EuReCa TWO

A prospective observational analysis over three month in cardiac arrest and resuscitation registries in 29 European countries

The EuReCa TWO study protocol

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Summary

EuReCa ONE was a one-month survey of epidemiology, treatment and outcome of patients suffering an out-of-hospital cardiac arrest (OHCA), across 27 European nations, in October 2014. The EuReCa ONE study showed a high degree of variation in incidence and outcome across Europe and raised questions about the cause of these variations. For example, different interpretations of the term `bystander CPR` was noted and confirmed by a subsequent European survey. The need to further understand the cause of variation led to the establishment of the EuReCa TWO project.

EuReCa TWO has three primary aims: **1)** Expand the EuReCa network; **2)** Improve the understanding of the role, age and gender profile of bystanders in OHCA in Europe; **3)** Generate estimates of European OHCA incidence and outcome for all patients as well as subgroups that make up a small proportion of overall cases at national level, e.g. traumatic aetiology, patients transferred to hospital with ongoing CPR.

In order to achieve these aims, the following objectives will be fulfilled: encourage participating countries to aim for national data collection and encourage additional countries to participate in the study; increase the data collection period in order to provide more robust estimates of incidence, management and outcome; identify consistency and variation in the use of the term 'bystander CPR'; describe the incidence of 'bystander CPR' and its influence on OHCA outcome.

With 29 countries now part of the EuReCa 'family', the EuReCa TWO study will use an expanded Utstein-based dataset and data collection tool over a three-month data collection period for all participating countries. The EuReCa TWO study is registered by ClinicalTrials.gov (ClinicalTrials.gov, Registration Number: NCT03130088).

Background

Cardiovascular disease is still one of the leading causes of death in the developed world. In Europe it account for approximately 4.1 million deaths per year [1]. In the literature there is considerable variation in the incidence of out-of-hospital cardiac arrest (OHCA) and the incidence of resuscitation attempted between communities and countries in Europe [2,3,4].

In the European Registry of Cardiac Arrest study ONE (EuReCa ONE) study 10,682 cases of confirmed OHCA in 27 nations, covering an estimated population on 174 million people, were reported. The number of reported cases per country ranged from 6 to over 1,500 during the study period. The reported incidence of cardiopulmonary (CPR) attempts varied from 19.0 to 104.0 per 100,000 population per year. Sustained ROSC on hospital arrival was reported for 25.2% of all patients [5].

Keywords
Out-of-hospital Cardiac Arrest – Cardiopulmonary Resuscitation – Resuscitation Outcome – European Resuscitation Council – Resuscitation Registry – European Registry of Cardiac Arrest (EuReCa) – EuReCa TWO – EuReCa ONE

Established by the European Resuscitation Council (ERC) in 2007, the European Registry of Cardiac arrest (EuReCa) pursues the goal of recording and analysing Europe-wide cases of cardiac arrest. EuReCa was established with the aim of allowing analysis of resuscitation treatments in different medical emergency service (EMS) systems. EuReCa is intended to offer existing registries an option to collaborate internationally, providing a platform for joint scientific activities, and also to offer additional countries and regions access to the scientific opportunities available [5,6,7,8].

The ERC appointed the Steering Committee which is responsible for the scientific conduct. The Study Management Team appointed by the Steering Committee is responsible for the administration of all project tasks. Together, both form the EuReCa Core group, conduct work together in the study, and are responsible for planning and reviewing the research activities and budget. All countries participating in the EuReCa TWO study have one National Coordinator (NC) each, approved by the Steering Committee. National Coordinators are responsible for: ensuring that mandatory approvals (e.g. ethical approval) are obtained; communication with the participating registry or registries; measures to generate good data quality; supervision of data collection; and complete transmission of the data of their country. The EuReCa network consists of all National Coordinators and the EuReCa Core group [9].

Since 1991, the Utstein dataset has provided a widely accepted and uniform template for the collection of OHCA data, and was updated in 2004 and 2015 [10]. The EuReCa TWO dataset is based on the revised Utstein template published in 2015 [11].

In the EuReCa ONE study it was shown that it was possible to collect uniform data on OHCA in 27 nations in Europe. As widely described in the literature, more evidence of the treatment of OHCA is needed [7]. The EuReCa TWO study will aim to gather more robust data on OHCA in the expanded network of 29 European countries.

