

MAIN TRIAL PROTOCOL, sept 2022

TANGO2

A randomized trial comparing the effect of a simplified form of Cardiopulmonary resuscitation (CPR) consisting of compressions only compared to CPR with compressions and rescue breaths

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List of abbreviations

AHA	American Heart Association
ACLS	Advanced Cardiac Life Support
AED	Automated External Defibrillator
CO-CPR	Compression-Only CPR
CPC	Cerebral Performance Category
CPR	Cardio-Pulmonary-Resuscitation
CRF	Clinical Report Form
DC	Dispatch Centre
DCO	Dispatch Centre Operator
DSMC	Data Safety Monitoring Committee
DNR	Do Not Resuscitate
EMS	Emergency Medical Service
ER	Emergency Room
ERC	European Resuscitation Council
FR	First Responder (fire-fighters or police)
ICD	Implantable Cardioversion Device
ITT	Intention to treat
OHCA	Out of hospital Cardiac Arrest
PAD	Public Access Defibrillator
PP	Per Protocol
PROM	Patient Reported Outcome Measures
ROSC	Return of Spontaneous Circulation
RCT	Randomized Controlled Trial
SCAR	Swedish Cardiac Arrest Register
S-CPR	Standard CPR
T-CPR	Telephone-assisted CPR
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

1. Summary

Title: TANGO2 “A randomized trial comparing the effect of a simplified form of cardiopulmonary resuscitation (CPR) consisting of Compression-only, compared to CPR with compressions and rescue breaths”

Background: In 2010, two large prospective, randomized trials showed no significant difference with respect to survival between instructions given by emergency medical dispatchers to bystanders without previous knowledge of CPR to administer compression-only CPR (CO-CPR) or standard CPR (S-CPR) in patients with witnessed out-of-hospital cardiac arrests (OHCA).(1, 2) Whether CO-CPR is no worse than, or even superior to, S-CPR when performed by bystanders with previous training in CPR remains unclear.

Purpose: To investigate whether bystander CPR (performed by bystanders with prior CPR-training) consisting of compressions only (CO-CPR) is non-inferior, or better, than standard CPR (S-CPR) in witnessed cases of OHCA.

Intervention: Cases of witnessed suspected OHCA, where bystanders have previous knowledge in CPR, will be randomized at the dispatch center to instructions to perform either CO-CPR (interventional group) or S-CPR (control group) until arrival of the EMS. Upon arrival of the EMS, all patients will receive standard advanced cardiac life support (ACLS) in accordance to current guidelines.

Design: Interventional, prospective, open label, multicenter randomized trial with 1:1 allocation. Since CO-CPR is a simplified form of CPR that could lead to a higher incidence of bystander-CPR in itself, a non-inferiority design has been chosen. This will be further discussed in part 10, “statistical analysis plan”.

Inclusion criteria:

- Unconsciousness with no, abnormal or agonal breathing (suspected OHCA)
- The suspected OHCA is witnessed (seen or heard)
- Any bystander at the scene has previous training in CPR

Exclusion criteria:

- Age 18 or younger
- Collapse is not witnessed
- Bystander has never been taught CPR. (*These bystanders should be instructed to administer CO-CPR in accordance to guidelines*)
- Obvious asphyxia, i.e. drowning, strangulation, hanging
- Obvious intoxication or drug overdose
- Pregnancy
- Trauma

Primary outcome: 30-day survival

Secondary outcomes: Survival to hospital admission, 1-year survival, survival with good neurologic outcome at discharge, defined as cerebral performance category (CPC) 1-2, survival with complete neurologically outcome defined as CPC 1

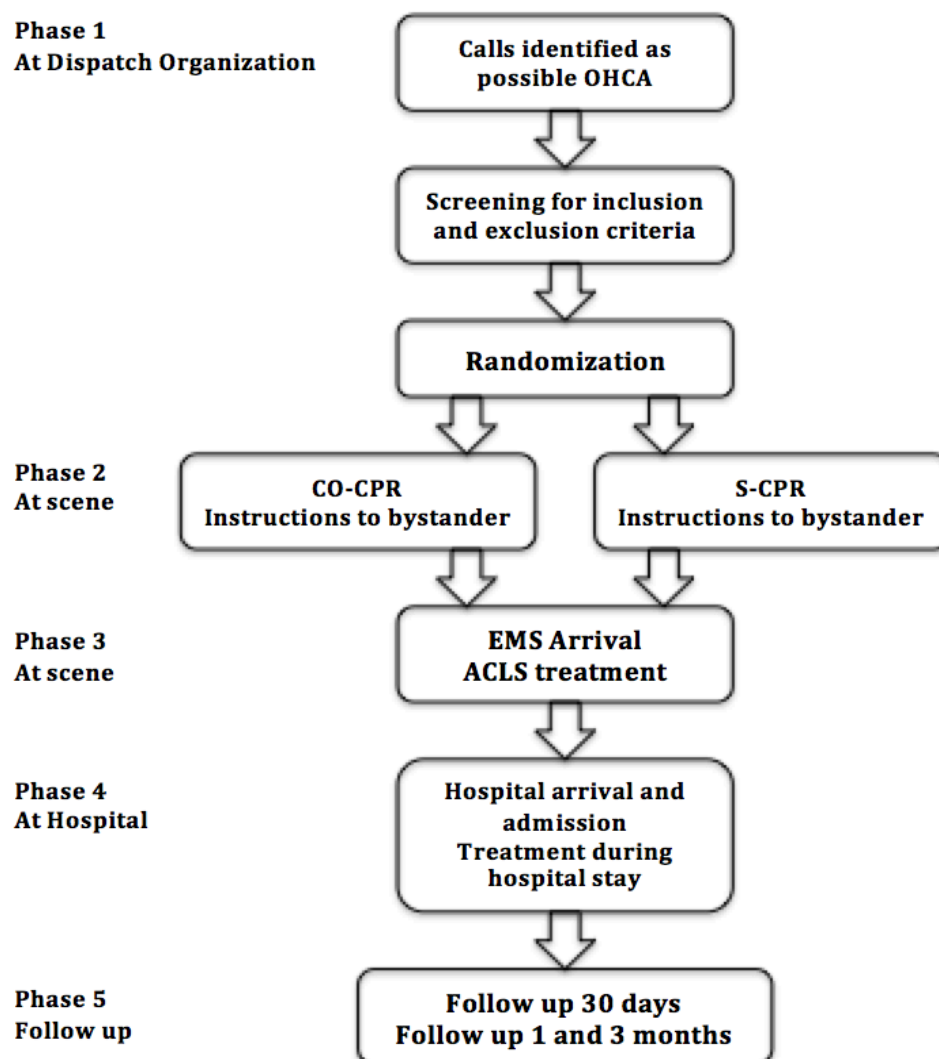
2. Trial overview

2.1. Flow chart

Trial flow-chart and the different phases are presented below in Figure 1.

