven, circumferential pressure 200–280 mm Hg, compression rate 60/min	LUCAS: Report generator, pneumatic driven piston, continuous compressions LUCAS 2: electric driven piston, c/v 30:2 or continuous compressions	Thumper (under licence for Europe: Siemens Sirepuls): model 1001, 1002, 1007CC: no ventilator, continuous compressions 1003, 1004, 1005, 1007, 1007CCV: c/v 5:1 or continuous compressions	n/a	n/a	n/a	n/a	X-CPR (SST-CPR), pneumatic driven piston and strap currently not selling in Europe and the USA currently not selling

Specifications according to manufacturer information. CPR, cardiopulmonary resuscitation; c/v, compression/ventilation ratio; n/a, not applicable.

Box 1 Searched databases
Journals@Ovid Full Text
Your Journals@Ovid
EBM reviews

- ▶ Cochrane Database of Systematic Reviews.
- ▶ ACP Journal Club.
- ▶ Database of Abstracts of Reviews of Effects.
- ▶ Cochrane Central Register of Controlled Trials.
- ▶ Cochrane Methodology Register.
- ▶ Health Technology Assessment.
- ▶ NHS Economic Evaluation Database.

BIOSIS Previews
Embase
Ovid MEDLINE

- ▶ In-process and other non-indexed citations.
- ▶ Daily update.

ACP, American College of Physicians; EBM, evidence-based medicine; NHS, National Health Service.

Search strategy and study selection
Search strategy

Our search strategy will comprise several steps: we will start with a combined, structured and keyword-based search containing search terms in the field of CPR, and the names of devices and techniques, as presented in [table 3](#). Backward reference searching may identify further literature eligible for inclusion by analysing the reference sections of the articles found by our search strategy. Forward reference searching will be executed to identify additional relevant studies that cite a study included. Pertinent study registries will be searched via the WHO International Clinical Trials Registry Platform (<http://apps.who.int/trialsearch>) for trials, which have been registered, but not published. Finally, we will ask manufacturers of mechanical CPR devices for unpublished data, and we will assess preprint servers and data repositories.

For literature search, we will use the proprietary search engine Ovid, Ovid Technologies, Wolters Kluwer Health, New York/USA.

Study selection

We will start by screening both the title and the abstract of the publications identified through our search for eligibility. If the study meets any inclusion but no exclusion criteria, we will assess the full text in order to extract study characteristics, results and risks of bias, as stated later.

Through our search strategy ([table 3](#)), duplicates will automatically be removed. Nevertheless, additional duplicates may occur if results of one study are published in several manuscripts with different titles, in different languages, or different modes of publication. We will regard publications as duplicates if the same authors, or

Table 3 Keyword-based search

#	Search item
1	mechanical chest compressors
2	mechanical CPR device
3	chest compression device
4	mechanical cardiopulmonary resuscitation
5	vest CPR
6	Thumper
7	AutoPulse
8	Lund University Cardiac Assist System
9	LUCAS-2 or LUCAS2 or LUCAS-3 or LUCAS3
10	LifeStat or Life-Stat
11	Miniaturized Chest Compressor
12	Animax
13	Corpuls CPR
14	LifeLinie ARM
15	EasyPulse
16	X-CPR
17	load distributing band
18	mechanical piston
19	resuscitation/ or resuscitator/ or advanced life support
20	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
21	19 and 20
22	remove duplicates from 21

Multiple entries are feasible. A slash indicates Medical Subject Headings terms.

CPR, cardiopulmonary resuscitation.

authors from the same centres, publish studies covering the same observation period, with comparable case numbers, similar design and related study objectives. In case of redundant publication, we will prefer full texts to abstracts, and we will merge the published data.

Study records
Data management

The characteristics and results of the studies included will be extracted and summarised in a table (Numbers V.10.3.9, Apple, Cupertino/USA). If eligible, frequencies of primary and secondary outcomes will be charted in forest plots (Review Manager V.5.3, The Nordic Cochrane Centre, Copenhagen/Denmark).

