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Early point-of-care focused echocardiographic asystole as a predictive factor for absence of return of spontaneous circulatory in out-of-hospital cardiac arrests : prospective multicenter observational study

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21

Abstract

Introduction

Out-of-hospital cardiac arrests (OHCA) are a major cause of mortality in France. Their management is performed by a particular prehospital system based on medicalisation of both ambulance dispatch and mobile intensive care units. It follows the European recommendations which advocate for the use of early point-of-care focused echocardiography (EPOCE) in particular to identify reversible causes of OHCA. Another ability of EPOCE is to predict the absence of return of spontaneous circulation (ROSC) in cases of absence of cardiac motion.

Methods

The ACE trial aims to assess the positive predictive value of absence of cardiac motion viewed with early EPOCE on the absence of ROSC. It is a prospective multicentre (n=8) prognosis study which will recruit a large sample of patients (n=624). Briefly, once the diagnosis of OHCA done and advanced life-support (ALS) initiated, an EPOCE will be performed during the defibrillator's analysis period. The physician will notice cardiac motion or lack and will look for a curable etiology. ALS will be terminated following ERC rules, the EPOCE results will not be used for that purpose. ROSC will be assessed after ALS termination.

Analysis

Primary endpoint is the positive predictive value of the absence of cardiac motion on the absence of ROSC. Secondary endpoints are predictive characteristics of EPOCE on morbimortality 30 days after OHCA, description of curable etiologies, analysis of EPOCE technique.

Ethic

ACE was approved by an ethical committee (2018-AO1491-54)

Dissemination

While ACE is adapted to the French prehospital system, its results will be translatable to other organisations. Actually, where ever the place where cardiac arrest is managed, the prognostic value of EPOCE on absence of ROSC will be the same.

Trial status

ACE has received a grant from the French Minister for Health, was registered in clinicaltrials.gov (RC17_0464) on April 11, 2018

Keywords :

Cardiac arrest, prognosis, cardiac ultrasound

Strength and limitations of the study

- First prospective multicentre prognosis study of Point-of-care Ultrasound in out-of-hospital cardiac arrest
- positive predictive value of early Point-of-care ultrasound absence of cardiac motion on absence of return of spontaneous circulation
- if positive, might allow for shorter delays before extracorporeal membrane oxygenation or organ donation processes

Introduction

Out-of-hospital cardiac arrests (OHCA) are a major cause of mortality in France (between 30,000 and 50,000 cases per year) [1][2]. The prognosis is particularly poor, since only 5 to 6% of patients will leave the hospital alive with satisfying neurological condition [2, 3, 4]. Their management in France is performed by a particular prehospital system based on medicalisation of both ambulance dispatch (SAMU) and mobile intensive care units (SMUR). It follows the European recommendations (cardiac massage, ventilation, cardiac rhythm analysis, drugs administration, and defibrillation if needed) [4, 5]. Based on published studies [5, 6, 7], 2015 European recommendations advocate for the use of point-of-care focused echocardiography (POCE) in emergency medicine, in particular to identify reversible causes of OHCA [4, 5]. Indeed, POCE can reveal various curable aetiologies such as tamponade, massive pulmonary embolism, deep hypovolaemia, or suffocating pneumothorax [5, 6]. Their identification allows the clinician to better adjust his therapeutic strategy and, accordingly, might improve the patient's prognosis.

Another ability of POCE is to predict the absence of return of spontaneous circulation (ROSC) in cases of absence of cardiac motion. Several studies found a strong correlation between absence of cardiac motion and absence of ROSC [6] [7], [8], [9], [10], [11]. This fact deeply impacts extracorporeal circulation indications and organ donation procedures. However, these studies, mainly performed in a hospital setting, included rather small populations and used different cardiac motion definitions and procedures. Furthermore, they cannot be extrapolated to OHCA because of differences in terms of delays, management, and

environment. In this context, the European Resuscitation Council (ERC) stated in 2015 that, while the absence of cardiac motion is highly predictive of death, sensitivity and specificity have not been reported. Thus, usage of this ascertainment for determination of premature termination of resuscitation is currently not recommended until publication of a pivotal study.

Methods and analysis

Objectives

The ACE French national trial fits precisely into this bibliographic gap. Our objectives are multiple:

- The main objective is to assess the positive predictive value of early POCE (EPOCE; i.e. < 12 min after initiation of advanced life support (ALS)) on the absence of ROSC
- Secondary objectives are:
    1. assess the prognostic value of early POCE on survival at hospital admission and on morbi-mortality at Day 30 after the OHCA (D30),
    2. assess prognostic performances of early POCE on the absence of ROSC,
    3. assess prognostic values of EPOCE according to timing of realisation,
    4. assess the relationship between EPOCE findings and ECG rhythms,
    5. describe frequency and typology of curable aetiologies in the context of OHCA,
    6. describe EPOCE characteristics: timing, quality assessed by the operator, and by an expert committee,
    7. assess prognostic performances of EPOCE in patients with ventricular tachycardia,

8. creation of a multifactorial score with EPOCE combined with other clinical parameters (composite prognostic tool combining myocardial and/or electrical activity, capnography, no/low flow duration, and clinical profile including sex and age on the absence of ROSC, and

9. measurement of the cardiac massage interruption associated with EPOCE realisation by video recording in three centres (Nantes, La Roche-sur-Yon, Bobigny).

Design

ACE was designed as a prospective, multicentre prognosis study. It is based on rigorous methodology, has a high proof-level design, and will recruit a large sample of patients (*n* = 624). Recruiting centres include both rural and urban community and university hospitals. This pragmatic approach intends to validate the performance of EPOCE for the prediction of absence of ROSC in cases of absence of cardiac motion in the out-of-hospital setting. If this hypothesis is validated, it will allow for shorter delays before extracorporeal membrane oxygenation (ECMO) or organ donation processes.

Echographic asystole is defined by the complete absence of cardiac motion (coordinated or fibrillation) and the absence of valve movements.

Methods

Patients

Inclusion criteria: patients > 18 years old presenting with an OHCA for whom an EPOCE was performed.

Non-inclusion criteria: do not resuscitate order, ALS not performed by the prehospital team, pregnancy, breastfeeding women, and inmates.

Procedure

After verification of inclusion and exclusion criteria, advanced life support intervention will replace basic life support with an overlap period, as usual. ALS will be performed according to the latest ERC regulations. Once standard ALS interventions are done, according to the focused echocardiographic evaluation in life support (FEEL) protocol and ERC recommendations [4, 5], the physician will perform a POCE during the defibrillator's analysis period, thus in less than 10 seconds. It will be done using a phased array probe with a subcostal view. It has to be done as early as possible and always before 12 min after ALS initiation. The physician will notice cardiac motion or lack thereof and will look for curable aetiologies. Video clips will be stored in the echographic device and secondarily uploaded in the electronic case report file (eCRF) for random reviewing by an expert committee. The whole ALS procedure will be closely monitored in order to assess diagnostic and therapeutic delays. ALS will be terminated following ERC rules, the POCE results will not be used for that purpose. Presence or absence of ROCS will be assessed after ALS termination. In the case of ROCS, the hospital pathway will be described. At D30, vital status of all patients will be assessed by either hospital file consult or phone call if the patient is still alive. For them, autonomy will be assessed using the Glasgow Outcome Scale.

