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European Resuscitation Council Guidelines 2021: Epidemiology of cardiac arrest in Europe

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Abstract

In this section of the European Resuscitation Council Guidelines 2021, key information on the epidemiology and outcome of in and out of hospital cardiac arrest are presented. Key contributions from the European Registry of Cardiac Arrest (EuReCa) collaboration are highlighted. Recommendations are presented to enable health systems to develop registries as a platform for quality improvement and to inform health system planning and responses to cardiac arrest.

Keywords: Cardiac arrest, Epidemiology, Incidence of cardiac arrest

Introduction and scope

Sudden cardiac arrest (SCA) is the third leading cause of death in Europe.^{1–3} Considerable effort has been made to understand the background and causes for cardiac arrest, and the differences in the incidence within and between countries. Factors influencing survival after out-of-hospital-cardiac arrest (OHCA) and in-hospital-cardiac arrest (IHCA) are well established but there remains considerable variation in incidence and outcome. Variation may arise from

differences in collecting data (e.g. case definition, ascertainment methods and outcome verification); case-mix (e.g. age, socio-economic status, co-morbidities), structure (e.g. different types of emergency medical services (EMS) systems or differences in the organisation of teams responding to IHCA; geographical variation, use of community responder schemes), process of care (e.g. EMS response time, time to defibrillation, post resuscitation care) as well as differences in the quality of treatment provided by individual practitioners (e.g. quality of CPR, interventions provided, decisions about when to start and stop resuscitation).⁴ In the early 1990s, the

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first Utstein recommendations were published to help researchers and practitioners report the same data points using the same definitions.⁵ It was anticipated that this would lead to a better understanding of the epidemiology of cardiac arrest, facilitate inter-system and intra-system comparisons, enable comparison of the benefits of different system approaches, act as a driver to quality improvement, identify gaps in knowledge, and support clinical research.⁶

Correct and reliable data are needed to understand causes, treatment and outcome after a cardiac arrest regardless of the place where it occurs. In this chapter, we provide an overview of causes, incidences and outcome of cardiac arrest in Europe. It is important that local situations are considered when results are benchmarked.

Search strategy

Individual search strategies were constructed for each section of this guideline. Searches were done in Medline. Only publications in English from the last 10 years were included, unless there was very little literature available. Abstracts were reviewed by at least two authors and relevant articles were read in full-text. Any studies that were obviously not about European patients and populations were excluded.

Europe and the world

The incidence of IHCA beyond Europe is most comprehensively described using data from the American Heart Association's Get With The Guidelines-Resuscitation Registry.² From 2003 to 2007, the estimated incidence of IHCA in the United States was approximately 6–7 cardiac arrests per 1,000 hospital admissions.⁷ Data also from the Get With The Guidelines-Resuscitation Registry from 2017 was used to estimate percentage survival to hospital discharge of 25%.⁸ Data from the UK National Cardiac Arrest Audit (NCAA) and from the Danish In-Hospital Cardiac Arrest Registry (DANARREST) both document lower incidences of IHCA (1.6 and 1.8 per 1,000 hospital admissions respectively) compared with the United States.^{9,10} Outside of Europe, multiple studies of OHCA incidence and outcome have been published reporting survival rates between 3–6% in Asia,¹¹ 11% in USA^{11a} and 12% in Australia and New Zealand.¹² While some of the variation observed between these studies is because of patient, area and, country-level differences, there are calculation and categorisation differences which add to the degree of variation.

These guidelines were drafted and agreed by the Epidemiology Writing Group members. The methodology used for guideline development is presented in the Executive summary. The guidelines were posted for public comment in October 2020. The feedback was reviewed by the writing group and the guideline was updated where relevant. The Guideline was presented to and approved by the ERC General Assembly on 10th December 2020.

Key facts

Out of hospital cardiac arrest

- Twenty-nine countries participated in the European Registry of Cardiac Arrest (EuReCa) collaboration.
- Out of hospital cardiac arrest registries exist in approximately 70% of European countries but the completeness of data captures varies widely.

- The annual incidence of OHCA in Europe is between 67 to 170 per 100,000 inhabitants.
- Resuscitation is attempted or continued by EMS personnel in about 50–60% of cases (between 19 to 97 per 100,000 inhabitants).
- The rate of bystander CPR varies between and within countries (average 58%, range 13%–83%).
- The use of automated external defibrillators (AEDs) remains low in Europe (average 28%, range 3.8%–59%).
- 80% of European countries provide dispatch assisted CPR and 75% have an AED registry. Most (90%) countries have access to cardiac arrest centres for post resuscitation care.
- Survival rates at hospital discharge are on average 8%, varying from 0% to 18%.
- Differences in EMS systems in Europe account for at least some of the differences observed in OHCA incidence and survival rates.

In hospital cardiac arrest

- The annual incidence of IHCA in Europe is between 1.5 and 2.8 per 1,000 hospital admissions.
- Factors associated with survival are the initial rhythm, the place of arrest and the degree of monitoring at the time of collapse.
- Survival rates at 30 days / hospital discharge range from 15% to 34%.

Long term outcomes

- In European countries where withdrawal of life sustaining treatment (WLST) is routinely practiced, a good neurological outcome is seen in > 90% of patients. Most patients are able to return to work.
- In countries where WLST is not practiced, poor neurological outcomes are more common (50% with 33% in a persistent vegetative state).
- Amongst survivors with a good neurological outcome, neuro-cognitive, fatigue and emotional problems are common and cause reduced health related quality of life.
- Patients and relatives may develop post-traumatic stress disorder.

Post cardiac arrest rehabilitation

- There is wide variation in the provision of rehabilitation services following cardiac arrest.
- Many patients do not have access to post cardiac arrest rehabilitation.