Selection process and collection of data

Study selection, quality assessment and data extraction will be performed independently by two reviewers, one of whom with clinical experience in resuscitation and one with methodological experience. Possible disagreements and discrepancies will be resolved by consensus or by consulting a third reviewer.

Table 4 Data extraction

Domain	Data items
Unambiguous study identification	<ul style="list-style-type: none"> ▶ Authors (up to three), year, title, journal or other source, volume, page(s). ▶ Identification as conference abstract, or research letter, if applicable. ▶ Identification number within a study registry, if applicable.
Study design	<ul style="list-style-type: none"> ▶ Study type. ▶ Chronological dimension (prospective, retrospective). ▶ Number of study centres (single-centre for 1; multi-centre for ≥5 centres). ▶ Characteristics of patients included. ▶ Type of intervention(s). ▶ Case number in total, distributed among intervention and control groups, and subgroups if applicable. ▶ Mechanical CPR system(s) examined. ▶ Guidelines version the study is based on.
Results	<ul style="list-style-type: none"> ▶ Qualitative summary. ▶ Quantitative summary.
Risks of bias	<ul style="list-style-type: none"> ▶ Risks of bias according to the Cochrane tool. ▶ Funding sources. ▶ Conflicts of interest.

Data collected from included studies.
CPR, cardiopulmonary resuscitation.

We will contact the corresponding authors of included studies to obtain key missing data as needed, or to clarify any issues and questions on a particular trial. If authors do not respond within 2 weeks, we will contact the corresponding author again, as well as first and senior authors. If this does not lead to an elaboration of the issue, we will exclude any outcomes whose context cannot be clarified from further analysis. We will only include results in our meta-analysis if their origin is transparent and accurate.

Data items

Data will be extracted by using a predefined data collection form according to the Cochrane Collaboration recommendations ([table 4](#)).⁶⁶

Assumptions and simplifications

Cardiac arrest is defined as the absence of cardiovascular circulation. This condition may be validated by evaluating signs of life, palpation of pulse of a major artery or invasive blood pressure measurement.

Some authors indicate piston-driven mechanical chest compressions as ‘manual CPR’, particularly when comparing them to compressions by a load-distributing band. Regardless of the denomination chosen by the authors, we will only consider chest compressions delivered by hand as ‘manual CPR’.

ROSC may be defined differently in studies with regard to the time of its evaluation (at any time, at specific time-points or at hospital handover). According to the Utstein definition cited above, we will only consider reportings of ‘ROSC at any time’ as our primary outcome ‘ROSC’. Reportings of ‘ROSC at hospital handover’ will be considered as secondary outcome ‘alive at hospital admission’.

If the underlying guideline is not stated within the text, we will collate the trial to the recommendations which were valid as per period of study.

In some publications, ‘hands-off time’ (in seconds) or ‘hands-off ratio’ (in percentage of ‘hands-on’ or compression time) may be indicated in lieu of ‘no-flow time’ (in seconds).

Risk of bias in individual studies

For each included RCT, we will follow Cochrane Risk of Bias tool, which is the standard tool for assessing risks of bias in RCTs.⁶⁴ Each of the following potential sources of bias will be evaluated where applicable:

- ▶ Random sequence generation.
- ▶ Allocation concealment.
- ▶ Blinding of participants and personnel.
- ▶ Blinding of outcome assessment.
- ▶ Incomplete outcome data.
- ▶ Selective outcome reporting.
- ▶ Other bias (including baseline imbalance, early termination of the trial, funding bias, etc).

Each will be graded as ‘high’, ‘low’ or ‘unclear’, and a justification for the judgement will be presented in the risk of bias table.