Endpoints

Primary endpoint

- Predictive prognostic value (PPV) of EPOCE asystole (i.e. within the first 12 min of ALS initiation) on resuscitation failure (absence of ROSC). We have chosen the predictive positive value (PPV) as the primary endpoint because we wish to limit the number of false positives as much as possible in order to isolate a population without ROCS with POCE asystole.

Secondary endpoints

1. Predictive prognostic value of EPOCE asystole (i.e. within the first 12 min of ALS initiation) on hospital admission and on morbimortality evaluated at 30 days.
2. Sensitivity, specificity, and positive (PPV) and negative predictive (NPV) values of EPOCE asystole on absence of ROSC.
3. Sensitivity, specificity, and positive and negative predictive values of EPOCE asystole on absence of ROSC according to their timing of realisation after ALS initiation on the absence of ROSC (by 2 min).
4. Patterns between ultrasound diagnosis (systole vs asystole) and electrocardiogram electrical activity (pulseless activity, asystole, ventricular fibrillation, and ventricular tachycardia).
5. Description of curable aetiologies, diagnostic and therapeutic delays, and the effectiveness of implemented curative strategies on ROCS and 30 day morbimortality.
6. Analysis of EPOCE technique during OHCA resuscitation: duration, quality of the video clips assessed by the operator (from 0 = impossible to 10 = excellent), and an expert committee reviewing a 10% random sample.
7. Sensitivity, specificity, and positive and negative predictive values of EPOCE asystole to predict ROSC absence in patients with ventricular fibrillation.

8. Main determinants of death (age, sex, comorbidities, suspected aetiology, no/low flow duration, initial treatment, electrical activity, and cardiac motion) associated with the absence of ROSC in order to determine a score with a 100% PPV.
9. Measure of duration of cardiac massage interruption in seconds during EPOCE, using a portable video recorder (three centres: Nantes, La Roche-sur-Yon, and Bobigny).

Recruiting centres

Recruiting centres will be university hospitals (Nantes, Brest, Tours, Angers, and Bobigny) and community hospitals (Saint-Nazaire, La Roche-sur-Yon, and Chateaubriant).

Sample size calculation

The principal objective is the PPV of absence of cardiac motion (asystole) for the absence of ROSC. For a PPV of 95 ± 3%, 203 patients without cardiac motion are required. Based on 37.5% asystole rate [10], 542 total patients are required. Taking into account a 15% attrition rate, the required population will, finally, be 624 patients.

Recruitment

Chosen prehospital teams were recruited because they are highly skilled in clinical ultrasound and already use this technique in their emergency department. A monthly newsletter will be published with individual and global recruitment trends. Patients will be followed-up until day 30 and defined gradually as: survival without neurological deficit, survival with neurological deficit, or death.

Data management

Electronic case report files will be used via a web-based interface and video clips will be uploaded. All data will be stored in the Nantes University Hospital secured databases. The data management team will be responsible for the entire process. Data will be anonymised with an incremental number assigned to each patient. The final database will be only available to the steering committee.

Monitoring

Monitoring will be performed both by electronic surveillance of recruitment and data quality. It will be done by the Clinical Research Department of Nantes University Hospital.

Statistical analysis

Sensibility, specificity, PPV, NPV, and likelihood ratio of EPOCE asystole on resuscitation failure (absence of ROSC) and on morbimortality will be estimated with 95% confidence interval. Logistic model regression and receiver operating characteristic (ROC) curve will be estimated to analyse the time of EPOCE realisation that allows the best prognostic performances on the absence of ROSC. Chi-squared and Fisher's test will be used to analyse the association between ultrasound diagnosis and electrocardiogram electrical patterns. Curable aetiologies, diagnostic and therapeutic delays, and the effectiveness of implemented curative strategies will be described. EPOCE technique during the OHCA resuscitation: duration and quality of the video clips will be described. Chi-squared and Student's tests will be used to test association between quality and duration of the videos. Prognostic performance of EPOCE to predict ROSC absence in patients with ventricular fibrillation without cardiac motion will be estimated. A multifactorial composite prognostic score

associated with the absence of ROSC will be constructed with a logistic regression model. Parameters that will be taken into account will be: myocardial and/or electrical activity, capnography, no/low flow duration, and clinical profile including sex and age. Measure of mean duration of cardiac massage interruption during EPOCE will be estimated. *P* values less than 0.05 will be considered statistically significant. All analyses will be performed using SAS version 9.4 ®.

Ethics

The ACE trial has been approved by the ethics committee (Comité de Protection des Personnes "Ile de France II" France, 2018-AO1491-54). In accordance with their recommendations, patient and/or legal authority consent will be requested only for survivors. Furthermore, regarding to the inclusion criteria, it will be impossible even to seek for relatives' consent. Regarding the very low survival rate of patients with OHCR (5%), anonymised database, and family induced traumatism, we have asked for a derogation to surrogates information for deceased patients. A consent will be requested for surviving patients.

Dissemination

We intend to publish ACE results in a major journal of Emergency Medicine, raw date will be available on reasonable request

Discussion

There is a strong rationale for the interest of early diagnosis of absence of ROSC in OHCA. Actually, it might allow to prematurely initiate ECMO indications or organ donation procedures

without waiting for a median time of 30 min after ALS onset. Conversely, in cases of cardiac motion visualisation, a far better prognosis is likely and prehospital teams might search for curative aetiologies.

Hard evidence is currently missing in the literature since the majority of published studies included small series of patients, in the hospital, and used different protocols [6] [7] [8] [9] [10] [11]. This was stated by the European Resuscitation Council in its 2015 recommendations [5]. ACE is adapted to the particularities of the French prehospital system but its results will be translatable to other organisations such as European or American ones. Actually, where ever the place where cardiac arrest is managed, the prognostic value of EPOCE on absence of ROSC will be the same.

ACE has the potential to provide a definitive response to this question. It is a multicentre, prospective trial with a rigorous methodology and a large sample of patients. Furthermore, it will answer the question of frequency of curable aetiologies and their management. This question also needs hard evidence, ACE has the potential to provide this since it will include 624 non-selected patients with OHCA.

POCE has been associated with delays in chest compressions [12] that would alter the prognosis. However, the training of physicians in POCE in this study was not reported [13] and might be low, regarding the number of included patients. Anyway, this potential flaw has to be addressed: in ACE, physicians will be trained before the trial's onset and cardiac massage interruption will be recorded and measured in a subgroup of patients.

Availability of data and material

Data will be available upon reasonable request.

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Authors' contributions

FJ, PP, IA and PLC conceived and wrote the protocol, AL and AO brought methodological and administrative help, CV was in charge of statistical aspect, EM reviewed the whole process.