For detailed description of Study phases please see Section 6.2 *“Trial phases and interventions”*.

Figure 1. Trial overview



OHCA = Out of Hospital Cardiac Arrest, CO-CPR = Compression Only Cardiopulmonary Resuscitation, S-CPR = Standard Cardiopulmonary Resuscitation (Chest compressions and rescue breaths 30:2) EMS = Emergency Medical Services, ACLS = Advanced Cardiac Life Support

2.2 Principal investigators and sponsors

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2.3 Trial sites

This is a national dispatch study where all dispatch centers participate. This includes all SOS Alarm AB dispatch centers as well as the dispatch centers of Sjukvårdens larmcentral

SOS Alarm dispatch centers:

- Falun
- Göteborg
- Halmstad
- Jönköping
- Karlstad
- Luleå
- Malmö
- Norrköping
- Stockholm
- Sundsvall
- Västerås
- Växjö
- Örebro
- Östersund

Sjukvårdens larmcentral dispatch centers:

- Uppsala
- Västerås
- Södermanland

2.4. Ethical approvals

The study has obtained ethical approval from the ethical vetting committee in Stockholm;

Dnr 2014/97-31/2. Main approval

Dnr 2015/1833-32. Amendment

Dnr 2019-0489. Amendment

3. Introduction

3.1 Background

Out-of-hospital cardiac arrest (OHCA) is one of the leading causes of mortality in the industrialized world. The etiology for OHCA is heterogeneous but cardiovascular disease remains the most common underlying cause. In Sweden, the yearly incidence of EMS treated OHCA is around 5,000 and overall survival has remained around 10 % over the last few years.(3) Several factors increase the chance of survival and neurological intact survival in OHCA, of which bystander cardio-pulmonary-resuscitation (CPR), early defibrillation and high quality post-resuscitation care are among the most important ones.(4, 5) Bystander CPR before arrival of the Emergency Medical Service (EMS) is a strong positive predictor of survival.(6) During the last decade, the best form of bystander CPR has been debated.(7-9) To perform rescue breathing is a complex task and bystanders not recently trained in CPR are likely to have difficulties in deliver good rescue breaths. Chest compression only CPR (CO-CPR) has been advocated as a preferable method in situations where the bystander has no previous knowledge in CPR, both because its believed to be equally efficient but also a simplified form of CPR that could lead to increased use of bystander-CPR.(10) Furthermore, this more simplified method has already been well spread in several parts of the US and Japan.(11, 12)

3.2 Preclinical results and data

Studies in porcine models show that CO-CPR increases the number of compressions given by the bystander per minute and minimizes interruptions in CPR.(13, 14) Therefore, it is believed to maintain cerebral and cardiac blood flow over a greater period of time during resuscitation. It is also believed that rescue breaths may increase the risk of reflux of gastric content and cause aspiration. Rescue breaths increase the intrathoracic pressure and therefore decrease venous return of blood to the right ventricle resulting in lower blood flow during compressions.(15) Furthermore, it has been demonstrated that hands-off time (*i.e.* pauses of chest compressions) both prior and after defibrillation is associated with worse outcome.(16) On the other hand, compression-only CPR leads to rescuer fatigue and poorer compressions.(17) It is also believed that the withdrawal of rescue breaths leads to a faster decrease in saturation of arterial blood and therefore is believed to not give crucial oxygen delivery to vital organs even though the blood flow to these organs is maintained.(13)

3.3 Previous published clinical results

Several registry-studies have showed similar or even increased survival rates with a simplified form of CPR, consisting of compressions only (CO-CPR), instead of standard CPR consisting of 30 compressions and two rescue breaths in non-traumatic/asphyxic OHCA.(10, 18-21) In 2010, two large prospective, randomized trials showed no significant difference with respect to survival between instructions given by emergency medical dispatchers for CO-CPR and instructions for standard CPR (S-CPR) in patients with witnessed OHCA in cases where the bystanders had no previous CPR-training.(1, 2) As a consequence, new guidelines recommend telephone-guided CO-CPR for untrained rescuers and

trained bystanders unwilling unable or unwilling to perform rescue breaths.(22, 23) The shift in recommendations is also based upon the assumption that a simplified CPR method would increase the number of bystanders performing CPR. In an initiative to increase CPR rates the American Heart Association has launched public campaigns such as the “hands-only CPR” promoting CO-CPR as an option to S-CPR for adult non-asphyxic cardiac arrest.(11) In the 2015 updates of the European resuscitation council guidelines it states that the confidence in the equivalence between the two methods is not sufficient to change current practice.(24) In Sweden there has been no public campaigns promoting CO-CPR.

Whether CO-CPR leads to a survival rate no worse than, equally effective, or even superior to standard CPR in situations where the bystander has previous CPR training however remains unclear. This clinical question remains unanswered while millions of people are trained in CPR worldwide each year.

4. Overall aim and purpose

The overall purpose with this research project is to investigate whether instructions to perform a simplified form of CPR consisting of compressions only (CO-CPR) to bystanders with prior CPR-training is non-inferior, or better than, standard CPR (S-CPR) in witnessed out-of-hospital cardiac arrest (OHCA).

4.1 Primary objective

To evaluate whether survival to 30 days following instructions to perform CO-CPR is non-inferior compared to instructions to perform S-CPR to bystanders with prior CPR training in witnessed OHCA.

4.2 Secondary objectives

To evaluate whether there is a difference between CO-CPR and S-CPR in survival to hospital admission, neurological favorable survival, defined as survival with cerebral performance category (CPC) 1-2, neurologically intact survival defined as CPC 1 and long-term survival, defined as survival to one year. To evaluate whether there is a difference between CO-CPR and S-CPR in VT/VF as first rhythm and Return of Spontaneous Circulation (ROSC). To compare 30-day survival between CO-CPR and S-CPR in pre specified subgroups.

4.3 PICO-question

P	Among adults suffering from non-traumatic witnessed OHCA (P),
I	Does instructions to perform CO-CPR performed by trained bystanders (I)
C	Compared to instructions to perform S-CPR (C)
O	Change 30-day survival (O)

5. Eligibility

Witnessed cases of adult OHCA with a non-asphyxic etiology will be the principal study population. Patients will be eligible for enrolment if they meet all the following inclusion criteria and none of the exclusion criteria. Inclusion and Exclusion criteria are unchanged throughout the different study phases (run-in, pilot and main study).