We will assess the risk of bias for included quasi-RCT with Cochrane Risk Of Bias in Non-randomized Studies - of Interventions (ROBINS-I) tool.⁶⁷ The following categories will be evaluated at study level:

- ▶ Confounding.
- ▶ Selection of participants into the study.
- ▶ Classification of interventions.
- ▶ Deviations from intended interventions.
- ▶ Missing data.
- ▶ Measurement of outcomes.

► Selection of the reported result.

Each domain will be categorised ‘critical’, ‘serious’, ‘moderate’, ‘low’ risk of bias or ‘no information’. We will also present the justification of the judgement in the risk of bias table. The overall risk of bias for one outcome of quasi-RCT will be determined by the highest risk of bias rating of the particular item.

Data synthesis and analysis

Statistical analytics

For dichotomous outcomes (primary and secondary outcomes), OR with its 95% CI will be used as effect measure per trial. In binary outcomes where rare or 0 events are expected in some trial-arms (ie, some of the secondary outcomes as trauma), the Peto OR will be used to avoid the necessity of a continuity correction. As the Peto OR is only suitable for rare events,⁶⁴ conventional OR will be used for all other binary outcomes. If possible, the OR and its SE will be extracted directly, preferably from an adjusted model. If the adjusted OR is not reported, the unadjusted OR along with its SE will be obtained when the events and numbers of patients per intervention group are available. For continuous outcomes, the standardised mean difference (SMD) with its 95% CI will be used as effect measure per trial. For survival outcomes, (adjusted) HR estimated in Cox regression models will be used if reported. Results extracted from log-rank tests, Kaplan-Meier curves or reported Kaplan-Meier estimates will be used as alternatives. If neither Cox-regression nor Kaplan-Meier estimators are reported, survival outcomes will be extracted as dichotomous outcome. ORs will be combined by using the Mantel-Haenszel method, and SMDs will be pooled by the inverse-variance method. Effect measures will be combined separated by study design (RCT and quasi-RCT).⁶⁴ Random-effects models will be used to account for the expected between-trial heterogeneity by estimating the overall effect, and the Hartung-Knapp method will be applied to the corresponding CI if at least five trials contribute information to an estimate.⁶⁸ Results of fixed-effects models will be provided and discussed in contrast to the results of the random-effects models. We will investigate all results for statistical heterogeneity by I^2 -statistics and by interpreting them in relation to the estimated between-trial variance τ^2 . If there is a considerable heterogeneity ($I^2 \geq 75\%$), no meta-analysis will be performed.

R V.3.5.0 or higher (R Foundation for Statistical Computing, Vienna, Austria) and the R meta package V.4.9–5 or higher (developed by Guido Schwarzer) will be used for all statistical analyses. For generating diagrams, we will use Review Manager, V.5.2.7 (The Nordic Cochrane Centre, Copenhagen, Denmark).

Meta-bias

We will perform a statistical investigation of potential publication bias based on a test of funnel plot asymmetry, if there have been at least 10 studies pooled for one outcome. Sensitivity analyses will be conducted with

regard to the quality of studies. Further sensitivity analyses will be performed during the course of the review, if irregularities of individual studies are found. We will set up ‘summary of findings’ as recommended by Cochrane Collaboration.^{64 66}

In order to detect reporting bias, we will compare the data reported in publications with a priori study protocols, or registrations.

Confidence in cumulative evidence

The quality of evidence will be analysed by using GRADEpro GDT (Guideline Development Tool, Grade Working Group, McMaster University and Evidence Prime, Hamilton, Canada). Grading of Recommendations Assessment, Development and Evaluation (GRADE) is an accepted tool for quality assessment and is used to grade the body of evidence at outcome level.⁶⁹

Interventions

Titles and/or abstracts of studies retrieved from the search and those from additional sources after tracing reference sections will be screened to identify studies which possibly meet the inclusion criteria. The full text of those potentially eligible studies will be retrieved and assessed for eligibility. We will use a standardised questionnaire to extract data from the included studies for assessment of study quality and evidence synthesis.