Key recommendations (expert consensus Fig. 1)

- Health systems should have population-based registries which monitor the incidence, case mix, treatment and outcomes for cardiac arrest.
- Registries should adhere to the Utstein recommendations for data definitions and outcome reporting.
- Data from registries should inform health system planning and responses to cardiac arrest.
- European countries are encouraged to participate in the EuReCa collaboration to enhance understanding of epidemiology and outcomes of cardiac arrest in Europe.



Fig. 1 – Epidemiology infographic summary.

- There is a need for more research and greater provision of post resuscitation rehabilitation services.
- It is expected that the clinical role of genetic and epigenetic factors will be increasingly understood as research in this area continues to grow. There are currently no specific resuscitation recommendations for patients with known genomic predispositions.

Out-of-hospital cardiac arrest

Incidence

The true incidence of OHCA in Europe is not known. The available literature is largely based on reports of OHCA attended by EMS. This

Table 1 – Reported incidence of out-of-hospital cardiac arrest and the corresponding figures of resuscitation started.

Country	Incidence of cardiac arrest per 100,000 inhabitants	Incidence of resuscitation attempted per 100,000 inhabitants	Reference
Spain	–	19	Rosell-Ortiz 2017 ²⁰
Ireland	–	54	Irish National Out of Hospital Cardiac Arrest Register, Annual Report 2019
Sweden	–	61	The Swedish Cardiopulmonary Resuscitation Registry; Det Svenska Hjärt-Lung räddningsregistret (www.hlrr.se)
Norway	64	51	Tjelmeland 2020 ^{20a}
Denmark	93	86	Danish Out-of Hospital Cardiac Arrest Registry www.ohca.dk
Poland	170	97	Gach 2016 ¹⁵

may underestimate the true incidence as in some countries, due to culture or belief, bystanders may not call the EMS when they witness a cardiac arrest. Other reasons for not calling EMS might be that the event was not witnessed, the patient was considered to be dead or had a do not attempt cardiopulmonary resuscitation (DNACPR) decision, or the patient had such severe comorbidities that it was not considered appropriate to request EMS resources. Cases of OHCA attended by EMS can be divided into two groups: 1) those where resuscitation was attempted and 2) those in whom resuscitation was not attempted. There is more information available on the number of OHCA patients who had resuscitation attempted by EMS than those patients who were attended by the EMS but not treated.

The European Registry of Cardiac Arrest (EuReCa), an international project of the European Resuscitation Council (ERC), provides the most comprehensive information on the epidemiology of cardiac arrest in Europe.^{1,13} The reported incidence of cardiac arrest varies greatly between countries, but also between regions within countries (Table 1).^{14–19} In the EuReCa ONE study the incidence of OHCA confirmed by EMS was estimated at 84 per 100,000 inhabitants per year, varying from 28 to 160. The estimated incidence of OHCA where resuscitation was attempted by EMS was 49 per 100,000 inhabitants, varying from 19 to 104.¹³ The follow-up study, EuReCa TWO, collected data for three months and reported OHCA confirmed by EMS to be 89 per 100,000 inhabitants per year, varying from 53 to 166, with resuscitation attempted by EMS reported as 56 per 100,000 inhabitants, varying from 27 to 91.¹ The studies report that resuscitation is attempted in about 50–60% of cases attended by EMS and considered for resuscitation. However, there is likely to be substantial underreporting and the variability between countries is considerable (see Table 1).

The number of reported OHCAs in Europe has increased in recent years when compared with the situation one or two decades ago. Whether these differences reflect an increased incidence or simply more comprehensive reporting is unclear. It is likely, at least in part, to be explained by improved case ascertainment methods and increased coverage by regional and national registries in recent years.

System configuration

Variability in EMS organisation is a common theme across international registries and epistries.^{12,22–25} It is therefore likely that differences in EMS systems in Europe account for at least some of the variation observed in OHCA survival rates. In preparation for revision of the ERC resuscitation guidelines, a survey of EMS systems was carried out across 28 European countries from October 2019 to January 2020. The survey mirrored previous findings internationally,

in demonstrating substantial variation in the number of EMS missions, level of training of EMS personnel, availability of helicopter emergency medical services (HEMS) and the availability of first responders across Europe.²¹

At the time of the survey, population density in participating countries varied from 3.6 to almost 510 people/km². While population characteristics explains some of the variation, there remains large differences in fundamental metrics of EMS activity. Examples include the number of EMS missions per 1,000 inhabitants, and response times. Most countries reported having hospitals capable of providing post-resuscitation care as recommended in the previous ERC resuscitation guidelines, but there were vast differences in the number of hospitals with 24/7 emergency departments per one million inhabitants. This variation in availability and structure of health care services may explain some of the differences in survival and outcomes after cardiac arrest.

All dispatch centres were reported as being part of the EMS system in 65% of the countries in the survey, in 14% some dispatch centres were part of the EMS. The number of dispatch centres varied between 0.35 and 3.3 per one million inhabitants, meaning the size of the country or the total population was not directly associated with the number of dispatch centres. Twenty-three of 28 countries reported offering dispatch-assisted CPR (DA-CPR) and most countries reported using standardised dispatch protocols and dispatch-assisted CPR instructions. Twenty-one countries reported having AED registries, the majority of which were available in dispatch centres.

Median EMS response times for urban areas in Europe of under ten minutes were reported to be achieved in only 32% of the countries. Less than ten-minute median response times in rural areas were achieved in some areas of most countries but were not achieved consistently in any country. It is therefore encouraging that the survey identified that at least 18 European countries had established first responder systems. However, another recent European survey described many kinds of first responder systems and highlighted that regions within countries had different approaches.²⁶ The introduction of first responder systems is positive but adds further difference which need to be considered when explaining variation in outcomes.

