

# European sudden cardiac arrest network: towards prevention, education, and new effective treatments

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Sudden cardiac arrest (SCA) is the sudden cessation of the heart's task to pump blood through the body to sustain the body's metabolic demands secondary to a cardiac cause.

If the normal pump function is not restored promptly, irreversible (brain) damage occurs and death ensues within 10–15 minutes. Accordingly, SCA is a major cause of death, whose contribution to total mortality in industrialised societies is estimated to be as high as 20 per cent. Clearly, SCA has grave societal impacts. Solving the problem of SCA has met with great challenges until recently.

In most cases, SCA results from a particular type of cardiac arrhythmia: ventricular fibrillation (VF). While the heart's pump function is initiated by coordinated electrical excitation, this regulated process is disrupted in VF, where electrical excitation is uncoordinated and far too rapid (>300/minute).

In order to save the life of an SCA victim, VF must be stopped (most effectively by application of a direct-current shock, so-called defibrillation), after which the heart resumes its normal rhythm and pump function, and the patient regains consciousness.

The timely application of defibrillation is, however, challenging since SCA events occur abruptly and in most cases unexpectedly and in society. Thus, care provision by emergency medical services (EMS) often arrives so late that the patient dies or only survives with irreversible (brain) damage. This delay also hinders the collection of data that are relevant for scientific studies that aim at solving the problem of SCA because some key data must be collected while the patient is still alive. For instance, even a diagnosis of SCA cannot be made with any certainty if the delay to data collection is long because the characteristic ECG signature of VF dissolves over time into asystole (flatline). Thus, asystole, seen in an ECG recorded after a long delay, may reflect the delay. However, this ECG cannot be distinguished from an ECG which started as asystole as a result of a non-cardiac cause of sudden collapse (e.g. pulmonary embolism).

Clearly, the collection of data for SCA research must be conducted rapidly, however difficult this is. Importantly, data collection must be highly detailed in order to untangle the great complexity of interacting inherited, acquired, and

environmental/socioeconomic factors that may cause SCA on an individual patient's level and to correctly analyse the effects of new interventions. To compound matters, this detailed dataset must be collected from a highly diverse set of sources, at a minimum, all actors in the chain-of-survival: EMS, citizen-rescuers, hospital emergency rooms, hospitals. Thus, collaboration with these data providers, who each collect their data using specific data formats, is often needed. Collaboration with them is also necessary to capture SCA events across all of society, thereby minimising the risk that data are only collected from specific subgroups in society and are therefore not representative for larger populations. Finally, while collecting these datasets is clearly challenging, large datasets containing many SCA victims are needed to conduct detailed scientific analyses in view of the high complexity of SCA and the diversity on an individual's level.

## The ESCAPE-NET project

These difficulties in data collection have been a major barrier for large-scale scientific studies into SCA and progress in the clinical management of SCA. The consortium of the Horizon2020-funded project ESCAPE-NET (European Sudden Cardiac Arrest network: towards Prevention, Education, and New Effective Treatments) have aimed to remove this barrier (Empana *et al.*, 2018).

The ESCAPE-NET project is a collaboration of 16 academic and non-academic partners across 10 EU countries who contributed their detailed datasets of SCA patients, specifically collected for SCA research over years, to achieve one of its major aims: the creation of a harmonised shared database of SCA patients of unprecedented size that significantly increases the statistical power to conduct scientific studies aimed at SCA.

The ESCAPE-NET consortium has completed the creation of this database that now contains >100,000 SCA cases and >10,000 DNA cases, and in which inclusion is ongoing. It has also created a governance structure that allows the use of the data in this database by investigators within or outside of the ESCAPE-NET consortium.