5.1 Inclusion criteria:

- Unconsciousness with no, abnormal or agonal breathing (suspected OHCA)
- The suspected OHCA is witnessed (seen or heard)
- Any bystander at the scene has previous training in CPR

5.2 Exclusion criteria:

- Age 18 or younger
- Collapse is not witnessed
- Bystander has never been taught CPR. *(These bystanders should be instructed to administer CO-CPR in accordance to guidelines)*
- Obvious asphyxia, *i.e.* drowning, strangulation, hanging
- Obvious intoxication or drug overdose
- Pregnancy
- Trauma

5.3: Post randomization exclusion from data analysis:

- Previous decision that CPR should not be initiated *i.e.* terminal illness or palliative care
- No cardiac arrest, other condition (cases where EMS did not start CPR)

6. Trial design

This is an interventional, prospective, randomized, 1:1 open label, multicenter trial comparing two different methods of bystander CPR in witnessed cases of OHCA. Since CO-CPR is a simplified form of CPR that could lead to a higher incidence of bystander-CPR by itself a non-inferiority design for the primary outcome has been chosen. Superiority testing will also be performed for the purpose of demonstrating a possible increase in survival with CO-CPR.

6.1 Principal study population and intervention

Witnessed cases of OHCA with a non-asphyxic etiology will be the principal study population. According to current guidelines an unresponsive patient with no or agonal breathing is handled as a suspected case of OHCA at the dispatch center. These cases are eligible for screening for inclusion. If the case is witnessed, any bystander at the scene has previous knowledge in CPR and no exclusion criteria are present, the case can be included and randomly assigned to instructions to perform either CO-CPR (intervention) or S-CPR (control).

The intervention arm will consist of instructions from a dispatcher at the dispatch center to the bystanders to perform CO-CPR with chest compressions only.

The control arm will consist the instructions from a dispatcher at the dispatch center to the bystanders to perform S-CPR with chest compressions and rescue breaths in a 30:2 ratio.

6.2 Trial phases and intervention:

6.2.1. Phase 1 and 2: The work at the dispatch center and CPR by bystander

- Identification of cases
- Screening for inclusion and exclusion
- Randomization
- Instructions according to allocation

Suspected OHCA identified at the dispatch centre, classified as unconscious with no or agonal breathing, are eligible for screening. When a dispatcher suspects a case of OHCA, inclusion criteria and exclusion criteria will automatically pop up on their computer screen. The first inclusion criterion is if the collapse is witnessed (has been seen or heard). The second inclusion criterion is if any bystander on the scene has previous CPR-training. According to current guidelines, the dispatch operator asks whether the witness has training in bystander CPR. If not, they are offered instructions on how to perform telephone-guided CPR (T-CPR) and the case is not further screened for inclusion in the study. If any bystander at the scene has previous CPR-training (any time), or if CPR is already on going, the case can be further screened for inclusion in the study. The dispatch operator will mark this on their desktop environment. This automatically triggers the appearance of exclusion criteria on the

operator's desktop: 1) OHCA victim aged 18 or younger? 2) Asphyxia (i.e. drowning, strangulation, hanging 3) intoxication, drug overdose? 4) trauma? or 5) pregnancy?

If any of the exclusion criteria are met, the case is not randomized (and is handled according to standard protocol). If no exclusion criteria are present, the case will undergo randomization using a Microsoft.NET Random Constructor (Int 32). This will generate a randomized allocation to either intervention (CO-CPR) or control (S-CPR). A new pop-up will then appear on the operator's desktop with detailed instructions to the caller in both groups. Simultaneously, the EMS will be dispatched.

The bystander will, in all cases included and randomized, obtain instructions from the dispatcher to provide either CO-CPR or S-CPR until arrival of the EMS.

The instructions from the dispatcher in INTERVENTION arm include:

- An ambulance is dispatched and is on its way to you
- Do CPR with chest compressions only
- Push hard on the chest with a pace of 100/minute without interruptions for rescue breathing.

The Instructions from the dispatcher in the CONTROL arm include:

- An ambulance is dispatched and is on its way to you
- Do CPR with chest compressions and rescue breathing
- Push hard on the chest 30 times and give 2 rescue breaths. The pace of the compressions should be 100/minute.

Dispatchers are furthermore instructed to encourage all callers in both groups to stay in connection with the callers until arrival of EMS or first responders, instruct callers to put the phone on loudspeaker when possible and to ask callers to count aloud while performing chest compressions. Dispatchers should try to aim for a compression rate of 100-120/minute and suggest switching CPR-provider every 2 minutes if multiple rescuers are on the scene.

6.2.2. Phase 3: The work and action at EMS arrival

Upon arrival of the EMS (or first responders) the intervention ends. EMS crew will further treat all patients with all guidelines (AHA/ERC)(24) recommended standard ACLS, including bag mask ventilation, advanced airway management with endotracheal tube or laryngeal mask, oxygen, defibrillation and i.v. drugs as well as if ROSC is not achieved (cessation of CPR).

6.2.3. Phase 4: The work and action during hospital stay and care

If the patient is admitted to hospital, patients are treated according to local hospital protocol and practice including diagnostic coronary angiography, therapeutic hypothermia (33 or 36 degrees Celsius) and intensive care. Hospital practitioners will not know the randomized allocation.

6.2.4. Phase 5: Follow-up of survival and neurological function

Survival is evaluated for primary endpoint at day 30 through the Swedish cardiac arrest register (SCAR) through linkage with the Swedish public population register (folkbokföringsregistret). For the secondary outcome of neurologically favorable outcome CPC is obtained through SCAR. In a subset of patients (survivors treated at specifically named hospitals), a comprehensive neurological assessment using Patient Reported Outcome Measurement (PROM) related follow-up is performed between 30-90 days. This follow-up is performed by a nurse and/or behavioral therapists blinded to the intervention allocation. This comprehensive follow up will not be possible in all sites of the TANGO2 trial.

6.3. Blinding

Because of the inherent logistical problems with blinding of CPR techniques for dispatchers, the trial is considered as an “open labeled” trial. Treatment allocation will, however, be blinded in data management and at follow-up, for personnel treating the patients at the hospitals and for all responsible researchers. Allocation concealment will be preserved.

6.4. Outcome

6.4.1 Primary outcome:

- 30-day survival

6.4.2 Secondary outcomes:

- Survival to hospital admission
- 1-year survival
- Survival with good neurologic outcome at discharge, defined as cerebral performance category (CPC) 1-2
- Survival with complete neurologically outcome defined as CPC 1

6.4.3 Exploratory outcomes:

- VT/VF as first rhythm
- Return of spontaneous circulation (ROSC)
- Repeated analysis of primary endpoint and all secondary endpoints at 24 months

7. Study phases: Pre study RUN-IN period, PILOT study and MAIN study

7.1. Study Overview: Pre study RUN-IN period, PILOT and MAIN studies

The overall study project is conducted in three different phases:

- 1) Pre study RUN-IN period, for establishing logistical and technical study procedures (completed)
- 2) PILOT STUDY, with focus feasibility, logistics and safety (completed)
- 3) MAIN STUDY with focus on 30-day survival (primary end point) and other important clinical outcomes (secondary outcomes)

7.1.1. Objective pre study RUN-IN period

In order to test the technical inclusion procedures, logistics, feasibility and data collection a pre-study RUN-IN period started in Stockholm during 2015.