On scene treatment of cardiac arrest patients was also reported to be different in countries across Europe. Some EMS services were obliged to start treatment when they arrived on scene and not to terminate treatment, giving a reported incidence of EMS treated OHCA over 90 per 100,000 inhabitants. In other countries EMS personnel could terminate treatment and transport patients to hospital only if they achieved return of spontaneous circulation (ROSC). Even when termination of resuscitation on scene was permitted, most countries permitted transport with ongoing CPR. However, for most

countries, specific circumstances were stipulated to allow this practice.

The previous ERC Resuscitation Guidelines recommended that patients with OHCA of presumed cardiac cause are transported to a hospital that can provide immediate cardiac revascularisation, targeted temperature control and the ability to perform neuro-prognostication. Since then there has been an increase in the number of cardiac arrest centres (CAC) in several European countries. Currently there is no unique definition of a CAC, but the usual understanding is that this is an acute care facility capable of providing early emergency coronary angiography (CAG) and intervention, target temperature management (TTM) and critical care facilities on a 24/7 basis.²⁷ Two post-resuscitation interventions are most closely associated with improved outcomes post-cardiac arrest: early CAG and TTM, particularly for patients with an initial shockable rhythm and a presumed cardiac cause of the arrest.^{28–37} The rationale behind these interventions is discussed elsewhere. The rate of CAG and TTM provided following OHCA in Europe differs, and in the survey three countries in Europe reported that they had no hospitals that could provide all these services for OHCA patients.

In 2012 the European Parliament published a written declaration (0011/2012) recommending that all member states adopt common programs for the training of lay people and implementation of AEDs in

public places, adjusting of legislation in order to facilitate CPR and defibrillation by non-medical persons, and organization of systematic data collection on cardiac arrest for feedback and quality management (<https://www.europarl.europa.eu/sides/getDoc.do?pubRef=-%2f%2fEP%2f%2fNONSGML%2bWDECL%2bP7-DCL-2012-0011%2b0%2bDOC%2bPDF%2bV0%2f%2fEN>)

Registry data collection alone is not a guarantee for improved survival, but if core data variables are not available, routine monitoring and surveillance of OHCA outcomes is may be difficult. In the survey, 6 countries reported having a registry with full population coverage and 14 countries reported having a registry with partial population coverage. In these 20 countries, only 13 (65%) reported that they had information on ROSC from all participating areas, and seven (35%) reported having information on ROSC from some areas.²¹ Having cardiac arrest registries in 20 out of the 28 responding countries means that registry data is available in many European countries. Results also suggest that a renewed focus is needed to encourage countries to ensure that survival data is a core component of data collection. This is essential to enable comparison of results and benchmarking against the countries that have achieved high survival rates (Fig. 2).⁶

The ILCOR systematic review found low certainty evidence that exposure to resuscitation skills rather than years of experience are associated with survival.³⁸ Whether a paramedic or physician-based

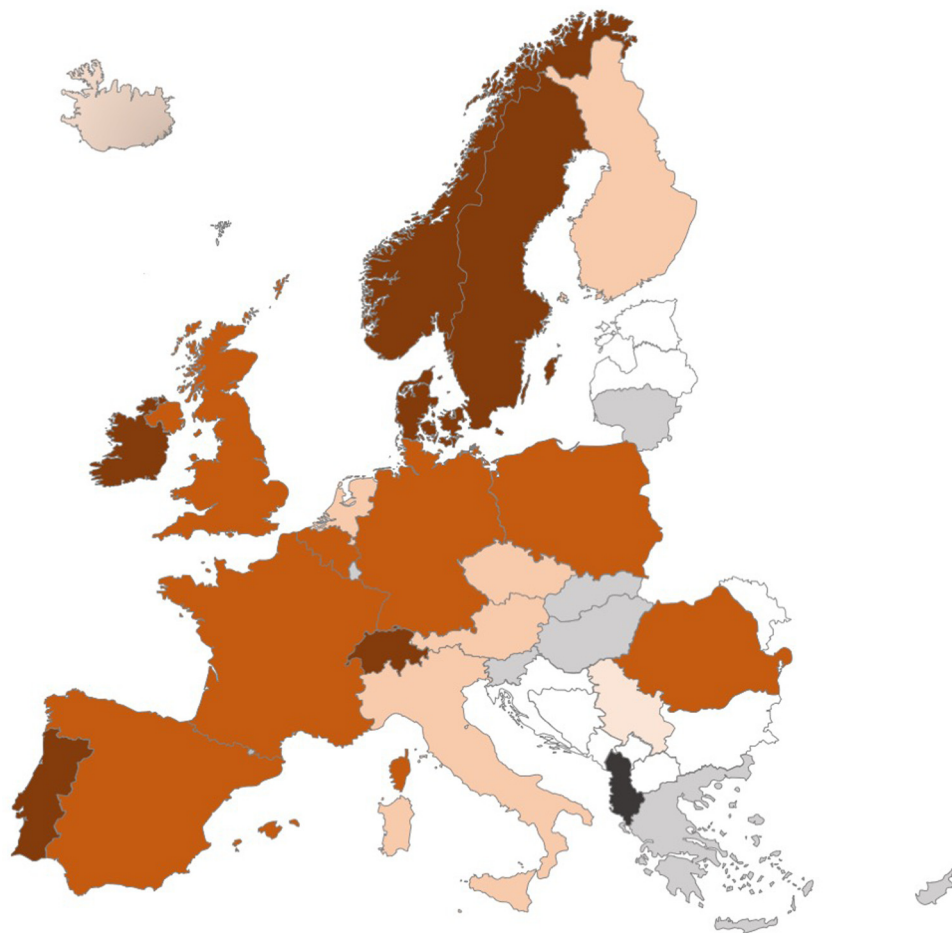


Fig. 2 – National registries across Europe. The darkest colour indicates a national registry covering the whole country, the second darkest colour indicates a national registry covering parts of the country, medium orange indicates several local registries, light with grey indicates one local registry, grey indicates no local registries and black is unknown. White colour indicates the country did not participate in the survey.²¹