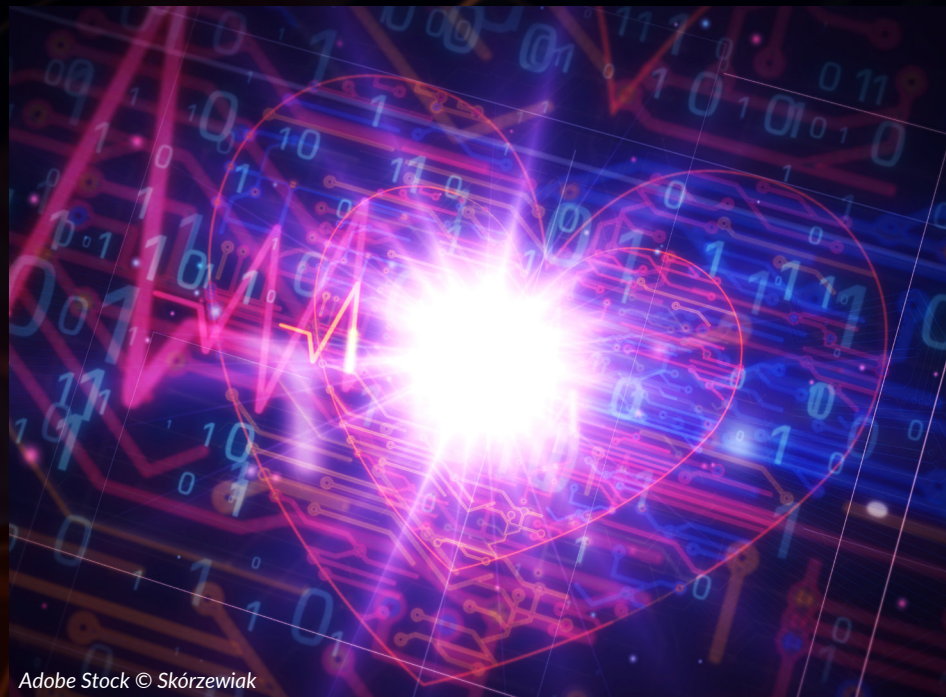
Importantly, the ESCAPE-NET project has also created a marketplace in which scientists from various disciplines may meet to conduct collaborative studies. This multidimensional approach is needed to resolve the complexity of SCA. Accordingly, the ESCAPE-NET consortium contains scientists from multiple dimensions, including cardiology, anesthesiology, emergency care, general practice, basic science, genetics, pharmacology, public health, data science and ethics. Together, they conduct studies to resolve the factors that contribute to the occurrence of SCA and studies to develop optimal resuscitation strategies. This has already resulted in 90 papers from members of the ESCAPE-NET consortium that cover multiple facets of SCA (a full list of publications is available on <https://zenodo.org/communities/escape-net/?page=1&size=20>) and that have importantly advanced the field of SCA research.

## Some discoveries of the ESCAPE-NET project Novel risk factors for SCA

At present, our ability to predict SCA risk on an individual's level is poor. This is largely due to the fact that not all risk factors for SCA have been discovered. For instance, there is a paucity of biomarkers (e.g. markers that can be measured from the body or its constituents such as blood) for increased SCA risk.

In our search for novel biomarkers, we focused on glycated haemoglobin (HbA1c) levels in the blood—that reflect an individual's average blood glucose levels over weeks and that is therefore used to monitor the quality of diabetes treatment in patients with diabetes—because this biomarker is known to be associated with various cardiovascular outcomes in persons with diabetes and those without. Whether HbA1c is associated with the risk of SCA has, however, been uncertain. We studied persons without diabetes, systematically studying HbA1c levels of patients who suffered SCA from all causes and found that elevated HbA1c levels are associated with increased SCA risk in these individuals (van Dongen *et al.*, 2020).





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In addition to this novel biomarker of SCA, ESCAPE-NET consortium members also discovered a behavioural risk factor for SCA, namely, physical inactivity (defined as <30 min/week of vigorous or moderate intensity). In a study that was specifically designed to study the inherited and acquired factors that contribute to the occurrence of SCA during a first acute myocardial infarction, it was found that the risk of SCA is almost doubled in patients with physical inactivity compared to those with physical activity (De Ferrari *et al.*, 2019).