7.1.2. Objective PILOT study

The original aim of the PILOT study was to assess safety and feasibility of the TANGO2 trial, as well as intermediate clinical outcomes. The TANGO2 trial started recruitment of patients on January 1st 2017. All patients from the PILOT study will be included in the MAIN STUDY in a seamless design (for details, see section 7.2 and 7.3 below).

7.1.2. Objective MAIN study

The aim of the MAIN study is to evaluate whether survival to 30 days following instructions to perform CO-CPR is non-inferior compared to instructions to perform S-CPR bystanders in witnessed OHCA where the bystander has previous CPR training. Secondary and exploratory objectives include the evaluation of neurological favorable survival, ROSC, admission to hospital, long-term survival and other clinical outcome variables as well as evaluations of 30-day survival between CO-CPR and S-CPR in pre-specified subgroups. The MAIN study will include patients from the PILOT phase in a seamless design (for details, see section 7.2 and 7.3 below).

7.2. Experiences from the pre study RUN-IN period and implications for the PILOT and MAIN studies.

The pre-study RUN-IN period started in Stockholm County in 2015 and analysis were performed during 2016. After continuous technological adjustments, the randomization module was integrated within the computer aided dispatch system and was found to function well in the end of 2016. However, during pre-study RUN-IN period, one major obstacle was identified. Due to unexpected technological difficulties and an unanticipated new organization of the dispatch centers in Sweden only about 15% of the cardiac arrest calls for patients suffering cardiac arrest in Stockholm were

actually answered by dispatchers in Stockholm; all other calls were transferred to other dispatch centers throughout Sweden. This meant that the dispatchers had to consider the geographical site of the suspected cardiac arrest and remember if that area was part of the study area. This new organization and logistics, where the call could be made in one area and answered and handled at another site and county during the pre-study RUN-IN period, resulted in a far slower inclusion rate than anticipated and made a correct follow-up of patients unmanageable and unreliable. This made it impossible to conduct a PILOT study in Stockholm only.

As a consequence, a decision was made by the steering committee:

A) To move the start of the PILOT study forward until completion of the national expansion of the study and not to start inclusion of patients into the PILOT study before January 1st 2017. The new length of the PILOT study was set to two years to assure sufficient inclusion of patients to assess safety in terms of survival to hospital admission.

B) That the PILOT study seamlessly will move on into the MAIN study in an inferentially seamless manner after the PILOT phase inclusion ended on Dec 31 2018. This means that patients from the PILOT study will also be included in the MAIN survival study. The outcomes for the PILOT study were changed to not interfere with the primary endpoint of the main survival study (see below). Inclusion and Exclusion criteria have remained unchanged throughout the whole TANGO2-project.

7.3 Summary of changes in protocol after experiences from the pre study RUN-IN period and effects of the Covid19 pandemic.

Previous changes from original protocol (February 2019):

- As described above, the start and size of the PILOT-study was modified to include all patients during 2 years (2017-18).
- As a consequence of the national expansion, enlargement of the PILOT study as well as the seamless design, the primary endpoints of the PILOT study was modified not only to assess feasibility but also to include assessment of safety as well as intermediate clinical outcomes until hospital admission.
- The initial secondary endpoint of 30-day survival is not evaluated in the PILOT study. The reason for this is to not interfere with the primary endpoint of the MAIN study.
- Inclusion / Exclusion criteria and intervention/control instructions have remained unchanged since the first initial protocol throughout all parts of the TANGO2 project.
- In Stockholm, first responders are dispatched in parallel to EMS in suspected OHCA. The initial protocol included first responders as a part of the trial. However, due to the national expansion of the study together with the fact that the information of assigned treatment (CO-CPR or S-CPR) to first

responders during dispatch in the RUN-IN phase was not feasible, the steering committee decided to remove first responders from participation in the PILOT study and the MAIN study.

- The initial protocol stated a randomization procedure through the opening of pre-printed envelopes with randomized allocation. This was changed before the start of the pre study RUN-IN period to an automated computerized randomization integrated in the dispatchers' software.
- For assessment of adherence to protocol a decision was made by the Steering Committee to audit all calls during the PILOT study and MAIN study using a standardized template for evaluation of dispatcher assisted CPR (cardiac arrest registry to enhance survival – CARES)(25) and that all audit evaluators will be blinded to allocation.

Effects of the Covid19 pandemic:

- Due to the outbreak of the Covid19 Pandemic, the ILCOR and the Swedish Resuscitation Council issued temporary guidelines for lay bystander CPR in OHCA, recommending only looking for signs of life and performing chest compressions only.(26, 27) Therefore, this study was put on hold on date: 12-03-2020.
- The initial plan was to publish the Pilot-study including years 2017 and 2018. Due to the uncertainty during the Covid19-pandemic regarding whether the trial would be able to restart a decision by the steering committee was made to postpone the pilot publication.
- During the pause due to the Covid19-pandemic an independent data monitoring committee reviewed all data up until 12-03-2020 (pre-Covid19). Their recommendation was to continue the trial without modifications, please see also "11. Interim analysis and data monitoring committee".
- When the temporary Covid-19 guidelines were removed the 1 April 2022 the main trail was relaunched, and inclusion started in August 2022.
- A decision was made to include all patients during the period pre-Covid19 in the Pilot-study and the dates of the pilot-study were changed accordingly.
- To assure follow-up all, all EMS records of all calls of suspected OHCA with no matching record in SCAR will be reviewed. Please see "8. Data Collection"

8. Data collection

From the dispatch organization (SOS-Alarm AB) the following variables will be collected:

Time of incoming call, time of dispatch of EMS, time of dispatch of first responders when applicable, time for screening for inclusion, time of randomization and time of arrival of EMS and first responders. Event times are automatically generated and stored in the dispatch organization's computer system. The randomized assignment for each call is stored in a separate data-file generated by the random sequence constructor.

For evaluation of included calls and adherence to protocol all randomized, EMS treated OHCA dispatch calls will be audited. All audit evaluators will be blinded to allocation. A standardized template for evaluation of dispatcher assisted CPR will be used (cardiac arrest registry to enhance survival – CARES).(25) The study specific inclusion criteria will be added as auxiliary variables (supplementary app).