EMS system effects outcomes is uncertain.^{39,40} Differences in EMS practice in initiation of resuscitation and transport among 10 US sites was found to contribute to variation in OHCA survival,⁴¹ and EMS agencies with the highest survival rates more often had: treatment from more than 6 EMS personnel; a shorter EMS call-response interval; more advanced airway attempts; and treatment from an ALS-BLS tiered system.⁴² The ERC survey showed differences in the types of personnel employed as part of the EMS, and in the levels and types of interventions that EMS personnel were allowed to carry out independently of medical doctor supervision. Team training in CPR involving all EMS personnel was reported for some parts of 26 countries and real-time CPR performance data was collected for feedback and debriefing purposes in 16 countries but used in all areas only in Cyprus. Defibrillators were available in all EMS vehicles dispatched to OHCA while mechanical CPR devices were available in all areas of only three countries.²¹

Chain of survival

In Europe, 112 is the universal emergency call number (<http://data.europa.eu/eli/dir/2002/21/oj>). By dialling 112, European citizens can reach an EMS dispatch centre either directly (1-step) or via an emergency call answering service which will route their call to an emergency medical dispatch centre (2-step). Most European countries also have a local emergency call number. It has been shown that the time from first ringtone to response from EMS dispatch centre is significantly longer when the call is routed via an emergency call answering service compared to directly received in an EMS dispatch centre.⁴³ In a French study it was shown that the 30-day survival for patients with OHCA was better when the initial call was received via a 1-step procedure compared with 2-step procedure.⁴⁴

The Chain of Survival for victims of OHCA was initially described by Friedrich Wilhelm Ahnefeld in 1967 to emphasise all the time-sensitive interventions (represented as links) to maximise the chance of survival.⁴⁵ The concept was built upon in 1988 by Mary M. Newman of the Sudden Cardiac Arrest Foundation in the United States.⁴⁶ It was subsequently modified and updated by the American Heart Association in 1991.⁴⁷ The first link in the chain of survival is early recognition of a cardiac arrest and call to EMS. This goes hand in hand with early CPR measures initiated by a bystander, with or without instructions from a dispatcher (DA-CPR). Bystander CPR remains one of the key interventions in improving survival after OHCA, it can be associated with a threefold increase in survival with favourable neurological outcome.^{48,49} Therefore, many different actions have been taken to improve bystander CPR rate throughout Europe and the world.⁵⁰ The ILCOR systematic review found very low certainty evidence that DA-CPR improves outcomes from cardiac arrest.⁵¹ In recent years, DA-CPR seems to be one driver of an increased bystander CPR rate.⁴⁸ It was shown in EuReCa ONE and EuReCa TWO that the DA-CPR rate increased from 29.9% in 2014 to 53.2% in 2017, respectively.^{1,13}

Nevertheless, bystander CPR rate varies enormously within and between European countries. The EuReCa ONE study estimated that the average bystander CPR rate across the 27 participating countries was 47.9%.¹³ Twenty-eight European countries were included in the 2017 EuReCa TWO study, which documented a bystander CPR rate overall of 58%, ranging from 13% in Serbia to 83% in Norway.¹

At least part of this variation in bystander CPR may be because the definition of bystander CPR is not uniformly interpreted across Europe. This is mainly because there has been an increasing variety of responders and responses prior to EMS arrival in the event of OHCA,

meaning it has become more difficult to define whether the person providing CPR is considered to be a bystander or lay person, or if they are considered to be part of the EMS response.⁵²

The use of AEDs remains infrequent in Europe. In some European regions the rate of use of an AED is higher. For example, the region around Amsterdam and North-Holland has achieved AED use in 23%–59% of all OHCA cases that were attended by EMS.^{53,54} In contrast, the use of AEDs was reported to be 15% in Sweden and in only 3.8% of OHCA cases in Copenhagen in Denmark.^{55,56} New initiatives have been proposed to increase the use of AEDs and to increase the likelihood of having an AED deployed to the scene e.g. the use of drones⁵⁷ and the use of App-based systems to locate and send bystanders to attend the OHCA and start CPR immediately as well as to send a second person to get an AED.^{54,58–60} Whether an AED is present also depends on the location of the OHCA. Approximately 49% of companies who took part in a questionnaire-based survey in Belgium in 2012 and 2014 had an AED on their premises.⁶¹

Outcome after out-of-hospital cardiac arrest

Scientific recommendations and policy recommendations from the European Parliament [Declaration of the European Parliament of 14 June 2012 on establishing a European cardiac arrest awareness week: <https://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP/TEXT+TA+P7-TA-2012-0266+0+DOC+XML+V0//EN>] have highlighted the importance of each country knowing its outcomes from OHCA and striving to improve them.⁶²

The EuReCa TWO study reported an overall survival rate of 8% after OHCA in Europe.¹ A systematic review and meta-analysis which included 56 studies from Europe reported a survival to discharge rate of 11.7% (95% CI 10.5–13.0%).⁶³ A survival rate of less than 8% (less than 3% with good neurological outcome, Cerebral Performance Category (CPC) 1-2) has been reported from the Pan-Asian registry,¹¹ the Australian Aus-ROC Epistry involving Australia and New Zealand.¹² reports a survival of 12%, and the US reports about 11% (9% with good neurological status).⁸ These average estimates are based on widely varying survival rates within and between participating countries. For example, in the EuReCa ONE study, average survival was estimated at 10.3%, ranging from 1.1% to 30.8% among the participating European countries. The most recent data from EuReCa TWO estimates average survival of 8% (range 0%–18%).¹ In recent years, survival rates have also been reported from individual European countries; England, 7.9%;¹⁶ France 4.9%;⁶⁴ Spain 13%;²⁰ Germany 13.2%; (<https://www.reanimationsregister.de/downloads/oeffentliche-jahresberichte/rettungsdienst/142-2019-ausserklinischer-jahresbericht-2018/file.html>) Ireland 6%;⁶⁵ Sweden 11.2%;⁶⁵ Denmark 16% [https://hjerterestopregister.dk/?page_id=428]; Norway 14%.²¹