We also exploited the rich dataset of the ESCAPE-NET project to increase our knowledge about already known risk factors of SCA, in particular, diabetes. Utilising these datasets provides us with the opportunity to obtain more detailed insights into the causes of SCA in persons with diabetes, in particular, those aged <49 years. We discovered that the incidence of SCA is elevated as much as eight times in these persons compared to persons without diabetes. We also found indications that, while the immediate cause of SCA in persons with diabetes is related to the sequelae of ischaemic heart disease—as is generally accepted in view of the fact that ischaemic heart disease is a major long-term effect of diabetes—other causes, yet to be discovered, are also more prevalent (Lynge *et al.*, 2020).

### Warning symptoms before SCA

It is generally acknowledged that SCA strikes unexpectedly in the vast majority of patients. The sudden and unexpected occurrence of SCA hinders our efforts to institute timely measures aimed at the prevention of SCA. Yet, utilising the large datasets of SCA victims in the ESCAPE-NET project and our ability to link them to datasets of clinical care provided by general practitioners and hospitals, we discovered that SCA does not strike unheralded in everyone as previously believed (Zylyftari *et al.*, 2021). In fact, the number of contacts with these health care providers of patients who suffered SCA nearly doubled in the six months leading up to the SCA event, with more than half of patients having health care contacts within two weeks before SCA. This suggests that we may have the opportunity to design strategies to prevent SCA if we are able to recognise the warning signs of impending SCA during these healthcare contacts.

### The role of often used medications in the occurrence of SCA

Medications may contribute importantly to the occurrence of SCA if they

impact the proteins that control the heart's electrical properties (cardiac ion channels), thereby causing the cardiac arrhythmias that underlie SCA. Such medications include drugs that are prescribed for the treatment of cardiac disease ('cardiac drugs') since these drugs derive their therapeutic effect from their interaction with cardiac ion channels and are designed for this effect. However, drugs that are not prescribed for the treatment of cardiac disease but are often used for various other common diseases ('non-cardiac drugs'), e.g. antidepressants, antiallergy drugs, antibiotics, may also interact with cardiac ion channels as an undesired side effect. Whether the use of these drugs leads to cardiac arrhythmias depends on an individual's vulnerability based on inherited factors or acquired factors (comorbidities) or their interaction.

Importantly, such non-cardiac drugs are generally prescribed by various non-cardiologist physicians (e.g. general practitioners, psychiatrists) who may not have sufficient experience dealing with this potential side effect and no means to test whether their patient has increased vulnerability. We studied whether this may result in an increased risk of SCA during the use of such drugs. We found that, while the use of cardiac drugs was associated with only a mild increase in SCA risk in the general population, the risk of non-cardiac drugs was larger (Eroglu *et al.*, 2021). This may indicate that appropriate drug prescription, taking the individual patient's vulnerability into consideration, may mitigate the risk of drug-associated SCA. This study has also utilised the large datasets (almost 40 000 SCA victims and their complete medication information) that were collected in clinical practice from the general population, thereby minimising inclusion bias.

### The effect of first-responder systems on survival after SCA

Conducting a Europe-wide study across 27 countries, we investigated why the survival chances after out-of-hospital SCA differs so strongly between these geographies (from less than 5 per cent to 27 per cent) (Oving *et al.*, 2021). We

found that this disparity is associated with differences in the organisation of care, in particular, the presence or absence of a system of first-responders who are dispatched to the SCA victim, i.e. non-ambulance personnel such as firefighters, police officers and citizen-rescuers. Survival chances were highest in regions with two or more types of first-responder systems and lowest in regions without a first-responder system. Moreover, we calculated that in regions without a first-responder system, survival chances would rise significantly if these regions would introduce a first-responder system.