Funding

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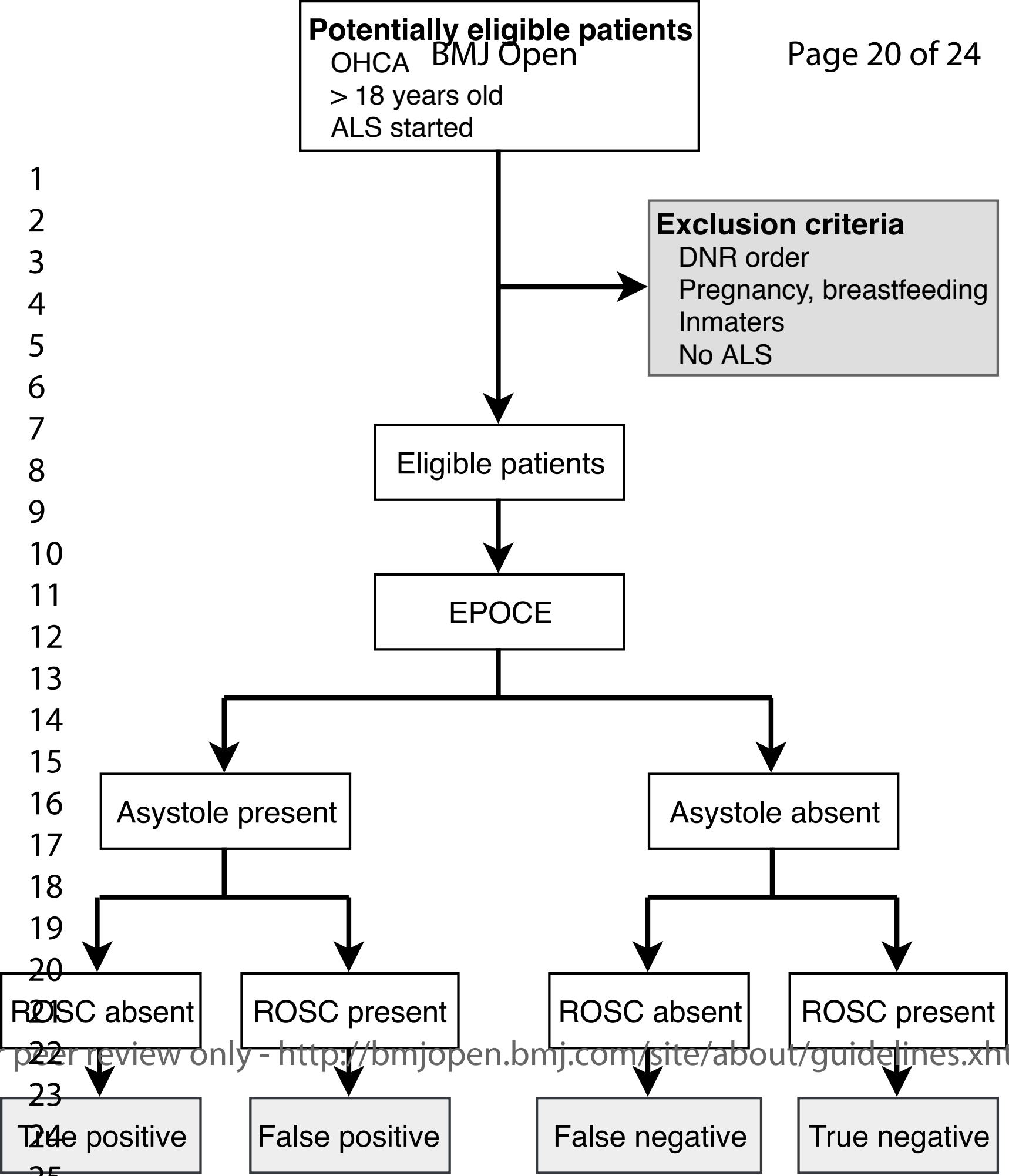
Competing interests statement

There was no conflict of interest for all contributors

Word count

3009 words



SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	6
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	6
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	6
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	6
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	6
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	3

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3-4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	4
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	6
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	ND
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	6
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Early point-of-care focused echocardiographic asystole as a predictive factor for absence of return of spontaneous circulatory in out-of-hospital cardiac arrests : prospective multicenter observational study: study protocol

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Primary Subject Heading:	Emergency medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	cardiac arrest, prognosis, Echocardiography < CARDIOLOGY

Early point-of-care focused echocardiographic asystole as a predictive factor for absence of return of spontaneous circulatory in out-of-hospital cardiac arrests, prospective multicenter observational study: study protocol

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Abstract

Introduction

Out-of-hospital cardiac arrests (OHCA) are a major cause of mortality in France. Their management is performed by a particular prehospital system based on medicalisation of both ambulance dispatch and mobile intensive care units composed by an emergency physician and an emergency nurse with all the required devices for advanced care. It follows the European recommendations [1] which advocate for the use of early point-of-care focused echocardiography (EPOCE) in the pre-hospital setting, in particular to identify reversible causes of OHCA. Another ability of EPOCE may be to predict the absence of return of spontaneous circulation (ROSC) in cases of absence of cardiac motion.

Methods

Our trial, The ACE trial, aims to assess the positive predictive value of absence of cardiac motion viewed with EPOCE for the absence of final ROSC. It is a prospective multicentre (n=8) prognosis study which will recruit a large sample of patients (n=624). Briefly, once the diagnosis of OHCA done and advanced life-support (ALS) initiated, an EPOCE will be performed during the defibrillator's analysis period. The physician will notice presence or not of cardiac motion and will look for a reversible cause. Since the prognosis value of absence of cardiac motion is not currently validated, the EPOCE results will not be used for ALS termination. It will be done following European Resuscitation Council rules. ROSC will be assessed for the study purpose at this moment.

Analysis

Primary endpoint is the positive predictive value of the absence of cardiac motion for the absence of final ROSC. Secondary endpoints are predictive characteristics of EPOCE on

morbimortality 30 days after OHCA, description of reversible cause, analysis of EPOCE technique.

Ethic

ACE was approved by an ethical committee (2018-AO1491-54)

Dissemination

While ACE is adapted to the French prehospital system, its results will be translatable to other organisations if inter-rater variability is not found. Actually, where ever the place where cardiac arrest is managed, the prognostic value of EPOCE for the absence of final ROSC will be the same.

Trial status

ACE has received a grant from the French Minister for Health, was registered in clinicaltrials.gov (NCT03494153) in 2018

Keywords :

Cardiac arrest, prognosis, cardiac ultrasound

Strength and limitations of the study

- Strengths
  - Broad inclusion criteria that would allow an extrapolation to rather all OHCA
  - High planned number of patients
  - Previous pilot study demonstrated the feasibility of this protocol
  - Verification of protocol's respect by the video recording
- Limitations
  - Cardiac massage interruption will be monitored in 3 centers out of 8
  - Planned missed patients rate of 15%: what characteristics for these patients? What consequences on results?
  - Observational not interventional study

Introduction

Out-of-hospital cardiac arrests (OHCA) are a major cause of mortality in France (between 30,000 and 50,000 cases per year) [1][2]. The prognosis is particularly poor, since only 5 to 6% of patients will leave the hospital alive with satisfying neurological condition [2] [3] [4]. Their management in France is performed by a particular prehospital system based on medicalisation of both ambulance dispatch (SAMU) and mobile intensive care units (SMUR). It follows the European recommendations (cardiac massage, ventilation, cardiac rhythm analysis, drugs administration, and defibrillation if needed) [1] [5] Based on published studies [6] [7] [8], 2015 European recommendations advocate for the use of point-of-care focused echocardiography (POCE) in in the pre-hospital setting, in particular to identify reversible causes of OHCA [1] [6]. Indeed, POCE can reveal various reversible causes such as tamponade, massive pulmonary embolism, deep hypovolaemia, or suffocating pneumothorax [6] [7]. Their identification allows the clinician to better adjust his therapeutic strategy and, accordingly, might improve the patient's prognosis.