From the Swedish Cardiac Arrest Register the following variables will be collected:

All EMS units participating in TANGO2 report to the SCAR. For all EMS treated OHCA the following variables will be collected from the Swedish Cardiac Arrest Register:

Date of OHCA, Age, Sex, Location of OHCA, CPR prior to EMS arrival, highest medical educational level of CPR provider, first recorded rhythm, defibrillation, airway management and drug administration, Return of spontaneous circulation (ROSC) and survival to admission to hospital.

In calls where there is no matching report in SCAR, ambulance records will be reviewed; if EMS has performed CPR or the patient had been defibrillated by an AED the case will be classified as "EMS treated" and corresponding variables will be extracted from ambulance records instead.

The EMS will obtain information on what type of CPR that was provided to the patient before their arrival at the scene. This information is obtained by observing on-going CPR at their arrival and asking bystanders what type of CPR they provided. EMS crew will also ask bystanders what kind of CPR training they have according to a three-leveled division of the bystander's medical educational level (a – off-duty professional caregiver, doctor, nurse; b – CPR-trained layman (including off-duty police and fire-fighters); or c – layman with no CPR training). This information is a part of SCAR, but there will be emphasis on obtaining this specific data in the TANGO2 trial. Survival is collected for primary endpoint at day 30 from SCAR through linkage with the Swedish public population register (folkbokföringsregistret). For the secondary outcome of neurologically favorable outcome CPC is obtained through SCAR. In a subset of patients (survivors treated at specifically named hospitals), a comprehensive neurological assessment using Patient Reported Outcome Measurement (PROM) related follow-up is performed between 30-90 days. This follow-up is performed by a nurse and/or behavioral therapists blinded to the intervention allocation. This comprehensive follow up will not be possible in all sites of the TANGO2 trial.

8.1 Data handling and record keeping

For each call to the dispatch center a unique log number automatically is generated. This log number is stored at the dispatch center and used to match calls with EMS records, SCAR reports and hospital data. All log numbers and audio-files related to the study will be saved and kept at SOS Alarm, Stockholm. A list with all log numbers will be exported to a study specific database at the center for resuscitation science. A list of all randomized calls with the randomization allocation for each case will be generated by the random sequence constructor and will be exported separately. Finally, data from call audit evaluation, SCAR reports and EMS and hospital records will be imported. All data will be merged and stored in a specific database at center for resuscitation science. This system fulfills all criteria for handling of patient data according to the Swedish legislation on management of personal data "GDPR". In the database, the allocation of each specific case will be blinded during the data collection to avoid any bias in reporting or collecting data. Allocation concealment will be preserved. In the central database there will be manual crosschecking and completion of missing data through EMS and hospital records.

9. Ethical considerations

9.1 Informed consent

This research group has a longstanding experience to perform studies in cardiac arrest patients, like the present, within the prehospital setting. In OHCA, the victim is unconscious and therefore incapacitated of providing informed consent. OHCA is however also a medical emergency and treatment has to be started immediately, making informed consent by a relative or legally authorized representative impossible due to practical reasons. As stated by the Helsinki declaration 2008, paragraph 30:

“Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.”

This study has been approved by the ethics committee of Stockholm; Dnr 2014/97-31/2 and reasons for involving patients unable to give informed consent have been stated in the research plan.

9.2 Potential risks

For the individual cardiac arrest patient, rapid actions by bystanders can lead to an increased chance of survival. Unless some form of life-support activity is performed before arrival of the EMS, survival is dismal. CPR itself rarely leads to damage other than rib fractures. Any pain and discomfort after a successful survival is not proportional to the gain of being rescued to life. This pain and discomfort is also relatively simple to treat. During CPR, the patient is unconscious and thus experiences no pain. The risk of injury associated with CPR is insignificant compared to the potential benefits of treatment. Those patients who survive to 30 days after a cardiac arrest often have good quality of life with only minor neurological disability. This contradicts the fear that an increased number of cases of successful resuscitation lead to a large number of surviving patients with severe disabilities. For the helper, however, some discomfort can arise. Potential risks with this trial are delayed start of CPR due to inclusion and randomization. These issues are separately evaluated in the TANGO2 RUN-IN and TANGO2 PILOT study. Performing CPR is associated with great emotional stress. It is important to be prepared for the reactions that can arise among the lay volunteers. Fear of transmission of contagious diseases associated with CPR is greatly exaggerated. Only a few such cases have been reported worldwide. A small but important population of all OHCA's are due to respiratory causes,

i.e. drowning, strangulation, hanging or intoxication, some of these involve children. These cases are filtered out at the dispatch center and excluded from the study as described in the study protocol. We believe that a small group of unclear cases that are not identified by either the witness or by the dispatcher at the dispatch center (severe renal failure, pulmonary embolism, hemorrhagic stroke or chronic obstructive pulmonary disease) could experience a small risk with this intervention. These are very few in numbers and already have a very poor prognosis.

9.3 Potential benefits

Survival after OHCA is very poor, in Sweden ranging between 10-12%.⁽³⁾ Experimental studies and previous randomized trials have shown that successful CPR can be achieved with CO-CPR.^(1, 2) Rescue breaths are technically difficult and take time from chest compressions. In non-cardiac causes of OHCA, rescue breathing might be more important. These cases are therefore excluded prior to randomization. CO-CPR could lead to an earlier start of CPR, no interruptions in chest-compressions and could therefore be beneficial for a majority of cases. In cases of OHCA immediate, effective chest compressions is of absolute necessity to increase the otherwise low chance of survival.

Today, Sweden has amongst the highest rates of bystander CPR in Europe making a study like this possible for the first time. An additional simplification of the CPR-algorithm introducing CO-CPR could perhaps increase survival rates in Sweden but has the potential to dramatically increase bystander rates throughout Europe and more.

A simplified method of CPR with shorter CO-CPR courses optimally provided by the Swedish CPR council will be more cost-effective in companies, schools and throughout society and could enhance the care for this patient group nationally and internationally. In summary, whether CO-CPR leads to a survival rate no worse than, equally effective, or even superior to standard CPR in situations where the bystander has previous CPR training remains unclear. This clinical question remains unanswered while millions of people are trained in CPR worldwide each year. The potential benefits of this study are two-fold in the sense that the results can lead to increased survival rates: 1) simplified CPR might be better than traditional CPR b) simplified CPR could lead to more people performing it.

10. Data analytic and statistical analysis plan (SAP)

10.1 General statistical analysis plan

This trial is designed to investigate whether CO-CPR is no worse than S-CPR using a non-inferiority design. It has also been designed for the possibility of a superiority testing. This statistical design has been chosen appropriately judged on the presumption that CO-CPR has potential clinical benefit but also is easier to perform (and therefore would lead to a higher number of patients receiving the treatment). The largest difference in 30-day survival (primary outcome) that is considered clinically relevant is 1.0 percentage point (please see also section 9.3).

