

Sudden cardiac arrest prediction and resuscitation network: improving the quality of care (PARQ)

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Sudden cardiac arrest (SCA) is one of the top causes of mortality in industrialised societies. SCA is the sudden failure of the heart to pump blood through the body, caused by cardiac arrhythmia (ventricular fibrillation), most commonly secondary to coronary heart disease (acute myocardial infarction, myocardial ischaemia). This devastating condition is responsible for 50 per cent of cardiac deaths (Bonow *et al.*, 2015), which corresponds to 2 million deaths in Europe (Wilkins *et al.*, 2017).

Much progress has been made in reducing the burden of SCA on society through improved coronary heart disease management, development of community-based cardiopulmonary resuscitation and increased use of implantable cardioverter defibrillators. Yet, SCA still causes 15–20 per cent of deaths in Western societies and 20 per cent of all natural deaths in Europe (Graf *et al.*, 2008; Deo and Albert, 2012).

Left untreated, SCA is fatal within minutes. It is challenging to provide timely and effective treatment since SCA often occurs unexpectedly and in the community (out-of-hospital SCA). To compound matters further, we currently lack the ability to predict SCA occurrence, and SCA mostly happens in individuals who have never been examined by a cardiologist (van Dongen *et al.*, 2015). Predicting and preventing SCA is challenging, and patients rely on first-response treatment by citizen-rescuers, police officers and firefighters before emergency medical services arrive.

Large regional differences exist across Europe in the survival rates after SCA. The EuReCa ONE study (Gräsner *et al.*, 2016) investigated survival chances following cardiopulmonary resuscitation of out-of-hospital SCA patients across 27 European countries. Survival percentage ranged from 1.1 per cent (Romania) to 30.8 per cent (Switzerland). These numbers indicate that regional differences in individual risk, prevention and treatment have a major impact on an individual's chance to experience SCA and the chance of survival after an SCA event.

To prevent SCA and improve survival rates across all European countries, it is imperative to investigate:

- causes of SCA— inherited, acquired and environmental risk factors and their interactions across European regions
- regional differences in preventive measures and first-response treatment strategies and their effectiveness.

Scientific and clinical research on SCA is highly scattered. Existing networks and initiatives such as the European Resuscitation Council (ERC) Research NET / EuReCa connect resuscitation science and emergency medicine professionals. Cardiologists and biologists have established study cohorts to collect biological samples and identify biomarkers to enable individual risk prediction. However, the collaboration between researchers from these different fields is limited to a few, primarily Western European, countries. The scientific community would greatly benefit from a network connecting resuscitation scientists and medical biologists investigating SCA across Europe to advance SCA research.

PARQ aims to establish a network of excellence in SCA and resuscitation science that enables breakthrough developments to both decrease SCA incidence and to improve the patient survival rate after SCA and differences therein across Europe.

PILLAR 1 Improving individual risk prediction and prevention research

Multiple risk factors are associated with SCA occurrence. In each individual, a unique interaction of inherited, acquired, and environmental risk factors determines the risk of SCA occurrence. Inherited risk factors may arise from variations in genes that control cardiac electrophysiology (Hofman *et al.*, 2013). Gender also accounts for variation in SCA risk; men have a higher risk of suffering SCA, but

women are less likely to be resuscitated and have lower chances of survival (Blom *et al.*, 2019). In addition, acquired risk factors, such as myocardial ischaemia, diabetes mellitus and environmental factors (in particular, socio-economic factors that may be related to psychosocial stress) can contribute to SCA (Xia *et al.*, 2017; Leor, Pool and Kloner, 1996). Inclusion of inherited, acquired and environmental factors as integral components of SCA occurrence and outcome is critical to establishing new guidelines and preventive actions with cross-border relevance.

Individualised prevention and treatment strategies require elucidation of the complex interplay of risk factors. Ongoing initiatives, including large European cohort studies, aim to unravel the interactions of inherited, acquired and environmental risk factors.