Another ability of POCE is to predict the absence of return of spontaneous circulation (ROSC) at the end of advanced life support (ALS) procedure in cases of absence of cardiac motion. ROSC was defined as a spontaneous cardiac rhythm accompanied by breathing, coughing, movements or fleeting palpated pulse in the Utstein registries recommendation [9]. Several studies found a strong correlation between absence of cardiac motion and absence of ROSC [6] [7] [8] [10] [11]. This fact deeply impacts extracorporeal circulation indications and organ donation procedures. However, these studies, mainly performed in a hospital setting, included rather small populations and used different cardiac motion definitions and procedures. Furthermore, they cannot be extrapolated to OHCA because of differences in terms of delays, management, and environment. In this context, the European Resuscitation Council (ERC) stated in 2015

that, while the absence of cardiac motion is highly predictive of death, sensitivity and specificity have not been reported. Thus, usage of this ascertainment for determination of premature termination of resuscitation is currently not recommended until publication of a pivotal study.

Methods and analysis

Objectives

The ACE French national trial fits precisely into this bibliographic gap, uncertainty on diagnosis value of absence of cardiac motion for absence of final ROSC. Our objectives are multiple:

- The main objective is to assess the positive predictive value of EPOCE (EPOCE; i.e. < 12 min after initiation of ALS) for the absence of final ROSC
- Secondary objectives are:

1. assess the prognostic value of EPOCE on survival at hospital admission and on morbi-mortality at Day 30 after the OHCA (D30),

2. assess prognostic performances of EPOCE for the absence of final ROSC,

3. assess prognostic values of EPOCE according to timing of initiation,

4. assess the relationship between EPOCE findings and ECG rhythms,

5. describe frequency and typology of reversible causes in the context of OHCA,

6. describe EPOCE characteristics: timing, quality assessed by the operator, and by an expert committee,

7. assess prognostic performances of EPOCE in patients with ventricular tachycardia,

8. creation of a multifactorial score with EPOCE combined with other clinical parameters (composite prognostic tool combining myocardial and/or electrical activity, capnography,

no/low flow duration, and clinical profile including sex and age for the absence of final ROSC, and

9. measurement of the cardiac massage interruption associated with EPOCE realisation by video recording in three centres (Nantes, La Roche-sur-Yon, Bobigny).

Design

ACE was designed as a prospective, multicentre prognosis study. It is based on rigorous methodology (prospective observational study with a unique protocol), has a high proof-level design, and will recruit a large sample of patients (*n* = 624). The SPIRIT check-list is in Supplementary files. Recruiting centres include both rural and urban community and university hospitals. This pragmatic approach intends to validate the performance of EPOCE for the prediction of absence of final ROSC in cases of absence of cardiac motion in the out-of-hospital setting. If this hypothesis is validated, it will allow for shorter delays before extracorporeal membrane oxygenation (ECMO) or organ donation processes.

Echographic asystole is defined by the complete absence of cardiac motion (coordinated or fibrillation) and the absence of valve movements.

Methods

Patients

Inclusion criteria: all patients > 18 years old presenting with an OHCA for whom an EPOCE could be initiated in less than 12 min after ALS initiation

Non-inclusion criteria: do not resuscitate order, ROSC prior EPOCE, ALS not performed by the prehospital team, pregnancy, breastfeeding women, and inmates.

Procedure

After verification of inclusion and exclusion criteria, advanced life support intervention will replace basic life support with an overlap period, as usual (Figure 1). ALS will be performed according to the latest ERC regulations. Once standard ALS interventions are

done, according to the focused echocardiographic evaluation in life support (FEEL) protocol and ERC recommendations [4, 5], FEEL protocol was designed and evaluated in a prospective observational study using an ALS compliant focused echocardiography. Briefly, once arrived on scene, CPR was started, ECG performed and a clinical diagnosis established. A focused echocardiography was then realized. Outcome defined as survival to admission was better regardless of initial rhythm when cardiac motion was present. the physician will perform a POCE during the defibrillator's analysis period, thus in less than 10 seconds. It will be done using a phased array probe with a subcostal view. It has to be done as early as possible and always before 12 min after ALS initiation. The physician will notice cardiac motion or lack thereof and will look for reversible causes. Video clips will be stored in the echographic device and secondarily uploaded in the electronic case report file (eCRF) for random reviewing by an expert committee. The whole ALS procedure will be closely monitored in order to assess diagnostic and therapeutic delays (defined as the interval between arrival time on scene and therapeutic initiations). ALS will be terminated following ERC rules, the EPOCE results will not be used for that purpose. For the study purpose, presence or absence of ROCS will be assessed after ALS termination. In the case of ROCS, the hospital course will be described. At D30, vital status of all patients will be assessed by either hospital file consult or phone call if the patient is still alive. For them, autonomy will be assessed using the Glasgow Outcome Scale. These two events (dead or alive and Glasgow Outcome Scale) define the morbimortality. They will be assessed by the research team of Nantes Hospital.

Endpoints

Primary endpoint

- Predictive prognostic value (PPV) of EPOCE asystole (i.e. within the first 12 min of ALS initiation) on resuscitation failure (absence of ROSC). We have chosen the

predictive positive value (PPV) as the primary endpoint because we wish to limit the number of false positives as much as possible in order to isolate a population without ROCS with EPOCE asystole.

Secondary endpoints

1. Predictive prognostic value of EPOCE asystole (i.e. within the first 12 min of ALS initiation) on hospital admission and on morbi-mortality (defined as dead or alive and Glasgow Outcome Scale) evaluated at 30 days.
2. Sensitivity, specificity, and negative predictive (NPV) values of EPOCE asystole for the absence of final ROSC.
3. Sensitivity, specificity, and positive and negative predictive values of EPOCE asystole for the absence of final ROSC according to their timing of initiation after ALS initiation (by 2 min).
4. Patterns between ultrasound diagnosis (systole vs asystole) and electrocardiogram electrical activity (pulse less activity, asystole, ventricular fibrillation, and ventricular tachycardia).
5. Description of reversible causes (tamponade, massive pulmonary embolism, deep hypovolaemia, or suffocating pneumothorax), diagnostic (time between ALS onset and diagnosis) and therapeutic delays (time between ALS onset and specific therapeutic intervention), and the effectiveness of implemented curative strategies defined by association with ROCS and 30 day morbimortality.
6. Analysis of EPOCE technique during OHCA resuscitation: duration, quality of the video clips assessed by the operator (from 0 = impossible to 10 = excellent), and an expert committee reviewing a 10% random sample.
7. Sensitivity, specificity, and positive and negative predictive values of EPOCE asystole to predict ROSC absence in patients with ventricular fibrillation.

8. Main determinants of death (age, sex, comorbidities, suspected aetiology, no/low flow duration, initial treatment, electrical activity, and cardiac motion) associated with the absence of ROSC in order to determine a score with a 100% PPV.
9. Measure of duration of cardiac massage interruption in seconds during EPOCE, using a portable video recorder (three centres: Nantes, La Roche-sur-Yon, and Bobigny).

Recruiting centres

Recruiting centres will be university hospitals (Nantes, Brest, Tours, Angers, and Bobigny) and community hospitals (Saint-Nazaire, La Roche-sur-Yon, and Chateaubriant).

Sample size calculation

The principal objective is the PPV of absence of cardiac motion (asystole) for the absence of final ROSC. For a PPV of 95 ± 3%, 203 patients without cardiac motion are required. Based on 37.5% asystole rate [10], 542 total patients are required. Taking into account that EPOCE could not be performed in 15% of OHCA, the required population will, finally, be 624 patients.