Survival after OHCA is dependent on many factors beyond the initial resuscitation attempt, and variation in survival rates reflect the heterogeneous factors that have led to the OHCA. Factors that contribute to heterogeneity in survival rate include: gender;^{66,67} cause; initial arrest rhythm;^{68–71} previous and existing comorbidities;^{72,73} event location;^{74,75} socioeconomic deprivation;^{76,77} and ethnicity.⁷⁸ The health organisation that provides care, the available resources and the organisation's capacity to coordinate and act in each and every one of the links in the chain of survival is also critical.⁷⁹ The ILCOR systematic review found very low certainty evidence that CACs improve survival from OHCA.⁸⁰ The availability of specific post-resuscitation measures, such as percutaneous coronary intervention

(PCI),^{20,35,81} and TTM^{82–85} or more centralised CAC,^{86,87} constitute further factors that may contribute to variability in patient survival.^{88–93} At a national level, public health policies, legal and strategic initiatives that are in operation in the broader societal network will influence the number of OHCA survivors and their subsequent quality of life.⁹⁴

It is well known that even within emergency services with similar structures or between regions of the same country, there is variability in survival even when demographic considerations, characteristics of the event and the community response are taken into account.¹³ There is also variability within the services themselves over different time periods, usually reflecting a tendency to improve survival as actions are implemented that have a demonstrated effect on final survival.^{25,94} Variability in the percentage of attempts at resuscitation was also observed between countries in Europe and between different EMS systems in the same country.^{1,13,95} Despite awareness of all these nuances, there remains an important part of the variability that is difficult to explain with current data capture systems.⁶⁵ Indeed, the variability reported between results when comparing data from prospective registries with a priori defined objectives compared with retrospective data from more administrative registries is of note.^{8,96} The same happens when comparing data from registries with clinical trials conducted by these same services.^{16,97–99}

Robust collection of key data elements (e.g. initial arrest rhythm, witnessed status, cause of collapse) enables analysis of survival in specific subgroups. The most recent Utstein guidelines recommend categorisation of patients⁶ and the Utstein comparator group (bystander witnessed, shockable initial rhythm) is particularly noteworthy as the group where the chances of patient survival is typically higher, with approximately 20% reported for England and just over 30% in EuReCa.^{1,8,100} Individual countries (Denmark, the Netherlands, Sweden, Czech Republic and Norway) in EuReCa TWO exceeded 40% survival for this group of patients.¹

Survival for patients with a traumatic aetiology has been less encouraging with estimated survival between 2% in the German registry and 2.8% in EuReCa TWO and up to 6.6% with good neurological status at discharge in a cohort from a specific Spanish EMS.^{1,101,102} Attempting resuscitation after traumatic cardiac arrest was previously considered futile,¹⁰³ but since 2015 a specific ERC algorithm provides specific recommendations and interventions that may result in survival.¹⁰⁴

Paediatric OHCA (POHCA)

The varying definition of paediatric age means that it is difficult to compare survival rates in POHCA. The most widespread definition is patients aged less than 18 years; however, some studies have included patients up to 21 years. Depending on the age groups analysed, there are different characteristics, causes and survival rates.¹⁰⁵ Most data on POHCA survival comes from American and Japanese registries,^{106,107} with only partial data from local registries.^{108,109} The most substantial data from Europe in terms of number of cases and trends over time, are those from the Swedish registry.¹¹⁰ From 1990 to 2012 the Swedish registry documented an incidence of 4.9 cases per 100,000 person-years under the age of 21 years, non EMS-witnessed cases. Survival reported was as follows: infants (less than 1 year) 5.1%; young children (1–4 years) 11.0%; older children (5–12 years) 7.5%; and adolescents (12–21 years) 12.6%. For EMS-witnessed cases during 2011 and 2012, survival was 14.9%, 22.2%, 21.2% and 17.9% for the same respective age groups.¹¹¹ Swedish data suggest that POHCA survival has been progressively increasing.

In-hospital cardiac arrest

As for OHCA, the true incidence of in-hospital-cardiac arrest (IHCA) is not known. The available literature is often from single centres, making generalizability difficult, and ultimately all patients who die in hospital die from a cardiac arrest. In 2019, an updated Utstein-style reporting template for IHCA was published, emphasising the importance of a common data set report form, to enable comparison between regions and countries.¹¹²

Incidence

The true incidence of IHCA is difficult to assess for several reasons. Ultimately, all patients who die in hospital have a cardiac arrest, but all these deaths are not considered a cardiac arrest that should be considered for resuscitation. A study from Gothenburg in Sweden compared the total number of in-hospital deaths during one year with the number of attempted resuscitations and found that resuscitation was started in only 12% of all in-hospital cardiac arrests.¹¹³ In Sweden, the ratio of OHCA to IHCA has been reported to be 1.7 to 1 (The Swedish Cardiopulmonary Resuscitation Register (Svenska Hjärt-Lung-räddningsregistret) [November 1 2012]; Available from: www.hlrr.se).

Many IHCA studies have limited generalisability because they were carried out in single centres. Differences in DNACPR policies between countries are likely to explain some of the variation seen in the incidence of IHCA.¹¹⁴ There may also be difficulties in the reporting of IHCA due to logistic problems. For example, patients who develop ventricular fibrillation (VF) during a coronary angiography, which is rapidly defibrillated, may not always be reported to a registry.