Qualitative synthesis

We will provide a narrative synthesis of the findings from the studies included, which will be structured around the mechanical chest compression techniques, and we will summarise study characteristics by including risks of bias and outcomes, in tables.

Quantitative synthesis

Whenever possible, we will provide summaries of the intervention effects by using the effect measures along with their 95% CI and p values for each trial and for the combined effect. The results will be graphically illustrated by forest plots.

Subgroups

We plan subgroup analyses for both techniques of mechanical chest compression (semi-circumferentially constricting load-distributing band vs vertically compressing piston), for the setting (in-hospital vs out-of-hospital, urban vs rural, and Europe vs the USA vs other regions) as well as for the initially presented rhythm (shockable vs non-shockable). If applicable, we will perform subgroup analysis of aetiology and concomitant treatment.

Heterogeneity

All results will be investigated for statistical heterogeneity by I^2 -statistics and by between-trial variance τ^2 .⁷⁰ If there is a considerable heterogeneity ($I^2 \geq 75\%$) for an outcome, no meta-analysis will be performed.

Sensitivity analysis will be performed to identify scenarios (like non-compliance, protocol violations, missing data, outcome definitions, clustering or correlation, competing risks, baseline imbalance, distributional assumptions or outliers) which influence the findings of the review.⁷¹ Results of sensitivity analysis will be presented together with the study assessment sheets.

Amendments

Any protocol amendment will be stated with reason in the Methods section of the subsequent publications.

Patient and public involvement

Patients and the public have not been involved in this protocol of a systematic review and meta-analysis. By defining neurologically intact survival as primary outcome, we will put our focus on the outcome which is most important to the patient. This topic is of specific interest to our patients, because the quality of CPR in general and the quality of chest compressions in particular will determine their abilities or disabilities, and their quality of life after the incident (ie, the 'neurological outcome'). Unfortunately, this constitutes an endpoint which is not easy to assess and therefore is uncommon in resuscitation studies.

ETHICS AND DISSEMINATION

No further ethical approval is needed as data from previous studies, whose authors declared clearance by the responsible ethics commissions, will be retrieved and analysed.

As resuscitation studies are conducted under an emergency, they cannot meet the demand of informed consent, which is an important issue laid down in the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.⁷² Though, these studies regularly use an emergency exception to the need for informed consent.^{73–76} In particular with regard to this predicament, the implementation of ethical considerations in resuscitation studies has to be assessed critically.

This publication contains data deriving from a preliminary project which was part of a doctoral thesis at Ulm University.^{22 23}

After the completion of this meta-analysis, we intend to prepare a manuscript for publication in an international peer-reviewed journal and to present the results at scientific conferences. Our scheduled timeline is detailed in [table 5](#).

DISCUSSION

A primary evaluation of this project identified 107 trials on 179505 patients, 444 pigs, 62 dogs and 723 manikin scenarios comparing mechanical to manual CPR. This evaluation did not meet established quality criteria of a systematic review, but we were able to become aware of the issues related to mechanical chest compressions and current evidence.^{22 23}

Several systematic reviews and meta-analyses of heterogeneous design and quality compare outcome rates following manual and mechanical CPR, with their limitations previously mentioned.^{22 31 32 34 35 38–44} A carefully performed Bayesian network meta-analysis by Khan and colleagues compares manually operated chest compressions with different mechanical chest compression techniques, but misses the opportunity to get a deeper insight into specific subgroups.⁷⁷ Traditionally, resuscitation studies assess effects of interventions in overall patient collectives on survival rates in order to answer the question if an intervention is superior to its control. However, this assumes a similar effect of the same intervention in heterogeneous patients and under varying circumstances. Up to now, only a few findings contribute to solving the clinical problem: if an individual patient may profit from mechanical chest compressions and if the team should strive for the application of an automated mechanical CPR device on a specific occasion. This implies the need of a review which may close this gap in knowledge by putting its focus on the identification of carefully selected subgroups concerning patient characteristics, settings,