Recruitment

Chosen prehospital teams were recruited because they are highly skilled in clinical ultrasound and already use this technique in their emergency department. A monthly newsletter will be published with individual and global recruitment trends. Patients will be followed-up until day 30 and defined gradually as: survival without neurological deficit, survival with neurological deficit, or death.

Data management

Electronic case report files will be used via a web-based interface and video clips will be uploaded. All data will be stored in the Nantes University Hospital secured databases. The data management team will be responsible for the entire process. Data will be anonymised with an incremental number assigned to each patient. The final database will be only available to the steering committee.

Monitoring

Monitoring will be performed both by electronic surveillance of recruitment and data quality. It will be done by the Clinical Research Department of Nantes University Hospital.

Statistical analysis

Sensibility, specificity, PPV, NPV, and likelihood ratio of EPOCE asystole on resuscitation failure (absence of ROSC) and on morbimortality will be estimated with 95% confidence interval. Logistic model regression and receiver operating characteristic (ROC) curve will be estimated to analyse the time of EPOCE initiation that allows the best prognostic performances for the absence of final ROSC. Chi-squared and Fisher's test will be used to analyse the association between ultrasound diagnosis and electrocardiogram electrical patterns. reversible causes, diagnostic and therapeutic delays, and the effectiveness of implemented curative strategies will be described. EPOCE technique during the OHCA resuscitation: duration and quality of the video clips will be described. Chi-squared and Student's tests will be used to test association between quality and duration of the videos. Prognostic performance of EPOCE to predict ROSC absence in patients with ventricular fibrillation without cardiac motion will be estimated. A multifactorial composite prognostic score associated with the absence of ROSC will be constructed with a logistic regression model. Parameters that will be taken into account will be: myocardial and/or electrical

activity, capnography, no/low flow duration, and clinical profile including sex and age. Measure of mean duration of cardiac massage interruption during EPOCE will be estimated. *P* values less than 0.05 will be considered statistically significant. All analyses will be performed using SAS version 9.4 ®.

Ethics

The ACE trial has been approved by the ethics committee (Comité de Protection des Personnes "Ile de France II" France, 2018-AO1491-54). In accordance with their recommendations, patient and/or legal authority consent will be requested only for survivors. Furthermore, regarding to the inclusion criteria, it will be impossible even to seek for relatives' consent. Regarding the very low survival rate of patients with OHCA (5%), anonymised database, and family induced traumatism, we have asked for a derogation to surrogates information for deceased patients. A consent will be requested for surviving patients.

Dissemination

We intend to publish ACE results in a major journal of Emergency Medicine, raw data will be available on reasonable request

Patient and Public Involvement

The patient's involvement will be to participate to the study when included after an OHCA. There will no public involvement for this study.

Discussion

There is a strong rationale for the interest of early diagnosis of absence of ROSC in OHCA. Actually, it might allow to prematurely initiate ECMO indications or organ donation procedures without waiting for a median time of 30 min after ALS onset. Conversely, in

cases of cardiac motion visualisation, a far better prognosis is likely and prehospital teams might search for reversible causes.

Hard evidence is currently missing in the literature since the majority of published studies included small series of patients, in the hospital, and used different protocols [6] [7] [8] [10]. A multicentre study was performed but EPOCE was performed in the ED even the cardiac arrest occurred out-of-hospital [12] This was stated by the European Resuscitation Council in its 2015 recommendations [1]. ACE is adapted to the particularities of the French prehospital system but its results will be translatable to other organisations such as European or American ones.

ACE has the potential to provide a definitive response to this question. Furthermore, it will answer the question of frequency of reversible causes and their management. This question also needs hard evidence, ACE has the potential to provide this since it will include 624 non-selected patients with OHCA.

POCE has been associated with delays in chest compressions [13] that would alter the prognosis. However, the training of physicians in POCE in this study was not reported [13] [14]. This study was performed in the United States and it might be assumed that the training was in line with established residency training requirement. Anyway, this potential flaw has to be addressed; in ACE, physicians will be trained before the trial's onset and cardiac massage interruption will be recorded and measured in a subgroup of patients.

Availability of data and material

Data will be available upon reasonable request.

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Authors' contributions

FJ, PP, IA and PLC conceived and wrote the protocol, AL and AO brought methodological and administrative help, CV was in charge of statistical aspect, EM reviewed the whole process.

Funding

ACE is supported by a €193,000 grant from the French Ministry for Health (PHRC-IR 2017), grant number API17/N/035. ACE is currently supported by the French Society of Emergency Medicine (Société Française de Médecine d'Urgence) and by Winfocus France without funding. There is ongoing discussions with Philips and Sonosite for the loan of echographic devices in order to increase the number of available devices for prehospital teams. Funders have no role in the ACE study.