Eligibility, allocation, inclusion and exclusion will be displayed in a Consort diagram. Differences in proportions between baseline characteristics and outcome will be tested by Fisher exact test. Differences in mean or medians between the treatment groups will be tested by either Student's t-test or Mann Whitney U test depending on distribution. Normality assumptions will be assessed with Kolmogorov Smirnov – test. The estimated between group differences will be presented as proportions and 95% confidence intervals (CI), which will be calculated by the asymptotic method without continuity correction. P-values below 0,05 will be considered statistically significant. Main results will be reported as proportions.

In addition, comparisons between the treatment groups (CO-CPR vs CPR) with respect to the outcomes will be adjusted for background characteristics factors through Binary logistic regression to adjust for possible imbalances due to randomization between the treatment groups. The association between treatment and primary outcome will be presented as odds ratios and corresponding 95% CI intervals. Statisticians at Karolinska Institutet will be responsible for the statistical analysis.

10.2 Statistical hypothesis for non-inferiority

10.2.1 Null hypothesis:

The percentage in 30-day survival for those on the standard treatment instruction CPR is better (higher) than the percentage for those on instruction CO-CPR by an amount of 1.0-percentage units.

10.2.2 Alternative hypothesis:

The percentage in 30-day survival for those on instruction CO-CPR is better than the standard treatment instruction CPR or only slightly worse (by no more than 1.0 percentage unit). We will call instruction of CO-CPR non-inferior to instruction of S-CPR with respect to 30-day survival if the null hypothesis is rejected.

10.3 General statistical methods

All statistical analyses will be performed using IBM SPSS version 25 and R version 3.3.0 *or higher*. Patient data listings, summary tables and graphical presentations will be provided as applicable. For continuous variables, descriptive statistics such as mean, standard deviation, median and range will be presented. For discrete variables, counts and percentages will be presented.

Unless otherwise stated, all statistical tests will be performed at the 5 % two-sided alpha significance level.

10.4 Analysis step and strategy of the whole study populations

The target study population is witnessed OHCA of medical origin where any bystander at the scene has previous CPR training. All randomized calls of suspected OHCA will be included.

Patient with previous decision that CPR should not be initiated i.e. terminal illness or palliative care and cases where EMS did not start CPR for other reasons (sure signs of death, not true OHCA) will be excluded from data analysis. The remaining patients will be analyzed in the ITT population.

Blinded call audit will be used to define type of CPR instructions provided. All randomized EMS treated OHCA receiving instructions in accordance with randomized allocation will be treated as the target study population treated per protocol (PP1).

Finally, patients who are randomized but later judged as not fulfilling all criteria for inclusion before randomization, as evaluated by call audit (not witnessed, asphyxic, bystanders with no previous CPR training), will be removed and remaining patients will be analyzed as PP2.

Thus, we perform ITT analysis, PP1 and PP2 analysis based on the following patients:

Intention to treat (ITT) analysis: We define the ITT population as all included and randomized EMS treated OHCA patients that not fulfilled any exclusion criteria's.

Per protocol 1 (PP1): We define the PP population as the subset of the ITT population where the bystanders received the allocated instructions by the dispatch operator, as defined by the call audit.

Per protocol 2 (PP2): We define the PP2 population as the subset of the PP1 population where the patients fulfilled all inclusion criteria, as defined by call audit.

Please see also Consort Diagram in section 10.5.

The reasoning behind excluding patients after randomization is two-folded:

First: Dispatchers suspecting OHCA based on initial information in a phone-call do patient inclusion and randomization. In this situation there is very limited information and dispatchers are encouraged to treat all calls where the patient is not conscious and not breathing normally as suspected OHCA

and start CPR instructions. Therefore, patients who do not have a treatable OHCA might be included and randomized. These patients can be divided in two categories, either it's not a true OHCA (the patient never suffered an OHCA, for example fainted and thus has a pulse at EMS arrival) or the patient is already dead or had a previous decision that CPR should not be initiated. Therefore, EMS treated OHCA will serve as the best possible evaluation of treatable OHCA.

Second: The reason for including all randomized EMS treated OHCA is because at the time of randomization the dispatch operator judges the call as meeting all inclusion criteria and no exclusion criteria. If call audit or EMS record later reveal that the OHCA was not witnessed, traumatic, caused by asphyxia or bystanders without previous CPR training, the initial selection still relied on the dispatcher. Therefore, further removal of patients in the PP1 analysis might interfere with the interpretation of the study intervention in a real-life setting. A secondary analysis will be performed in all patient fulfilling all inclusion (PP2).