As stated in the current ERC Guidelines in 2015 CPR being initiated by a bystander and a short compression free interval are two of the most important measures to enhance survival after OHCA. Therefore the focus of EuReCa TWO is on the first two links of the chain of survival, namely the early recognition of a cardiac arrest and the start of early high quality chest compressions by a bystander [12].

Funding

The EuReCa TWO study is funded by the ERC and the national resuscitation registries or institutes conducting the study.

Research questions

In order to build on previous work and improve the robustness of estimates, the research questions in EuReCa TWO will closely mirror those of EuReCa ONE:

- What proportion of each country's national population is covered by data collection?
- What is the incidence of confirmed OHCA attended by the EMS in different European regions?
- What is the incidence of any CPR (cardiopulmonary resuscitation) attempted in OHCA throughout Europe?
- What proportion of CPR is started by:
  - Bystander – on scene by chance
  - Person alerted to scene by ambulance dispatch
  - Emergency Medical Services (EMS)?
- What is the age and gender profile of those who provide CPR before EMS arrival?
- In OHCA, what is the initial cardiac arrest rhythm of the patients where bystanders or EMS start CPR or any other resuscitation intervention – shockable or non-shockable?
- In patients where CPR was started by bystanders or EMS, what is the incidence and rate of any return of spontaneous circulation (ROSC) after out-of-hospital cardiac arrest?
- What is the incidence of patients never transported due to being declared dead on scene?
- What is the patient status at handover from EMS to emergency department or hospital system with on-going additional treatment in the next step of care (ROSC, on-going CPR, dead)?
- What is the incidence of patients who are still alive at 30 days (whether in-hospital or discharged) after their cardiac arrest event and/or what is the incidence of patients who are discharged alive from hospital?
- In patients with a witnessed collapse (witnessed by bystanders and/or EMS), found in a shockable rhythm and with an event of medical aetiology (i.e. Utstein comparator group):
  - What is the incidence of ROSC at hospital admission (at time of being handed over from EMS to emergency department or hospital system with on-going additional treatment, e.g. percutaneous coronary intervention (PCI)) for the Utstein group
  - What is the incidence of patients who are still alive at 30 days (whether in-hospital or discharged) after their cardiac arrest event and/or what is the incidence of patients who are discharged alive from hospital in the Utstein group?
- What factors determine ROSC, hospital admission and survival (as defined in questions above)?

Secondary Research Questions

- What is the European incidence and percentage of 30-day survival from OHCA with a traumatic aetiology?
- What is the European incidence and percentage of 30-day survival from OHCA in cases brought to hospital with unsustained ROSC and/or on-going CPR?

Material and methods

In the period of three months from October 1st to December 31st 2017 the EuReCa TWO multinational multicentre study will include all patients – irrespective of age, gender or any personal factor – who suffer a presumed OHCA occurring in any location other than an

acute hospital. Patients may be attended by the EMS at any stage during the event, including events where dispatch CPR is provided, even if cardiac arrest is not confirmed by the EMS.

The inclusion criteria include all patients who receive resuscitation in the form of chest compression and/or defibrillation of any type by the EMS or before the arrival of the EMS with continued resuscitation by the EMS or before the arrival of the EMS, that is immediately stopped (for any reason) when the EMS arrives. Patients who achieve ROSC before the arrival of the EMS are included as well. Patients found or declared dead are also included (for any reason).

The core Utstein variables are the basis of the EuReCa TWO dataset to ensure consistency and uniformity of data and to obtain comparable study results. Participating registries must ensure that their collected data comply with the definitions and descriptions of the dataset. The data items are divided into 'core' and 'optional'. All data must be submitted by each National Coordinator to the EuReCa TWO database. Patient-related data will be submitted in an anonymised format.

Statistical Analysis

As for EuReCa ONE, statistical analysis of the data collected will be performed centrally by a professional statistician.

Each submitted national dataset will be checked for completeness and plausibility before being merged into a central database for analysis. In the case of inconsistencies or critical missing data, the National Coordinator will be contacted to resolve the problem.