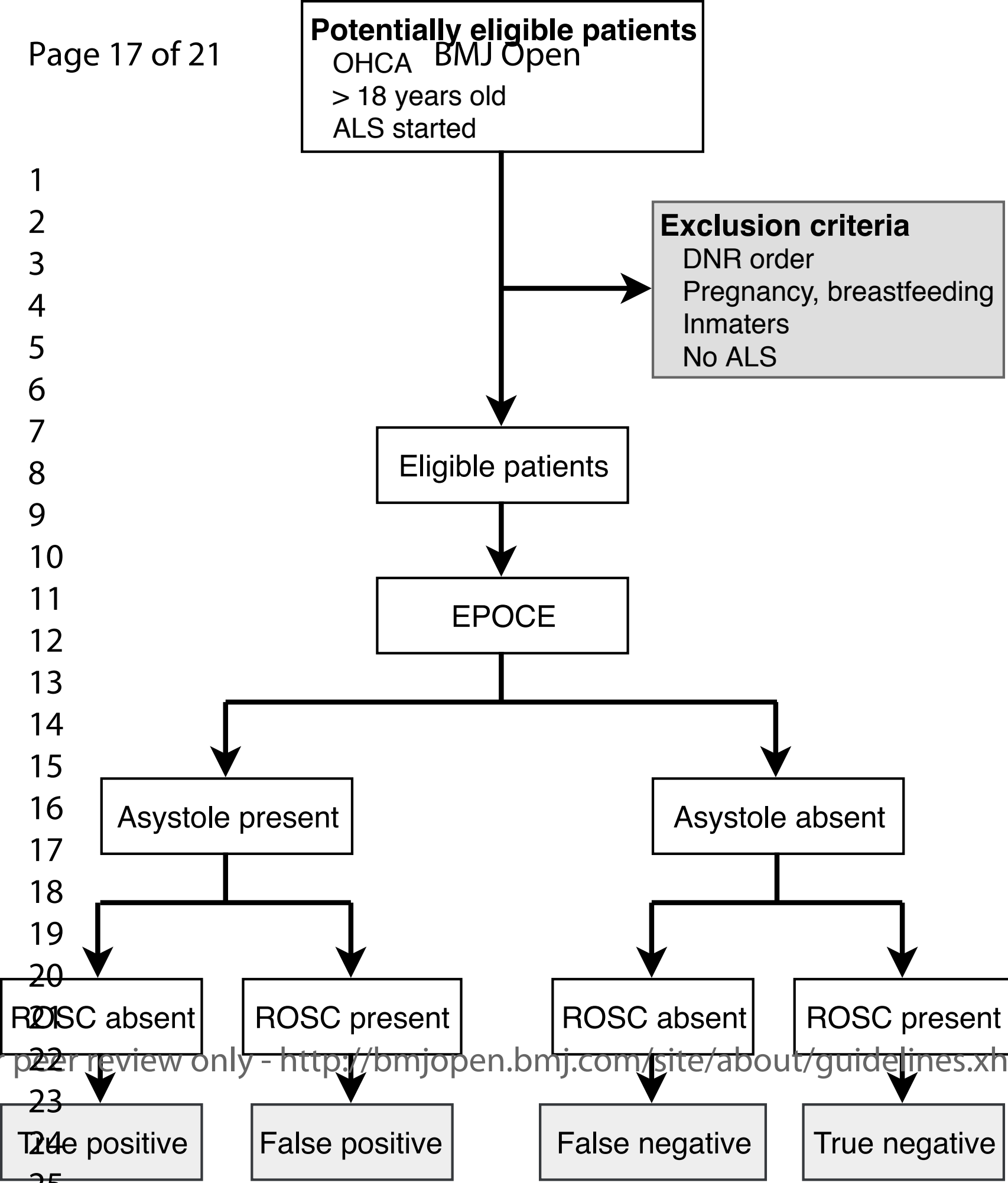
Competing interests statement

There was no conflict of interest for all contributors

Word count

3267 words

Figure 1 legend : patient's flow chart of ACE trial



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	6
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	6
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	6
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	6
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	6
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	3

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3-4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	4
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	6
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	ND

Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial registries, journals, regulators)	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	6
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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BMJ Open

Early point-of-care focused echocardiographic asystole as a predictive factor for absence of return of spontaneous circulatory in out-of-hospital cardiac arrests : prospective multicenter observational study: study protocol

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Keywords:	cardiac arrest, prognosis, Echocardiography < CARDIOLOGY

Early point-of-care focused echocardiographic asystole as a predictive factor for absence of return of spontaneous circulatory in out-of-hospital cardiac arrests, prospective multicenter observational study: study protocol

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Abstract

Introduction

Management of Out-of-hospital cardiac arrests (OHCA) in France is performed by a particular prehospital system based on medicalisation of mobile intensive care units composed by emergency physician and nurse with all the required devices for advanced care. It follows the European recommendations which advocate for the use of early point-of-care focused echocardiography (EPOCE) in the pre-hospital setting. An ability of EPOCE may be to predict the absence of return of spontaneous circulation (ROSC) in cases of absence of cardiac motion. We thus intended to investigate this predicting value with a prospective multicenter study. This paper describes the study protocol while the first patients were included in December 2018.

Methods

ACE is a prospective multicentre (n=8) prognosis study. Briefly, as soon as the OHCA is diagnosed and advanced life-support (ALS) initiated, EPOCE will be performed during an analysis period of the automated external defibrillator. The physician will assess detectable motion within the heart and reversible causes of OHCA. However, as the prognosis value of absence of cardiac motion is not currently validated, the EPOCE results will not be used to withdraw ALS, and decision to withdraw life support will be done following European Resuscitation Council recommendations during our study.

Analysis

Primary endpoint is the positive predictive value of the absence of cardiac motion for the absence of final ROSC. Secondary endpoints are predictive characteristics of EPOCE asystole on morbimortality 30 days after OHCA, description of reversible cause, analysis of EPOCE technique.

Ethic

ACE was approved by an ethical committee (2018-AO1491-54)

Dissemination

While ACE is adapted to the French prehospital system, its results will be translatable to other organisations if inter-rater variability is not found.

Trial status

ACE has received a grant from the French Minister for Health, was registered in clinicaltrials.gov (NCT03494153) in 2018

Keywords :

Cardiac arrest, prognosis, cardiac ultrasound

Strength and limitations of the study

- Strengths
  - Broad inclusion criteria that would allow an extrapolation to rather all OHCA
  - High planned number of patients
  - Previous pilot study demonstrated the feasibility of this protocol
- Limitations
  - Cardiac massage interruption will be monitored in 3 centers out of 8
  - Observational not interventional study

Introduction

Out-of-hospital cardiac arrests (OHCA) are a major cause of mortality in France (between 30,000 and 50,000 cases per year) [1][2]. The prognosis is particularly poor, since only 5 to 6% of patients will leave the hospital alive with satisfying neurological condition [2] [3] [4]. Their management in France is performed by a particular prehospital system based on medicalisation of both ambulance dispatch (SAMU) and mobile intensive care units (SMUR). It follows the European recommendations (cardiac massage, ventilation, cardiac rhythm analysis, drugs administration, and defibrillation if needed) [1] [5] Based on published studies [6] [7] [8], 2015 European recommendations advocate for the use of point-of-care focused echocardiography (POCE) in in the pre-hospital setting, in particular to identify reversible causes of OHCA [1] [6]. Indeed, POCE can reveal various reversible causes such as tamponade, massive pulmonary embolism, deep hypovolaemia, or suffocating pneumothorax [6] [7]. Their identification allows the clinician to better adjust his therapeutic strategy and, accordingly, might improve the patient's prognosis.

Another ability of POCE is to predict the absence of return of spontaneous circulation (ROSC) at the end of advanced life support (ALS) procedure in cases of absence of cardiac motion. ROSC was defined as a spontaneous cardiac rhythm accompanied by breathing, coughing, movements or fleeting palpated pulse in the Utstein registries recommendation [9]. Several studies found a strong correlation between absence of cardiac motion and absence of ROSC [6] [7] [8] [10] [11]. This fact deeply impacts extracorporeal circulation indications and organ donation procedures. However, these studies, mainly performed in a hospital setting, included rather small populations and used different cardiac motion definitions and procedures. Furthermore, they cannot be extrapolated to OHCA because of differences in terms of delays, management, and environment. In this context, the European Resuscitation Council (ERC) stated in 2015

that, while the absence of cardiac motion is highly predictive of death, sensitivity and specificity have not been reported. Thus, usage of this ascertainment for determination of premature termination of resuscitation is currently not recommended until publication of a pivotal study.

Methods and analysis

Objectives

The ACE French national trial fits precisely into this bibliographic gap, uncertainty on diagnosis value of absence of cardiac motion for absence of final ROSC. Our objectives are multiple:

- The main objective is to assess the positive predictive value of EPOCE asystole for the absence of final ROSC
- Secondary objectives are:

1. assess the prognostic value of EPOCE asystole (i.e. within the first 12 min of ALS initiation) on survival at hospital admission and on morbi-mortality at Day 30 after the OHCA (D30),
2. assess prognostic performances of EPOCE asystole for the absence of final ROSC,
3. assess prognostic values of EPOCE asystole according to timing of initiation after ALS initiation (by 2 min increment).
4. assess the relationship between EPOCE findings and ECG rhythms,
5. describe frequency and typology of reversible causes (tamponade, massive pulmonary embolism, deep hypovolaemia, or suffocating pneumothorax) in the context of OHCA,
6. describe EPOCE characteristics: timing, quality assessed by the operator, and by an expert committee,
7. assess prognostic performances of EPOCE in patients with ventricular tachycardia,

8. creation of a multifactorial score with EPOCE combined with other clinical parameters (composite prognostic tool combining myocardial and/or electrical activity, capnography, no/low flow duration, and clinical profile including sex and age for the absence of final ROSC, and

9. measurement of the cardiac massage interruption associated with EPOCE realisation by video recording in three centres (Nantes, La Roche-sur-Yon, Bobigny).