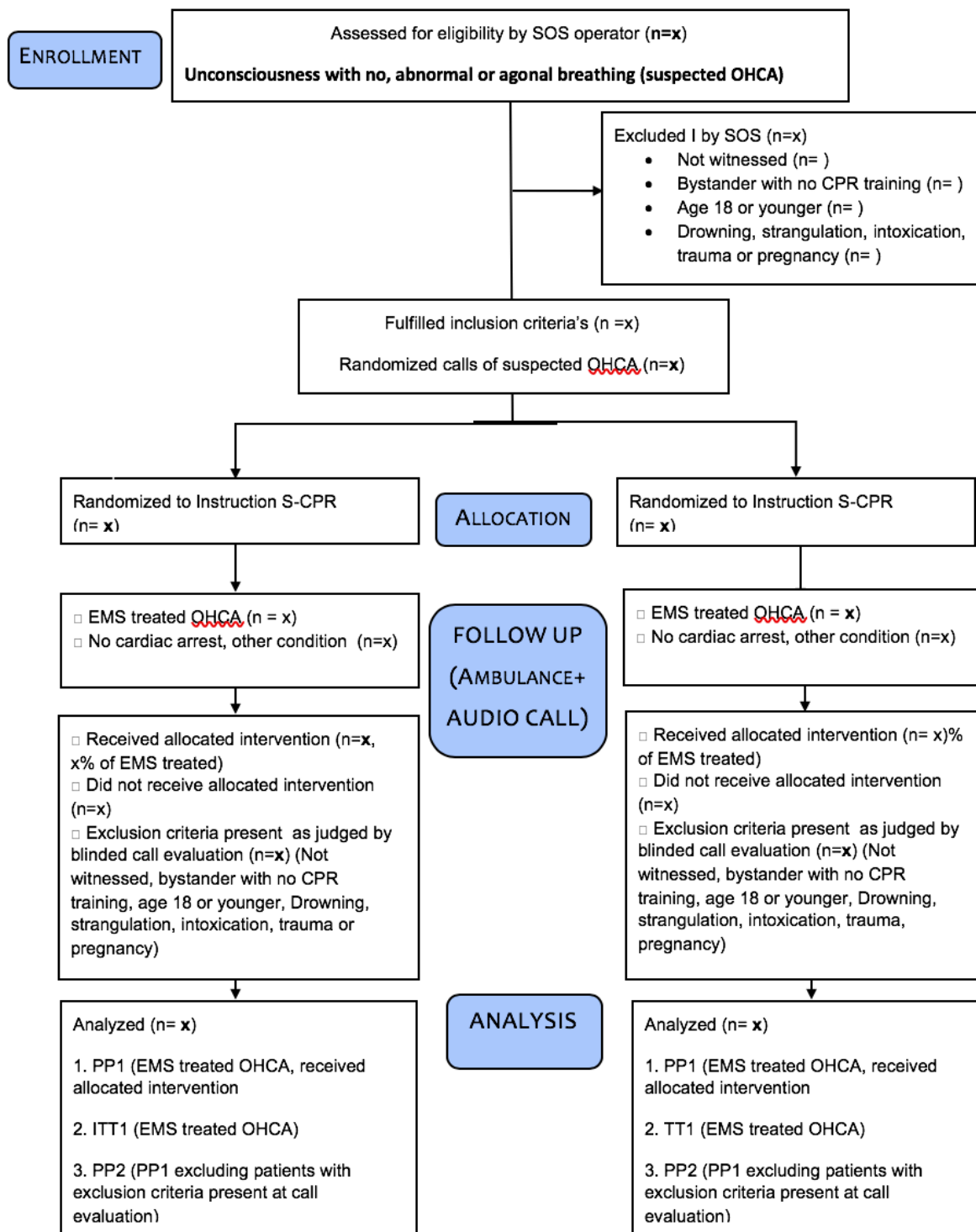
10.5 Power and sample size estimation

We estimated that 3260 patients (1630 in each group) would be needed in the primary analysis PP1 to have 80% power to show that CO-CPR is non-inferior to standard CPR. This calculation is based on the assumptions that the true survival rates after 30 days (primary outcome) in the population for standard CPR is 11% compared with 13.1% for CO-CPR, and that alpha (1 tailed) is set at 2.5%.

We defined 1.0 percentage point or less as the largest difference in survival that is clinically acceptable (i.e. the non-inferiority level which imply that a difference bigger than this would matter in practise). This difference is equivalent to an NNT of 100 (one person of 100 will die among those recommended CO-CPR, due to this recommendation). The reason for accepting this difference relies on the assumption that CO-CPR is easier to teach and perform, and therefore the treatment can be offered to more victims (please see also section 9.3).

In addition, we assumed that 20% will not receive the allocated intervention (e.g. randomized to CO-CPR but received S-CPR instructions or vice versa). We also assumed that 40% of the included patients will be excluded because of exclusion criteria's not possible to detect at the randomization (not OHCA, see section 5.3). Therefore, the recruitment goal was set to 6792 ($3260 / (0.8 * 0.6)$) randomized cases of suspected out-of-hospital cardiac arrest in order to receive 3260 in the primary PP1 analysis. (Please see also Consort Flow Diagram below)

CONSORT 2010 Flow Diagram



10.6 Non-Inferiority and Superiority testing

First, the primary analysis will be performed for non-inferiority in the PP1 population. If the primary analysis rejects the null hypothesis (i.e. CO-CPR is non-inferior to CPR with respect to the primary or some secondary outcomes), the comparisons between the treatment groups will also be done for superiority using 95% two sided confidence interval.(28) Second, the same analysis (first non-inferiority and then superiority) as above will be done for the ITT and PP2 population. The non-inferiority limit 1% will be used for both primary and secondary outcomes.

10.7 Subgroup analyses

Subgroup analyses will be performed for the primary outcome variable using logistic regression models with test of treatment-subgroup interaction for each of the predefined subgroup variables. The results will be presented as the odds ratio with 95 % confidence interval for each subgroup and the corresponding p-value for interaction between treatment and each subgroup variable.

Subgroups will be analyzed according to the following pre-defined variables:

- Gender
- Age
- Cause of OHCA
- Initial rhythm
- Place of cardiac arrest
- Time to start of CPR
- Time to arrival of EMS
- Neurological severity classification (CPC)

10.8 Randomization

Randomization will be performed by a computerized random generator (Microsoft.NET Random Constructor (Int 32)) in a 1:1 allocation ratio. The random generator is integrated in the dispatcher's software and there is no possibility for a dispatcher to see or guess randomization results before randomizing, therefore allocation concealment is preserved before randomization. For implementation the random generator is programmed so one dispatcher can only randomize a specific call one time. The computerized random generator is implemented by SOS-alarm into their software "Cord-comp".

11. Interim analysis and data monitoring committee

The trial will be monitored by an independent Data Safety Monitoring Committee (DSMC) that will receive unblinded summaries of data at the two interim analyses scheduled at 750 and 1500 patients. The DSMC will have mandate to evaluate specific safety concerns), as well as efficacy, with the option to either declare sufficient difference in the primary outcome variable, or to recommend that the study is continued until 3260 patients have been enrolled. Early stopping for efficacy reasons will only be considered if primary outcome differences are seen between the groups according to the Peto-Haybittle rule with a p-value ≤ 0.001 . The DSMC will be able to request unblinding of data if they find it necessary. The DSMC can initiate analysis at any time they request.

A Interim analysis was performed by an independent data monitoring committee in early 2022, reviewing all data including 30-day survival, after a total of 1250 patients (out of which 696 patients were included in the main PP1 population). The recommendation by the data monitoring committee was to continue the trial without modification.

12. Publication plan and author policy

The trial will be analyzed by an independent statistician and the results interpreted by the steering group. The principal investigator will prepare the manuscript before the allocation code is broken. The final manuscript will be submitted to a peer-reviewed international journal. Authorship will be granted using the Vancouver definitions and depending on personal involvement. The author list will start with Gabriel Riva and the last name will be Jacob Hollenberg. A separate publication list for all authors including the main study, as well as sub studies, has been created.