There are several ways of calculating IHCA incidence: IHCA/hospital bed, IHCA/hospital admission, IHCA/country/region/city/state. The incidence of IHCA per 1,000 hospital admissions has been reported as 2.8 in Poland,¹¹⁵ 1.8 in Denmark¹⁰ and Norway (unpublished observation), 1.7 in Sweden,¹¹⁶ 1.6 in the United Kingdom,⁹ and 1.5 in the Piedmont region in Italy.¹¹⁷ A study from Trondheim in Norway documented 72 IHCA events per 1,000 hospital beds.¹¹⁸

Gender also influences incidence. The incidence ratio of men to women for IHCA has been reported to be 1.4–1.6 to 1.¹¹⁸ This may largely be explained by a higher prevalence and a higher mortality from cardiovascular disease in men.¹¹⁹

In a recently performed European survey 18 of 28 countries reported having a national registry for IHCA, but only two countries (Sweden and Denmark) reported that all hospitals were included.²¹

System configuration and chain of survival

In 2017, 89.4 million people were treated on wards in hospitals throughout Europe, a number that has increased in recent years [Eurostat. Hospital discharges and length of stay statistics - Statistics Explained [cited 2020 Jan 18]. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php/Hospital_discharges_and_length_of_stay_statistics#Hospital_discharge] Unfortunately, medical care in the hospital is not devoid of complications and serious adverse events, which occur in approximately 10%–20% of all patients.¹²⁰ In a large European observational study which included approximately 46,000 post surgical patients, mortality was 4%, with large differences between countries.¹²¹ The most alarming finding

from this study however, was the high proportion of 'failure to rescue', since 73% of patients who died were not admitted to critical care at any stage after surgery. Adverse events were partly caused by sub-optimal care but the majority were due to a deterioration of the underlying disease. There are two main differences between IHCA and OHCA in respect of the detection and prevention of cardiac arrest. First, in most cases, life-threatening events in hospital are heralded by a deterioration of vital signs hours or even days before the catastrophic event occurs and therefore may be detectable early and therefore preventable.¹²⁰ Secondly, adequate monitoring of patients should enable early detection of patients at risk and therefore the dedicated resuscitation team should preferentially function as a medical emergency team (MET) or rapid response team (RRT) instead of a pure cardiopulmonary resuscitation (CPR) team. If these patients are monitored inadequately the life-threatening situation may be noticed too late, and an increase in rates of in-hospital CPR and unexpected deaths may follow.¹²² This development may even accelerate due to increasing workload in the hospitals and increasing comorbidities of patients. The ILCOR 2020 Consensus on Science and Treatment Recommendations found low certainty evidence that rapid response systems reduced the incidence of IHCA and improved mortality, leading to a weak recommendation supporting the introduction of rapid response system (rapid response team/medical emergency team).³⁸ This compliments the guidance introduced by the ERC supporting the establishment of an early warning system for unexpected emergencies.¹²²

IHCA - Systems to detect critical illness

On June 23, 2017, The European Resuscitation Council, the European Board of Anaesthesiology and the European Society of Anaesthesiology issued a joint statement calling upon European hospitals all to use the same internal telephone number (2222) to summon help when one of their patients has a cardiac arrest. It is hoped that by implementing one emergency call number in hospital, time to call for help might be reduced.¹²³

IHCA – response times

Medical emergency teams (METs) or rapid response teams (RRTs) differ from pure resuscitation or cardiac arrest teams in that their goal is the timely identification and treatment of in-hospital emergencies in order to avoid cardiac arrests and unexpected deaths.¹²⁴ (see advanced life support guidelines). In contrast to OHCA, where the time from cardiac arrest to the initiation of resuscitation efforts (either by bystanders or the EMS) is key, data on RRT performance largely pertain to criteria triggering the alarm, comorbidities, and pre-alarm hospital length of stay of the affected patients.¹²⁵ Delays in treatment are associated with worse outcome.¹²⁶

Data on traditional resuscitation team response times after IHCA are also scarce. However, data from a large Swedish registry showed that a delay of more than one minute from cardiac arrest to call or to start of CPR, a delay of more than 2 min from call until the arrival of the rescue team, and a delay of more than 3 min from cardiac arrest to defibrillation were all associated with worse overall outcome.¹²⁷

There have been few studies that evaluate the efficacy of METs in decreasing the incidence of unexpected deaths, unplanned admission to the Intensive Care Unit (ICU), or both. A major problem is that high certainty evidence cannot be achieved because randomisation of individual patients to care delivered by a MET versus a control group is impossible. Therefore, available evidence derives mostly from observational studies, before-after designs or protocols where some

hospitals introduced a MET while other hospitals in the same area or belonging to the same hospital organization had not. In the most recent meta-analysis on this topic, which included 29 studies with 2,160,213 patients (1,107,492 in the intervention group and 1,1083,80 in the control group), METs were associated with a significantly decreased hospital mortality and incidence of cardiopulmonary arrest.¹²⁴ Even though it is difficult to prove the efficacy of MET implementation using evidence-based criteria, pathophysiological reasoning suggests that detection and adequate treatment of patients before a catastrophic event occurs is the right thing to do. Timing is important in many areas of acute care such as sepsis, myocardial infarction and stroke.

IHCA outcome

Many factors will determine the outcome of patients who have an IHCA. Some of these factors can be modified and others cannot. Factors that cannot be modified include patients' age, sex and comorbidities. For example, elderly patients have a lower chance of survival after IHCA.^{128,129} In most cases, the cause of the cardiac arrest cannot be changed. A patient who has a cardiac arrest caused by myocardial infarction/ischaemia has a much better chance of survival than a patient who has a cardiac arrest from other causes, e.g. heart failure.