Design

ACE was designed as a prospective, multicentre prognosis study. It is based on rigorous methodology (prospective observational study with a unique protocol), has a high proof-level design, and will recruit a large sample of patients (*n* = 624). The SPIRIT check-list is in Supplementary files. Recruiting centres include both rural and urban community and university hospitals. This pragmatic approach intends to validate the performance of EPOCE for the prediction of absence of final ROSC in cases of absence of cardiac motion in the out-of-hospital setting. If this hypothesis is validated, it will allow for shorter delays before extracorporeal membrane oxygenation (ECMO) or organ donation processes.

Echographic or EPOCE asystole is defined by the complete absence of cardiac motion (coordinated or fibrillation) and the absence of valve movements.

Methods

Patients

Inclusion criteria: all patients > 18 years old presenting with an OHCA for whom an EPOCE has been initiated in less than 12 min after ALS initiation

Non-inclusion criteria: do not resuscitate order, ROSC prior EPOCE, ALS not performed by the prehospital team, pregnancy, breastfeeding women, and inmates.

Procedure

After verification of inclusion and exclusion criteria, advanced life support intervention will replace basic life support with an overlap period, as usual (Figure 1). ALS will be performed according to the latest ERC regulations including realisation of an ECG. Once standard ALS interventions are done according to the focused echocardiographic evaluation in life support (FEEL) protocol and ERC recommendations [4, 5]. FEEL protocol was designed and evaluated in a prospective observational study using an ALS compliant focused echocardiography. Briefly, once arrived on scene, if the patient was in cardiac arrest, CPR was started, ECG performed and a clinical diagnosis established. A focused echocardiography was then realized. Outcome defined as survival to admission was better regardless of initial rhythm when cardiac motion was present. In our study, the physician will perform a EPOCE during the defibrillator's analysis period, thus in less than 10 seconds. It will be done using a phased array probe with a subcostal view. It has to be done as early as possible and always before 12 min after ALS initiation. The physician will notice cardiac motion or lack thereof and will look for reversible causes. Video clips will be stored in the echographic device and secondarily uploaded in the electronic case report file (eCRF) for random reviewing by an expert committee. The whole ALS procedure will be closely monitored in order to assess diagnostic and therapeutic delays (defined as the interval between arrival time on scene and therapeutic initiations). ALS will be terminated following ERC rules, the EPOCE results will not be used for that purpose. For the study purpose, presence or absence of ROCS will be assessed after ALS termination. In the case of ROCS, the hospital course (Intensive care unit, medicine ward..) will be described. At D30, vital status of all patients will be assessed by either hospital file consult or phone call if the patient is still alive. For them, autonomy will be assessed using the Glasgow Outcome Scale. These two events (dead or alive and Glasgow Outcome Scale) define the morbimortality. They will be assessed by the research team of Nantes Hospital. In three

centres, the whole resuscitation procedure will be monitored via a mobile video recorder. Video clips will be uploaded and analysed in order to measure the duration of cardiac massage interruptions.

Endpoints

Primary endpoint

- Predictive prognostic value (PPV) of EPOCE asystole (i.e. within the first 12 min of ALS initiation) on resuscitation failure (absence of ROSC). We have chosen the predictive positive value (PPV) as the primary endpoint because we want to isolate a population without ROCS with EPOCE asystole.

Secondary endpoints

1. Predictive prognostic value of EPOCE asystole (i.e. within the first 12 min of ALS initiation) on hospital admission and on morbi-mortality (defined as dead or alive and Glasgow Outcome Scale) evaluated at 30 days.
2. Sensitivity, specificity, and negative predictive (NPV) values of EPOCE asystole for the absence of final ROSC.
3. Sensitivity, specificity, and positive and negative predictive values of EPOCE asystole for the absence of final ROSC according to their timing of initiation after ALS initiation (by 2 min).
4. Association between the ultrasound asystole rate according to the cardiac electrical activity (pulse less activity, asystole, ventricular fibrillation, and ventricular tachycardia)
5. Description of reversible causes (tamponade, massive pulmonary embolism, deep hypovolaemia, or suffocating pneumothorax), diagnostic (time between ALS onset and diagnosis) and therapeutic delays (time between ALS onset and specific

therapeutic intervention), and the effectiveness of implemented curative strategies defined by association with ROCS and 30 day morbimortality.

6. Analysis of EPOCE technique during OHCA resuscitation: duration, whole quality of the video clips assessed by the operator on a predetermined scale (from 0 = impossible to 10 = excellent), and an expert committee reviewing a 10% random sample.
7. Sensitivity, specificity, and positive and negative predictive values of EPOCE asystole to predict ROSC absence in the sub-group of patients with ventricular fibrillation on the ECG.
8. Main determinants of death (age, sex, comorbidities, suspected aetiology, no/low flow duration, initial treatment, electrical activity, and cardiac motion) associated with the absence of ROSC in order to determine a score with a 100% PPV.
9. Measure of duration of cardiac massage interruption in seconds during EPOCE, using a portable video recorder (three centres: Nantes, La Roche-sur-Yon, and Bobigny).

Recruiting centres

Recruiting centres will be university hospitals (Nantes, Brest, Tours, Angers, and Bobigny) and community hospitals (Saint-Nazaire, La Roche-sur-Yon, and Chateaubriant).

Sample size calculation

The principal objective is the PPV of absence of cardiac motion (asystole) for the absence of final ROSC. To specify the width of the confidence interval at ± 3% with a 95% PPV, 203 patients without cardiac motion are required. Based on 37.5% ultrasound asystole rate [10], 542 total patients are required. Taking into account a +15% attrition rate (incomplete

data, too poor quality of the ultrasound for interpretation, etc...), the required population will, finally, be 624 patients.

Recruitment

Chosen prehospital teams were recruited because they are highly skilled in clinical ultrasound and already use this technique in their emergency department. A monthly newsletter will be published with individual and global recruitment trends. Patients will be followed-up until day 30 and defined gradually as: survival without neurological deficit, survival with neurological deficit, or death.

Data management

Electronic case report files will be used via a web-based interface and video clips will be uploaded. All data will be stored in the Nantes University Hospital secured databases. The data management team will be responsible for the entire process. Data will be anonymised with an incremental number assigned to each patient. The final database will be only available to the steering committee. Subjects with missing data for the primary endpoint will not be analyzed (+15% subjects in sample size calculation)

Monitoring

Monitoring will be performed both by electronic surveillance of recruitment and data quality. It will be done by the Clinical Research Department of Nantes University Hospital.

Statistical analysis

Sensibility, specificity, PPV, NPV, and likelihood ratio of EPOCE asystole on resuscitation failure (absence of ROSC) and on morbimortality will be estimated with 95% confidence interval. Logistic model regression and receiver operating characteristic (ROC) curve will be estimated to analyse the time of EPOCE initiation that allows the best prognostic

performances for the absence of final ROSC. Chi-squared and Fisher's test will be used to analyse the association between ultrasound diagnosis and electrocardiogram electrical patterns. reversible causes, diagnostic and therapeutic delays, and the effectiveness of implemented curative strategies will be described. EPOCE technique during the OHCA resuscitation: duration and quality of the video clips will be described. Chi-squared and Student's tests will be used to test association between quality and duration of the videos. Prognostic performance of EPOCE to predict ROSC absence in patients with ventricular fibrillation without cardiac motion will be estimated. A multifactorial composite prognostic score associated with the absence of ROSC will be constructed with a logistic regression model. Parameters that will be taken into account will be: myocardial and/or electrical activity, capnography, no/low flow duration, and clinical profile including sex and age. Measure of mean duration of cardiac massage interruption during EPOCE will be estimated. *P* values less than 0.05 will be considered statistically significant. All analyses will be performed using SAS version 9.4 ®.