Table 5 Timeline

Task/duration (months)	1	2	3	4	5	6	7	8	9	10
Study design and drafting the manuscript for the study protocol	█									
Critical revision by collaborators		█								
Publication phase (study protocol), possibly revisions/resubmissions			█							
Study assessment (reviewer #1) study assessment (reviewer #2)				█						
Revision of judgements, forging consensus for discrepancies					█					
Data extraction (reviewer #1) data extraction (reviewer #2)						█				
Qualitative and quantitative synthesis (meta-analyses)							█			
Drafting the manuscripts for publication and presentations								█		
Critical revision by collaborators									█	
Publication phase (meta-analysis), possibly revisions/resubmissions										█

Scheduled duration of the systematic review and meta-analysis in months.

situations, environments and circumstances when automated mechanical chest compressions are superior to manual CPR.

Mechanical CPR devices are considered potential advanced life support adjuvants in a public draft of the upcoming guidelines on CPR. While guidelines do not support the routine use of these devices, they state several special circumstances when mechanical chest compressions may be considered (issues such as quality, safety, feasibility and practicability). But the recommendations do not make it clear when mechanical CPR should be considered, that is for which patients, in which situations, or at which point of time.⁷⁸

Strengths and limitations

When comparing mechanical to manual CPR, several confounders may influence the patients' outcome, which in their entirety are complex to detect. Any prospective study may be subject to a Hawthorne-like effect, when individuals (in this case, emergency or critical care teams) show a different behaviour due to the knowledge that they participate in a study leading to performance bias in or between intervention and control groups. The first automated CPR systems have been developed just shortly after the description of manual chest compression in the 1960s.⁷⁹ Therefore, studies of over half a century will have to be assessed, and guideline revisions will have to be considered in the meantime. On the other hand, it is yet to determine to what extent study designs comply with particular recommendations.

Publication bias is a common problem in evidence-based medicine, as only studies may be assessed if the authors are aware of their existence. In order to reduce publication bias, we will ask stakeholders for unpublished data, but the risk of publication bias will depend on their cooperativeness.

Conference abstracts are typically subject to word limits, impairing the possibility of responding to all aspects of study design and conduction in a short text. To prevent bias due to the lack of information in abstracts, we will ask the authors for additional information. As mentioned earlier, the prevention of bias will require their cooperativeness.

The reliability of this review may be affected by heterogeneous design and quality of the studies included. Through our previous work, we have become aware of a variability in individual patient characteristics, treatment performance, timing of the installation of devices and outcome definitions in studies of automated mechanical CPR.

By including quasi-RCT, risks of bias in random sequence generation, blinding and allocation concealment must be considered. It is generally difficult to assign allocation concealment to an intervention like mechanical chest compression, even in randomised studies. The blinding of rescuers is impossible due to the intervention, but patients may be considered blinded because they are

unconscious. Though, with predictable risks, we decided to include quasi-RCT in our review.

Surrogate outcomes like ROSC or survival rate until hospital admission are easier to obtain than 'hard' clinical outcomes which require considerable resources for study design, funding, recruitment, conduction and follow-up. But patients are interested neither in survival rates nor in rates of ROSC—the relevant outcome from our patients' point of view is at which neurological state they may survive. Hence, neurologically intact survival should be considered as a matter of most particular interest.

The most important strength of this systematic review and meta-analysis will be the subgroup analyses of automated mechanical chest compression techniques, setting, region, initially presented rhythm, aetiology and concomitant treatment. This is of clinical relevance with regard to increasing treatment options in hospital, where automated mechanical CPR devices might provide a 'bridge' to definitive treatment for designated patient groups under certain conditions and in specific environments. We hope that this systematic review and meta-analysis may contribute to implicate future clinical and scientific issues towards an individualised decision-making.

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