Annual incidence rates of OHCA and performance of CPR for each country will be calculated per 100,000 inhabitants per year, based on the reported population covered. In case of significant deviation from the average rate, the covered population will be verified together with the National Coordinator.

Statistical analysis will be based on the research questions. The basic patient group is defined as all persons with confirmed cardiac arrest attended by EMS in whom CPR was attempted (group 1 in the flow chart below). In the cases where CPR is not attempted (group 2), the reasons will be listed. group 1 will be used for determining the ROSC rate and for descriptive analysis (e.g. aetiology incident, location, witness status, bystander, demographics, interventions).

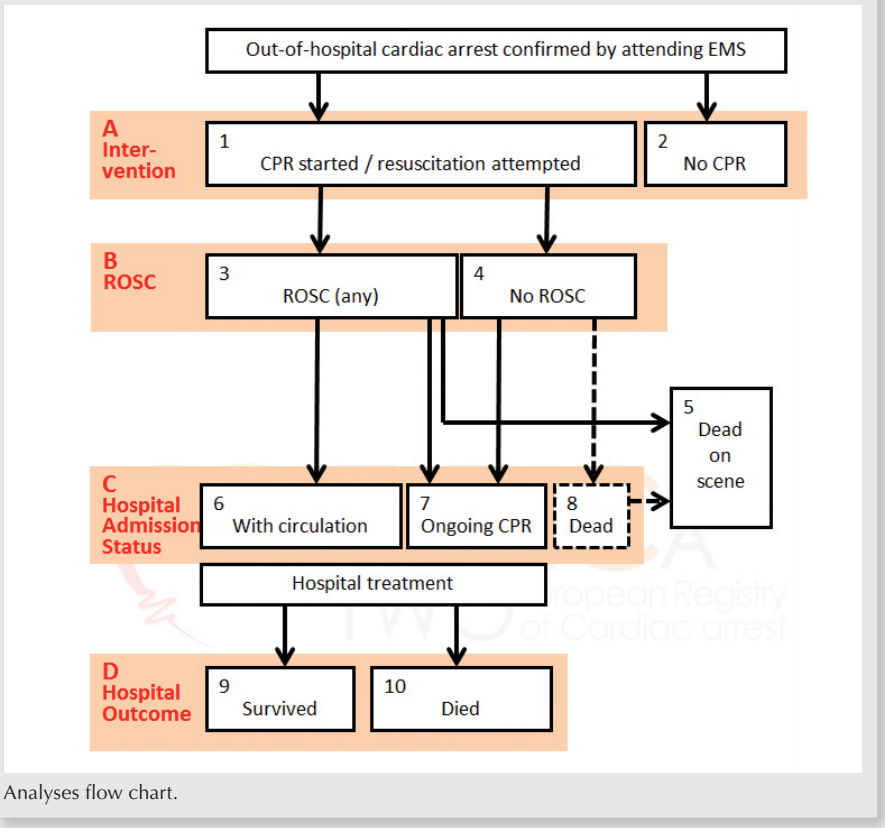
It is expected that all patients in group 1 will either be admitted to hospital or will be pronounced dead on scene (group 5). Patients brought to hospital but without therapeutic interventions in hospital (group 8) will also be classified as 'dead on scene'. Hospital outcome will be calculated for patients admitted to hospital with sustained ROSC (group 6) or with on-going CPR (group 7) (Fig. 1).

The rate of ROSC and hospital outcome will also be calculated within the Utstein comparator group. This group is defined as patients with a cardiac arrest due to a cardiac cause, with shockable rhythm, whose collapse has been witnessed by a bystander.

Most analyses will be performed for the whole patient group in which resuscitation was attempted (group 1) as well as for each participating country. The 95% confidence intervals (CI95) will be calculated for country-specific values and both rates and mean values, in order to reflect the statistical uncertainty in varying sample sizes.

Specific subgroups with very low incidence rates will be calculated for the whole database but not at a national level due to the potential limitations of small sample size. These analyses will include, but are not limited to, the outcome of trauma-associated OHCA, the outcome in cases with non-sustained ROSC on admission to hospital and in those who never have had any ROSC in the preclinical phase (subgroups of group 7).