### Women have lower chances to survive SCA

We found important differences between men and women in the incidence of out-of-hospital SCA and the chances of receiving treatment for it and surviving it (Blom *et al.*, 2019). While men suffer out-of-hospital SCA more than twice as often as women, women had lower chances than men to survive an out-of-hospital SCA episode. This was partly associated with a lower chance of women receiving immediate resuscitation treatment by bystanders, even when the collapse was witnessed. While the reasons for this delay remain to be investigated, we found indications that the lower level of resuscitation treatment received by women does not fully explain their lower survival chances and that biologic factors—yet to be discovered—also play a role.

### The effects of socioeconomic position on the chances to survive SCA

Socioeconomic position is known to impact on various health outcomes. By linking our large SCA datasets with datasets that contain socioeconomic information, we discovered that higher socioeconomic position, measured with an individual's income and education level, is associated with a higher chance to survive an SCA compared to lower position (Jonsson *et al.*, 2021). This finding may have to be considered when designing resuscitation strategies for SCA.

### The effects of the COVID-19 pandemic on SCA

ESCAPE-NET consortium partners, some located in Northern Italy, have discovered that, among the negative health effects occurring during the COVID-19 pandemic, there was an increased incidence of SCA and a lower chance to survive SCA (Baldi *et al.*, 2020; Marijon *et al.*, 2020). The underlying causes of these changes await discovery but are likely to be multifactorial and to include the same dimensions that are also relevant for SCA in general (Tan, 2020).

### Summary

The ESCAPE-NET project has provided an important boost to the field of SCA research in two key ways:

- it has created a marketplace to conduct SCA research in multiple dimensions
- it has created a shared, harmonised database and DNA bank of SCA patients that is world-leading in regards to size and quality.

The ESCAPE-NET consortium members have recognised the need to maintain this momentum. To achieve this, they actively reach out to other scientists to join this effort, e.g. by creating the PARQ project—Sudden cardiac arrest Prediction And Resuscitation network: improving the Quality of care, supported by COST (European Cooperation in Science and Technology, grant agreement No CA19137, <https://parq-cost.eu>).

The PARQ project aims to extend the SCA research community beyond the ESCAPE-NET network by involving other regions within and outside of Europe and stimulating exchanges between junior and senior SCA investigators across Europe. It is the ambition that, through the PARQ project and the implementation of a business model, the SCA research marketplace and its shared harmonised database may be maintained and further expanded, thereby offering the opportunity to alleviate the societal problem of SCA.

**R** References [click here](#)



### PROJECT SUMMARY

ESCAPE-NET aims to discover inherited, acquired and environmental causes of sudden cardiac arrest (SCA) and to improve resuscitation treatment for SCA. A shared database of >100,000 SCA patients has been created and >10,000 DNA samples collected, with procedures for data access by researchers outside the project consortium. ESCAPE-NET has generated 90 peer-reviewed scientific papers.

### PROJECT PARTNERS

16 partners, 10 European countries:  
6 universities: AMC University of Amsterdam, VU University Amsterdam, Copenhagen University, University Pavia, Université Paris Descartes, Karolinska Institute  
4 research institutions: Istituto Auxologico Italiano, Istituto Mario Negri, Helmholtz Center Munich, Fundacio IMIM  
2 professional societies: European Society of Cardiology, European Resuscitation Council  
1 Emergency Medical Service: Hradec Kralove Region  
3 SMEs: Catalyze, Panaxea, BC Platforms.

### PROJECT LEAD PROFILE

Coordinator Hanno L. Tan is a cardiologist at Amsterdam University Medical Center AMC. He conducts various research projects on SCA, both in the general population and in specific subgroups such as patients with cardiogenetic diseases associated with SCA. He works towards elucidating the causes of SCA and developing novel treatments, including device-based therapies and molecular therapies such as gene therapy.

### PROJECT CONTACTS

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