13. Enrolment and timeline

Q1-2 2014	Application to ethics committee
Q3-4 2014	Preparation
2015-2016	RUN-IN study
2017-2020	PILOT study
2022-2026	MAIN STUDY

14. References

1. Svensson L, Bohm K, Castren M, Pettersson H, Engerstrom L, Herlitz J, et al. Compression-only CPR or standard CPR in out-of-hospital cardiac arrest. *N Engl J Med*. 2010;363(5):434-42.
2. Rea TD, Fahrenbruch C, Culley L, Donohoe RT, Hambly C, Innes J, et al. CPR with chest compression alone or with rescue breathing. *N Engl J Med*. 2010;363(5):423-33.
3. Herlitz J. Annual report on Out-of-Hospital-Cardiac-Arrest <https://docs.google.com/file/d/0B6j4zddszpvyUG9IWTNlbkFWemM/edit?pli=1>: Swedish Cardiac Arrest Register; 2013 [
4. Sasson C, Rogers MAM, Dahl J, Kellermann AL. Predictors of Survival From Out-of-Hospital Cardiac Arrest A Systematic Review and Meta-Analysis. *Circulation-Cardiovascular Quality and Outcomes*. 2010;3(1):63-U111.
5. Valenzuela TD, Roe DJ, Nichol G, Clark LL, Spaite DW, Hardman RG. Outcomes of rapid defibrillation by security officers after cardiac arrest in casinos. *N Engl J Med*. 2000;343(17):1206-9.
6. Hasselqvist-Ax I, Riva G, Herlitz J, Rosenqvist M, Hollenberg J, Nordberg P, et al. Early cardiopulmonary resuscitation in out-of-hospital cardiac arrest. *N Engl J Med*. 2015;372(24):2307-15.
7. Weisfeldt ML. In CPR, less may be better. *N Engl J Med*. 2010;363(5):481-3.
8. Anantharaman V. Chest compression-only CPR or good quality 30:2 CPR. *Singapore medical journal*. 2011;52(8):576-81.
9. Cabrini L, Biondi-Zoccai G, Landoni G, Greco M, Vinciguerra F, Greco T, et al. Bystander-initiated chest compression-only CPR is better than standard CPR in out-of-hospital cardiac arrest. *HSR proceedings in intensive care & cardiovascular anesthesia*. 2010;2(4):279-85.
10. Bobrow BJ, Spaite DW, Berg RA, Stolz U, Sanders AB, Kern KB, et al. Chest compression-only CPR by lay rescuers and survival from out-of-hospital cardiac arrest. *JAMA : the journal of the American Medical Association*. 2010;304(13):1447-54.
11. Sayre MR, Berg RA, Cave DM, Page RL, Potts J, White RD. Hands-only (compression-only) cardiopulmonary resuscitation: A call to action for bystander response to adults who experience out-of-hospital sudden cardiac arrest - A science advisory for the public from the American Heart Association Emergency Cardiovascular Care Committee. *Circulation*. 2008;117(16):2162-7.
12. Iwami T, Kitamura T, Kiyohara K, Kawamura T. Dissemination of Chest Compression-Only Cardiopulmonary Resuscitation and Survival After Out-of-Hospital Cardiac Arrest. *Circulation*. 2015;132(5):415-22.
13. Sanders AB, Kern KB, Berg RA, Hilwig RW, Heidenrich J, Ewy GA. Survival and neurologic outcome after cardiopulmonary resuscitation with four different chest compression-ventilation ratios. *Annals of emergency medicine*. 2002;40(6):553-62.
14. Ewy GA, Zuercher M, Hilwig RW, Sanders AB, Berg RA, Otto CW, et al. Improved neurological outcome with continuous chest compressions compared with 30:2 compressions-to-ventilations cardiopulmonary resuscitation in a realistic swine model of out-of-hospital cardiac arrest. *Circulation*. 2007;116(22):2525-30.
15. Berg RA, Sanders AB, Kern KB, Hilwig RW, Heidenreich JW, Porter ME, et al. Adverse hemodynamic effects of interrupting chest compressions for rescue breathing during

- cardiopulmonary resuscitation for ventricular fibrillation cardiac arrest. *Circulation*. 2001;104(20):2465-70.
16. Sell RE, Sarno R, Lawrence B, Castillo EM, Fisher R, Brainard C, et al. Minimizing pre- and post-defibrillation pauses increases the likelihood of return of spontaneous circulation (ROSC). *Resuscitation*. 2010;81(7):822-5.
 17. Sugerman NT, Edelson DP, Leary M, Weidman EK, Herzberg DL, Vanden Hoek TL, et al. Rescuer fatigue during actual in-hospital cardiopulmonary resuscitation with audiovisual feedback: a prospective multicenter study. *Resuscitation*. 2009;80(9):981-4.
 18. group S-Ks. Cardiopulmonary resuscitation by bystanders with chest compression only (SOS-KANTO): an observational study. *Lancet*. 2007;369(9565):920-6.
 19. Iwami T, Kitamura T, Kawamura T, Mitamura H, Nagao K, Takayama M, et al. Chest compression-only cardiopulmonary resuscitation for out-of-hospital cardiac arrest with public-access defibrillation: a nationwide cohort study. *Circulation*. 2012;126(24):2844-51.
 20. Bohm K, Rosenqvist M, Herlitz J, Hollenberg J, Svensson L. Survival is similar after standard treatment and chest compression only in out-of-hospital bystander cardiopulmonary resuscitation. *Circulation*. 2007;116(25):2908-12.
 21. Japanese Circulation Society Resuscitation Science Study G. Chest-Compression-Only Bystander Cardiopulmonary Resuscitation in the 30:2 Compression-to-Ventilation Ratio Era. *Circ J*. 2013.
 22. Travers AH, Rea TD, Bobrow BJ, Edelson DP, Berg RA, Sayre MR, et al. Part 4: CPR overview: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122(18 Suppl 3):S676-84.
 23. Council ER. Summary of the main changes in the resuscitation guidelines. European Resuscitation Council Secretariat vzw; 2010.
 24. Monsieurs KG, Nolan JP, Bossaert LL, Greif R, Maconochie IK, Nikolaou NI, et al. European Resuscitation Council Guidelines for Resuscitation 2015 Section 1. Executive summary. *Resuscitation*. 2015;95:1-80.
 25. Shah M, Bartram C, Irwin K, Vellano K, McNally B, Gallagher T, et al. Evaluating Dispatch-Assisted CPR Using the CARES Registry. *Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors*. 2018;22(2):222-8.
 26. Couper K, Taylor-Phillips S, Grove A, Freeman K, Osokogu O, Court R, et al. COVID-19 in cardiac arrest and infection risk to rescuers: A systematic review. *Resuscitation*. 2020;151:59-66.
 27. Council ER. Resuscitation practices during the COVID-19 pandemic (ENG202005) 2020 [Available from: https://cosy.erc.edu/en/online-course-preview/356a192b7913b04c54574d18c28d46e6395428ab/index#/lessons/DqAxkWGEKeM3V_Pc7l8KyrEVQ36bzQ1J].
 28. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG, Group C. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA : the journal of the American Medical Association*. 2012;308(24):2594-604.