



## Clinical paper

## Determinants of occurrence and survival after sudden cardiac arrest—A European perspective: The ESCAPE-NET project<sup>☆</sup>



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## ABSTRACT

**Aims:** The ESCAPE-NET project (“European Sudden Cardiac Arrest network– towards Prevention, Education and New Effective Treatments”) aims to study: (1) risk factors and mechanisms for the occurrence of sudden cardiac arrest (SCA) in the population, and (2) risk factors and treatment strategies for survival after SCA on a European scale.

**Methods:** This is an Horizon2020 funded program of the European Union, performed by a European public-private consortium of 16 partners across 10 EU countries. There are 11 deep-phenotyped SCA cohorts for the study of risk factors and treatment strategies for survival after SCA, and 5 deep-phenotyped observational prospective population cohorts for the study of risk factors for occurrence of SCA. Personalized risk scores for predicting SCA onset and for predicting survival after SCA will be derived and validated.

**Results:** The 11 clinical studies with SCA cases comprise 85,790 SCA cases; the 5 observational prospective population cohorts include 53,060 subjects. A total of 15,000 SCA samples will be genotyped for common and rare variants at the Helmholtz Zentrum München (Germany) using the Illumina Global Screening Array which contains > 770,000 SNPs, and after imputation, a database of an estimated > 9 million variants will be available for genome wide association studies. Standardization of risk factors definition and outcomes is ongoing. An Executive Committee has been created along with a Collaboration Policy document.

**Conclusion:** ESCAPE-NET will complement ongoing efforts on SCA outside Europe and within Europe including the EuReCa project.

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## Introduction

Despite recent improvements in cardiopulmonary resuscitation and post-resuscitation care, survival after out-of hospital sudden cardiac arrest (SCA) remains as low as 10% on average when considering the whole spectrum of SCA including SCA with no attempts of resuscitation by Emergency Medical Services [1]. The challenges ahead of us include a better capacity to identify individuals from the population who are at risk of SCA, improvement in resuscitation strategies, and a better understanding of the mechanisms of SCA.

Multiple studies have reported on individual risk factors for SCA occurrence including traditional acquired risk factors or comorbidities (diabetes, myocardial infarction, hypertension, smoking, obesity) [2], familial predisposition [3] or neural control of heart rhythm [4] (Fig. 1 left). Still, we lack sensitive risk stratification algorithms for SCA [5]. Previous attempts at risk prediction modelling were conducted in specific subgroups such as patients with acute myocardial infarction [6] or, when addressing the general population, considered a limited set of covariates [7]. Moreover, while evidence for a role of hitherto little studied risk factors has recently emerged (socio-economic and psychosocial stress [8], and environmental factors such as air pollution [9] and roadway proximity [10]), the extent to which these emerging factors contribute to the occurrence of SCA beyond the effect of already known risk factors remains to be studied. Finally, the possible effect of drugs on SCA occurrence and their interaction with other risk factors has been insufficiently addressed. There are some reports on the associations between antipsychotics [11] with ventricular arrhythmias and/or SCA. However, they are usually based on a single geographic area or country. Furthermore, data on trajectories of exposures to different drugs, taking into account duration and dose, are lacking. Clearly, class and drug effects need to be evaluated. Risk stratification algorithms based on findings from epidemiological studies that evaluate traditional risk factors, acquired risk factors, environmental risk factors, and genetic variants *in combination* may aid in the identification of susceptible individuals and subgroups within the population (Fig. 1 right).

Improvements in survival after SCA are possible as new treatment strategies for SCA—in particular focusing on early start of resuscitation procedures—have shown to markedly increase survival rates [12–14]. To date, however, there has not been a large systematic study aimed at comparing the efficacy of the different treatment protocols across Europe and to establish which first-response treatment strategy for SCA offers the highest chance of survival. Importantly, in addition to treatment strategies, patient characteristics and organization of care may further impact on survival, although these factors are poorly considered simultaneously. This integrative approach has important implications as it may help to identify the respective weights of the determinants of survival after SCA and to prioritize necessary improvements. Also, accounting for differences in patients characteristics, treatment strategies and organization of care may help to understand and ultimately reduce the disparities in SCA incidence and survival rates after SCA across Europe and the world [15,16].

To obtain mechanistic insights, studies have focused on discovery of genetic factors on cardiomyopathies and inherited arrhythmia syndromes, which account for 10–15% of SCA in industrialized societies, and have identified relevant pathways [17]. For SCA in the general population, only few genetic analyses have been conducted so far, mostly because sufficiently large DNA collections have been lacking. Most prior studies used a candidate approach on common variants [18] and so far only 2 genome wide association studies on SCA have been performed

by members of the ESCAPE-NET consortium [19,20]. In general, recognizing risk gene (profiles) is of practical importance in clinical decision making, e.g., when a drug with potential arrhythmia risk (e.g., QT prolonging cardiac or noncardiac drugs) must be prescribed to an individual (pharmacogenetics).

## Aims

The ESCAPE-NET project (ESCAPE-NET: “European Sudden Cardiac Arrest network—towards Prevention, Education and New Effective Treatments”) has two main objectives: (1) to improve our knowledge of the determinants and mechanisms for the occurrence of SCA, and (2) to improve our capacities to increase the survival after SCA on a European scale.

Its specific aims are:

Towards population cohort integration:

1. To combine Europe’s largest deep-phenotyped SCA cohorts for full exploitation of the data
2. To improve and maximize data sharing and stimulate hypothesis-driven research by using new technologies in building and maintaining this large-scale database
3. To develop a financial strategy to keep the database alive after the duration of the project
4. To reach out to other SCA investigators with interest in collaboration and data sharing

Towards prevention:

1. To identify genetic, epigenetic, acquired, and environmental risk factors, and their interactions, for SCA occurrence in a combined large-scale European study population
2. To design a personalized risk score for SCA occurrence
3. To validate the personalized risk score

Towards treatment

1. To relate differences in first-response SCA treatment strategies to survival across different European countries
2. To evaluate effects of novel technologies for SCA treatment by utilizing smartphone applications (for rapid deployment of lay rescuers) and novel technological solutions (e.g., based on ventricular fibrillation [VF] waveform analysis)
3. To design a personalized risk score for survival after SCA

## The consortium

The ESCAPE-NET project is funded by the Horizon2020 program of the European Union, and addresses the specific challenges and scope of the Horizon2020 call ‘PM04: Networking and optimizing the use of population and patient cohorts at EU level’. This 5-year project will be performed by a European public-private consortium of 16 partners across 10 EU countries (Fig. 2, Table 1), including academic institutions that provide large patient cohorts, European scientific societies/associations for SCA research who will translate the outcomes into European clinical practice to prevent SCA and improve survival after SCA, and small and medium-sized enterprises who contribute specific expertise. The consortium consists of Europeans key cardiology and emergency medicine departments focusing on SCA, together with expert research departments in the field of Public Health, Ethics, Biomedical Informatics, Epidemiology and Statistics.

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