A modifiable factor of great importance is the location in the hospital where the cardiac arrest occurs. If the cardiac arrest occurs on a general ward, the patient is not usually adequately monitored, and the cardiac arrest may not be witnessed. These factors are associated with a lower chance of survival.^{116,130} Monitoring of the ECG at the time of collapse is associated with a 38% reduction in adjusted risk of death after IHCA. Location in hospital and the geographical locality are the main predictors of ECG monitoring being in place at the time of cardiac arrest.¹³¹ The significant variability in ECG monitoring at different centres may indicate the need for guidelines on the use of ECG monitoring.

A first recorded rhythm of VF is predictive of a higher likelihood of survival.^{130,132} The earlier the ECG is recorded, the higher the likelihood that the patient will present with VF.¹³³ Another factor that most often cannot be influenced is the time when the arrest is taking place. There is a higher likelihood of survival if the arrest occurs during regular working hours Monday to Friday.¹³³ Time to delivery of treatment is associated with survival among IHCA patients found in a shockable as well as a non-shockable rhythm.¹¹⁶

Finally, an important factor determining the chance of survival after resuscitation is the hospital's policy on DNACPR decisions. Hospitals in which a very high proportion of cardiac arrest patients have a DNACPR decision are expected to have a higher survival rate among patients with IHCA in whom resuscitation is attempted compared with hospitals in which resuscitation attempts in futile cases are more common. Thus, it is not surprising that reports on ROSC and survival to hospital discharge or 30-day survival vary considerably.^{9,115–118,134–137} The chance of ROSC varies from 36%¹¹⁷ to 54%¹³⁵ and the chance of survival to discharge/30 days varies from 15%¹¹⁷ to 34%.¹³⁵

Long term survival

Recovery and rehabilitation of cardiac arrest survivors

The Utstein-style template defines the variables to be collected in the event of OHCA and the recording methodology to be used.⁵ Since the

introduction of the Utstein-style template, patient survival and subsequent neurological status has received increasing focus.⁶ The number of patients who achieve sustained ROSC has remained a key variable as this is one of the first criteria in deciding whether post-resuscitation care is appropriate. In the Utstein style, neurological outcome may be reported using the Cerebral Performance Category (CPC) or modified Rankin Scale (mRS).^{138,139} However, while these variables provide a general sense of neurological status, they do not provide specific information on the quality of life that is experienced by OHCA survivors.

Measurement of long-term recovery in cardiac arrest patients

A systematic review from 2015 identified that 89% of randomised controlled trials of cardiac arrest did not evaluate recovery after hospital discharge, and none included the patient perspective in terms of Health-Related Quality of Life (HRQoL) or societal participation.¹⁴⁰ More recent clinical trials have included such measures, but these are still relatively rare.¹⁴¹ A recent survey found few registries in Europe included HRQoL measurements, despite collection of these data being encouraged in the update of the Utstein reporting framework for resuscitation registries.^{6,21,112}

In 2018 a Core Outcome Set for Cardiac Arrest (COSCA) was published to provide guidance for standardising outcome definition, recovery assessment tools, and time-points for clinical trials involving adults.^{141,142} More recently, further guidance for paediatric clinical trials (P-COSCA) has been published.^{142a} Both core outcome sets were based on extensive work to identify outcomes that are important from several perspectives including patients, families, health care professionals and researchers. The adult-COSCA recommends as a minimum assessment of survival at 30-days or hospital discharge, neurological function at 30 days or hospital discharge with the mRS, and assessment of HRQoL at 90 days (and later) with either the HUI-3 (Health Utilities Index version 3), SF-36 (Short-Form 36-item Health Survey) or EQ-5D-5L (EuroQoL 5 dimensions 5 Level version). Similarly, the P-COSCA also recommends the assessment of survival and neurological outcome, assessed with the Paediatric Cerebral Performance Category (PCPC). However, three further core components of HRQoL, or life impact, are specified: cognitive function, physical function and basic daily life skills, all to be assessed with the PEDSQL (Pediatric Quality of Life Inventory) at six-months (and later). A more widespread use of the COSCA recommendations can potentially improve knowledge of long-term outcomes for cardiac arrest survivors. A limitation of COSCA guidance is that they include only a minimum number of measurements, therefore it is recommended that symptom and condition-specific measures are also used, depending on the aim of the study.

Neurological outcome

Severe hypoxic-ischaemic brain injury is the most detrimental outcome for cardiac arrest survivors, commonly described by using ordinal hierarchical functional outcome scales such as Cerebral Performance Category scale (CPC), modified Rankin Scale (mRS) or the Glasgow Outcome Scale/Extended (GOS/GOSE). These scales are often simplified into a 'good' or 'poor' outcome by categorising patients as independent for basic activities of daily living versus dependent on others, in a vegetative state, or dead. A favourable neurological outcome is usually considered as a CPC 1 or 2, mRS 0 to 3 or GOS 4-5/GOSE 5-8.

In most European countries where Withdrawal of Life Sustaining Treatment (WLST) is routinely practiced, a poor neurological outcome

is seen in <10% of cardiac arrest survivors (Irish National Out-of-Hospital Cardiac Arrest Register 2018 available from <https://www.nuigalway.ie/ohcar/>).¹⁴³ In situations where WLST is not applied, severe hypoxic-ischaemic brain injury is substantially more common. For example, an Italian study reported more than 50% (n = 119) of survivors had a poor outcome six months post-event, with one third (n = 68) in a persistent vegetative state.¹⁴⁴

Among cardiac arrest survivors classified with a good outcome, the effects of hypoxic-ischaemic brain injury may impact on everyday life. The most frequently reported neurological sequela is neurocognitive impairment for all survivors in the early phase¹⁴⁵ and, in around 40-50%, in the long-term.^{146–150} Most improvement in cognition occurs during the first three months,^{151,152} but individual improvement has been reported up to one year post-event.¹⁵¹ In a Spanish study, half of survivors (n = 79) three years post-event had cognitive impairment.¹⁴⁶ Cognitive impairment in the chronic phase is mostly mild-to-moderate, but moderate-to-severe impairment is identified in 20-26% of survivors.^{148,150,153} Cognitive domains most often affected include: episodic/long-term memory;^{146,148–150,153} attention/processing speed,^{146,148,149,153} and executive functions.^{146,149,150,152,153} Impairments in other domains have also been reported.^{147,153}