Challenge 1

Cohort integration. Although efforts to collect clinical data and biological samples exist at national and international levels, coordination and harmonisation between such study networks is lacking. PARQ will provide the network to discuss standards for harmonisation of data collection and analysis, to enforce collaboration and data sharing between cohorts. In addition, the project will include European countries and regions that are not equally well represented in existing research efforts, with a strong focus on Eastern Europe.

Data collection and analysis. Standards will be developed for collecting, storing, and analysing genomic data, pharmacological data, electrocardiogram measurements, socio-economic data, and resuscitation data using the Utstein-style guidelines. These guidelines refer to an established consensus process, endorsed by the international resuscitation community, to facilitate and structure resuscitation research and publication.

Project members offer expertise in state-of-the-art genetic analysis methods (genome-wide association studies, whole exome/genome analysis) and will select optimal methods for data handling.

To support the complex bioinformatics analyses of large-scale phenotype and genotype data across Europe, the project has access to existing parallelisation frameworks for SCA data analysis. Such frameworks will facilitate the use of statistical tools and analyses in parallel in different environments, including computer clusters and cloud environments. In addition, the project will include medical ethics experts to evaluate ethical issues related to the use and exchange of information and personal data of SCA patients from different EU countries.

Inclusion of general practitioner (GP) files. SCA strikes individuals who are often unaware of their health risk and not monitored by cardiologists. The recognition of individuals at risk must be improved. Novel insights could be derived from clinical information present in personal health records and GP files. PARQ has formulated the unique ambition to include clinical information from GP files to strengthen research on the identification of relevant but so far unsuspected SCA risk factors. These GP files will be fully exploited using data mining methods, developed by consortium members, which utilise advanced machine learning algorithms that do not require an up-front selection of variables but identify useful variables themselves based on the data. Data mining has the power to improve prediction models, in part because temporal information, so far untapped, is utilised, e.g. the number of GP visits preceding the study endpoint and/or the evolution over time from nonspecific signs/symptoms towards ever more specific signs/symptoms. In addition, the data mining algorithms may reveal signs/symptoms at GP visits that are so far unsuspected to be associated with SCA. We will first apply the pipeline previously described to extract potential predictors. Thereafter, we apply advanced machine learning algorithms to create risk scores for patients. A dedicated GP task force will design a strategic plan for the collection, harmonisation, safe handling and storage of GP data per member country.

PILLAR 2 Improving first-response treatment

Multiple factors influence the chances of survival after SCA. The first minutes after SCA critically impact patient prognosis, yet the first care often occurs in an out-of-hospital setting. The delay between SCA and first-response treatment is the most important determinant of survival. European Resuscitation Council guidelines for resuscitation have been established and include instructions for first-response treatment: early recognition and call for help; early cardiopulmonary resuscitation, early defibrillation and standardised post-resuscitation treatment (Perkins *et al.*, 2015). Still, large disparities between SCA survival rates across Europe exist (Deo and Albert, 2012). Other determinants of survival, such as patient characteristics and regional differences in SCA management, should be considered to understand how these differences arise.

Challenge 2

The resuscitation science community has implemented Utstein guidelines for uniform reporting of SCA. However, first-response management and patient characteristics should be systematically reviewed to understand the variation in survival rates better. The challenge that PARQ will address is establishing the network to exchange new knowledge related to SCA management, including regional differences in financial resources. The network will focus on sharing data related to the effectiveness of text-message and app-based deployment of lay rescuers to understand how new technologies and treatment deployment strategies can enhance the effectiveness of bystander response. This requires that consensus is established on best practices for harmonising application-derived data. In addition, health economics experts in the PARQ network will evaluate the financial drivers behind the emergency response and treatment procedures established in European countries.