Ethics

The ACE trial has been approved by the ethics committee (Comité de Protection des Personnes "Ile de France II" France, 2018-AO1491-54). In accordance with their recommendations, patient and/or legal authority consent will be requested only for survivors. Furthermore, regarding to the inclusion criteria, it will be impossible even to seek for relatives' consent. Regarding the very low survival rate of patients with OHCA (5%), anonymised database, and family induced traumatism, we have asked for a derogation to surrogates information for deceased patients. A consent will be requested for surviving patients.

Dissemination

We intend to publish ACE results in a major journal of Emergency Medicine, raw data will be available on reasonable request

Patient and Public Involvement

Patients and public had no involvement in the design or the planning of the study

Discussion

There is a strong rationale for the interest of early diagnosis of absence of ROSC in OHCA. Actually, it might allow to prematurely initiate ECMO indications or organ donation procedures without waiting for a median time of 30 min after ALS onset. Conversely, in cases of cardiac motion visualisation, a far better prognosis is likely and prehospital teams might search for reversible causes.

Hard evidence is currently missing in the literature since the majority of published studies included small series of patients, in the hospital, and used different protocols [6] [7] [8] [10]. A multicentre study was performed but EPOCE was performed in the ED even the cardiac arrest occurred out-of-hospital [12] This was stated by the European Resuscitation Council in its 2015 recommendations [1]. ACE is adapted to the particularities of the French prehospital system but its results will be translatable to other organisations such as European or American ones.

ACE has the potential to provide a definitive response to this question. Furthermore, it will answer the question of frequency of reversible causes and their management. This question also needs hard evidence, ACE has the potential to provide this since it will include 624 non-selected patients with OHCA.

POCE has been associated with delays in chest compressions [13] that would alter the prognosis. However, the training of physicians in POCE in this study was not reported [13]

[14]. This study was performed in the United States and it might be assumed that the training was in line with established residency training requirement. Anyway, this potential flaw has to be addressed; in ACE, physicians will be trained before the trial's onset and cardiac massage interruption will be recorded and measured in a subgroup of patients.

Availability of data and material

Data will be available upon reasonable request.

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Authors' contributions

FJ, PP, IA and PLC conceived and wrote the protocol, AL and AO brought methodological and administrative help, CV was in charge of statistical aspect, EM reviewed the whole process.

Funding

ACE is supported by a €193,000 grant from the French Ministry for Health (PHRC-IR 2017), grant number API17/N/035. ACE is currently supported by the French Society of Emergency Medicine (Société Française de Médecine d'Urgence) and by Winfocus France without funding. There is ongoing discussions with Philips and Sonosite for the loan of echographic devices in order to increase the number of available devices for prehospital teams. Funders have no role in the ACE study.

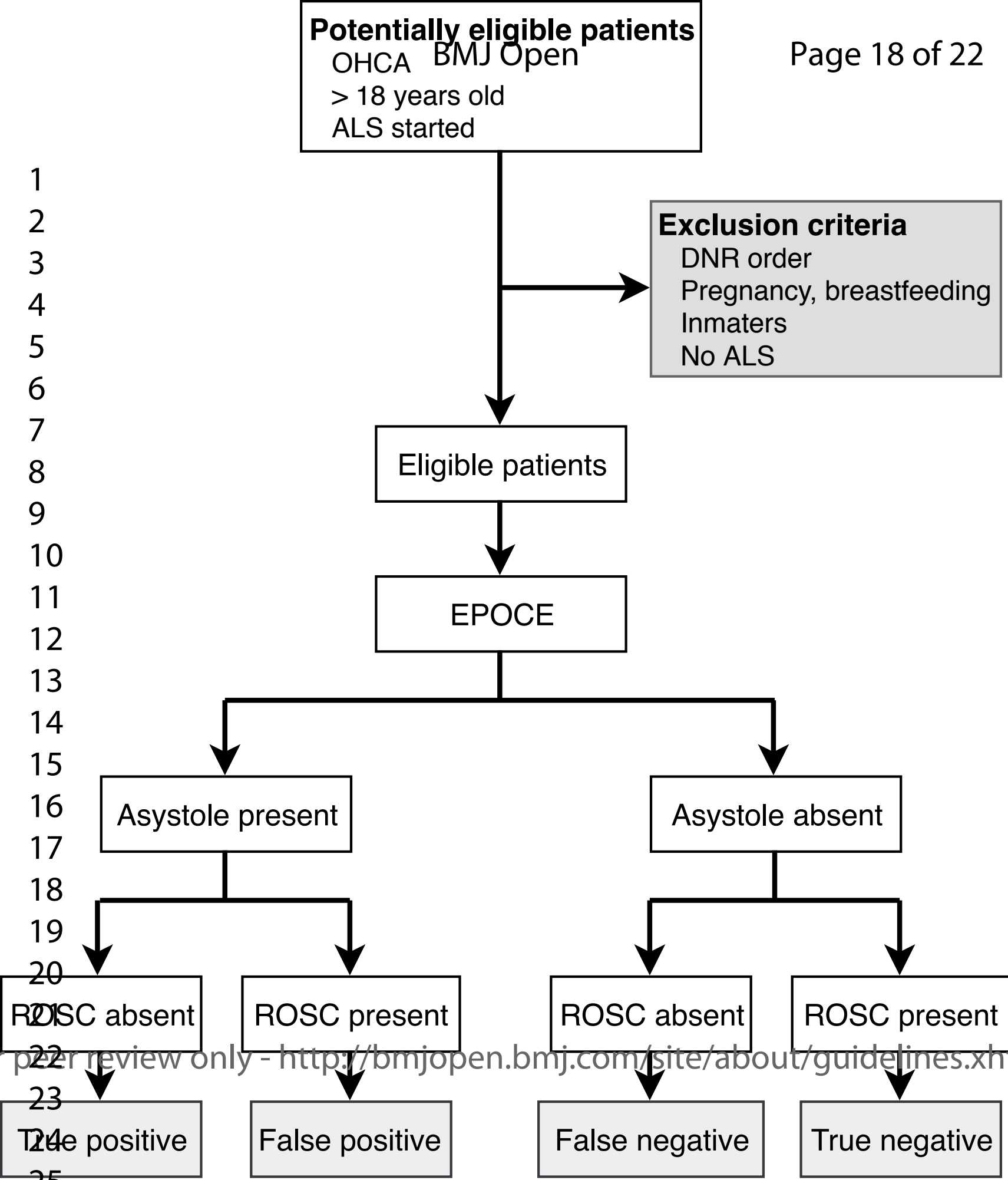
Competing interests statement

There was no conflict of interest for all contributors

Word count

3435 words

Figure 1 legend : patient's flow chart of ACE trial



SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	6
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	6
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	6
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	6
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	6
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	3

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3-4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	4
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	6
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	ND

Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial registries, journals, regulators)	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	6
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.