Figure 1



Analyses flow chart.

Multivariate logistic regression analysis will be performed on the whole dataset for the endpoints (dependent variables) '30-day survival' and 'Sustained ROSC'. Sustained ROSC (group 4) will be considered in group 1 with prehospital and demographic variables as independent predictors. Survival to 30 days will be considered in group 1 as well as in groups 6 and 7 (i.e. survival after hospital admission). The country will be included as independent predictor in the prediction models.

Ethical approval

Every National Coordinator from each participating country is responsible for obtaining ethical approval unless a documented waiver is acceptable in that country. Participants are prohibited from submitting data unless a documented waiver or ethical approval is submitted to the Study Management Team. As only anonymised data will be reported and the data is recorded as part of routine data, a requirement for patient consent is not expected. It is however the responsibility of each National Coordinator to ensure that patient consent is not required in his/her jurisdiction.

The EuReCa TWO study is approved by the Ethic Committee of Christian Albrechts University Kiel, Germany (Register Number D480/17).

The EuReCa TWO trial is registered with ClinicalTrials.gov (ClinicalTrials.gov Registration Number: NCT03130088).

Data collection

The dataset will be collected and submitted in electronic format to the Study Management Team by each NC. NCs will be responsible for ensuring the quality of the data submitted from their respective countries.

In some countries OHCA registries are already established, or at least for OHCA cases where resuscitation is attempted. These countries will submit an extraction of their routinely collected data. Some variables might require a recoding process in order to fit with the data definitions for EuReCa TWO. In case that all data items required are not currently available, collection of additional data points for the three months' study period may be considered. If an existing resuscitation registry does not include OHCA cases where resuscitation is not attempted, submission of 'resuscitation-only' OHCA cases will be accepted. It will however be necessary to exclude these countries from calculation of overall OHCA incidence rates.

In countries where OHCA registries have not been established, the required data will be collected prospectively, for example, with paper-based documentation. Data collection may be limited to a representative subset of regions, or EMS areas, or even a single (representative) region.

Every participating registry must provide basic information on the EMS organisation, and the inhabitants of the region served as part of data submission. National Coordinators will transfer unprocessed data which is anonymous to the Study Management Team who will receive the data for analysis. National Coordinators however must retain an identifier for each case in case of any queries regarding incompleteness or inconsistencies in any single case. Data quality checks will be carried out by the Study Management Team and the Steering Committee prior to analysis.

Conclusion

The EuReCa ONE study in October 2014 described variation in incidence, ROSC, hospital survival rate and even in bystander CPR after OHCA throughout 27 nations in Europe. Further investigations are needed to explain the differences in incidence and outcome in these countries.

In the EuReCa TWO trial the data collection period is extended to three months to improve the robustness of OHCA estimates across Europe and in the participating countries. Our final aim is to increase survival after OHCA in the 29 European countries that will participate in EuReCa TWO.

Competing interests and conflicts of interest

JTG is the principle investigator of the EuReCa TWO Study; BWB, LB, JTG, JH, RWK, FRO and GP are the members of the steering committee of EuReCa TWO; HM, SM, IT, JW, RL (as statistician) and JE (as student assistant) are the members of the Study Management Team of EuReCa TWO. BWB is European Resuscitation Council (ERC) Board Director Science and Research; Associated Editor, European Journal of Anaesthesiology (EJA); Speakers honorarium from Medupdate, FoMF, Baxalta, Bayer Vital; Chairman, German Resuscitation Council (GRC); Board Member, German Society of Interdisciplinary Intensive Care and Emergency Medicine (DIVI); Associated Editor, Resuscitation.

Authors' contributions

JW and JE drafted the manuscript. JTG, JE, BWB, LB, RWK, IT, SM, FRO, LB, RL, HM, GP and JH are responsible for the study design and the revision of the manuscript. The EuReCa TWO SMT and SC revised the manuscript and gave substantial contributions. JTG is the principle investigator of the EuReCa TWO Study; BWB, LB, JTG, JH, RWK, FRO and GP are the members of the Steering Committee of EuReCa TWO; HM, SM, IT, JW, RL (as statistician) and JE (as student assistant) are the members of the SMT of EuReCa TWO.

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