Challenge 3

Overall, improvement of individual risk prediction and intervention methods is required to achieve the lowest incidence of SCA and the highest chance of survival from SCA. The project members aim to develop first-response treatment strategies that are as much as possible tailored to an individual (e.g. based on comorbidity, drug use, or medical/genetic background and biomarkers). Traditionally, the research communities that focus on pillar 1 (typically cardiologist and molecular biologists) do not sufficiently interact with the pillar 2 research communities (typically emergency medicine and resuscitation scientists), and vice versa. A key challenge addressed by PARQ is connecting these researchers to create a critical mass of participants and establishing education programmes and workshops to foster interdisciplinary training.

To address these principal challenges, the PARQ will:

- promote science, training and education on advanced molecular biology, genetics and metabolomics techniques for the accurate analysis of SCA patient samples via training schools and exchange programmes
- promote standardisation of data collection and harmonisation through the definition of best practice standard operating procedures
- link and further expand existing SCA cohorts for a multidisciplinary approach to SCA research that will result in a more comprehensive analysis of potential risk factors, interconnect researchers involved in EU-funded initiatives and cohort studies such as ESCAPE-NET (Empana *et al.*, 2018), the resuscitation science community, and networks in the EU, including EuReCa and COSTA
- establish region-specific clinical guidelines for SCA first-response treatment
- expand the PARQ network and develop a dissemination strategy to enhance awareness of best practice strategies produced by PARQ members.

Working groups

WORKING GROUP 1 Coordination of sample collection and harmonisation of data

This group aims to coordinate biological and personal data collection to enable future studies into risk prediction and prevention of SCA (working group 2) and resuscitation strategies (working group 3). The group's focus points are the organisation and expansion of current SCA population cohort studies, the coordination of the development of best practice guidelines for harmonisation of data handling and analysis across Europe, and the coordination of collection and integration of personal health records derived from general practitioners in cohort studies.

WORKING GROUP 2 Coordination of research aimed at the prevention of SCA

This group aims to coordinate genome-wide association analysis, identify risk factors, and develop prediction models. The group's focus points are coordination of the inclusion of European samples in genome-wide association analysis, coordination of the identification of risk factors in multiple cohort studies, and the facilitation of the development of prediction models.

WORKING GROUP 3 Identification of procedural variations in SCA treatment and best practice definition

This group will identify the regional and national differences in emergency response and treatment procedures for out-of-hospital SCA between network members. This is envisioned as a continuously expanding process since the network will keep growing with new members from other countries.

WORKING GROUP 4 Capacity building

This group aims to expand the PARQ network through communication and dissemination activities. This will strengthen the interactions between experts in SCA risk prediction and resuscitation science to establish research collaborations in these areas.

Conclusion

SCA remains a general health problem because of our present inability to predict its occurrence and recognise vulnerable individuals. Moreover, chances of surviving an SCA event remain low because most SCA cases occur in the community, where life-saving treatment often arrives too late. To solve these complexities, the collection of large datasets in a harmonised fashion and the collaboration of various care providers, researchers and other stakeholders are needed. The PARQ project aims to strengthen such harmonisation and collaboration across various countries in Europe.

R References [click here](#)



PARQ COST Action

PROJECT SUMMARY

PARQ aims to create a network of researchers across Europe whose overall aim is to reduce the societal burden of sudden cardiac arrest (SCA). To reach this aim, PARQ will conduct studies that focus on two dimensions: (1) prevention of SCA through the discovery of its inherited, acquired, and environmental causes, and their interaction, and improved recognition of individuals at risk; and (2) improvement of survival chances after SCA through the development and implementation of resuscitation treatments in the community.

PROJECT PARTNERS

At present, the PARQ consortium consists of partners from 17 COST countries across Europe: Belgium, Denmark, France, Germany, Greece, Ireland, Italy, Luxembourg, Malta, The Netherlands, North Macedonia, Norway, Romania, Slovakia, Spain, Sweden and Turkey.

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