There are currently few studies covering the neurological outcome for paediatric cardiac arrest survivors in Europe. The most comprehensive data comes from a team in the Netherlands that performed a neuropsychological examination on a sample of 41 paediatric cardiac arrest survivors (age 0–18) at two to eleven years after cardiac arrest.¹⁵⁴ At a group level general intelligence was lower compared with normal means, and domains of memory and divided attention were especially affected.¹⁵⁴ Teachers (n = 15) of the cardiac arrest survivors reported planning/organisation problems, while parents (n = 31) and patients (n = 8) did not report dysexecutive problems.¹⁵⁴ The same authors also report significantly worse attention problems among these paediatric cardiac arrest survivors,¹⁵⁵ and 15% were in need of special education.¹⁵⁶

Patient-reported outcomes

There is no specific Patient-reported outcome measures (PROM) for cardiac arrest.¹⁵⁷ Patient-reported outcomes of overall generic HRQoL indicate that cardiac arrest survivors – at a group level – do not differ from the general population.^{158,159} Despite this, detailed analyses showed that several HRQoL sub-domains are poorer in cardiac arrest survivors, and symptom-specific questionnaires reveal that nuanced cardiac, cognitive, physical and emotional problems are common.^{147,160,161} In a Swiss study, only 29% of cardiac arrest survivors (n = 50) reported no complaints,¹⁵³ while in another study almost 43% of survivors (n = 442) at 6 months post-arrest reported their health as worse than one year ago.¹⁶² It is of note that HRQoL has been reported to continue to improve for at least the first year after cardiac arrest.¹⁵⁹

The most prevalent patient-reported symptom after cardiac arrest is fatigue, reported by 50–71% of survivors.^{153,159,161} Many survivors also report cognitive problems including a perception of “slowing” or problems with attention or memory.^{153,163,164} Associations between self-reported cognitive complaints and objective cognitive performance-based measures have been mixed.^{152,153}

Another frequently patient-reported outcome is emotional problems, which tend to be most severe in the first weeks post-arrest,^{159,165,166} and associated with worse HRQoL.¹⁶⁷ After three months, emotional status was reported by different studies to be stable,¹⁵⁹ better,¹⁶⁸ or worse¹⁵¹ compared with twelve months

post-arrest. Emotional problems were more common in females,^{168–170} younger patients,^{162,164,168,170} those with cognitive problem,¹⁷⁰ and those with comorbidities.¹⁶⁸

Cardiac arrest survivors with hypoxic-ischaemic brain injury also have an increased risk of emotional problems,¹⁷¹ but as these patients are often missing from analyses, the frequency of emotional problems in cardiac arrest survivors may be underestimated.¹⁷⁰ Larger studies in this area (>100 patients) using symptom-specific questionnaires report anxiety in 15–24% and/or depression in 13–15% in the long-term.^{159,164,169,170} Symptoms of stress and post-traumatic stress disorder (PTSD) are less well studied but identified in 16–28% of survivors.^{159,166,172,173} In one study, half of survivors reported a change in behaviour and emotion six months post-cardiac arrest (n=50).¹⁵³ Apathy, lack of drive and motivation were also reported in 70% of patients participating in a cognitive rehabilitation program after cardiac arrest (n=38), although this finding was more closely associated with cognitive impairment than depression.¹⁷⁴

Relatives of cardiac arrest patients are also at significant risk of emotional problems.^{175–177} One study from Switzerland found that 40% of relatives suffered from PTSD.¹⁷⁷ Female gender, history of depression and perception of insufficient therapeutic measures in the ICU increased the risk for PTSD, while the patient's outcome, including mortality, had no association.¹⁷⁷ Being a witness to a relation's cardiac arrest increased the risk for emotional problems,¹⁷⁶ and cognitive impairment in the survivor was associated with increased caregiver strain.^{175,178}

Physical problems after cardiac arrest have received limited attention but results from HRQoL measurement show that many cardiac arrest survivors report physical problems.^{158,162,175,179} Half of cardiac arrest survivors described problems working or performing other activities because of physical problems,¹⁶² and 30–50% reported problems with physical health,¹⁷⁵ physical function,¹⁶² or mobility.^{159,161,169} Physical problems are more common in older survivors^{162,175} and females.¹⁶²

Patient/parent reported outcomes in paediatric cardiac arrest survivors are rare. One study (n=57) reported that the majority of paediatric survivors (2–11 years post-ICU) have no problems, while 30% reported physical problems, and 34% reported chronic symptoms such as fatigue, headache and behavioural problems.¹⁵⁶ Children (n=8) reported a HRQoL comparable to normal means, while proxy-reported HRQoL by a parent (n=45) indicated lower generic HRQoL and more physical problems. The parents own HRQoL was however better than that of the general population.¹⁵⁶

Ability to return to previous activities and roles (societal participation)

In a Finnish study the vast majority (>90%) of cardiac arrest survivors were able to live at home and most survivors were able to return to previous roles and high levels of participation in society.¹⁶⁴ For those of working age, 60–76% returned to at least some degree of work at six to twelve months post-arrest.^{158,161,164,167,180} However, 47–74% of cardiac arrest survivors report restricted societal participation,^{147,161} and many remain on sick leave,^{146,159,161,164,181} although the amount of sick leave varies across European countries.¹⁶¹ Feelings of less satisfaction with family and leisure time,¹⁴⁷ and problems performing usual activities are also reported.^{150,162,169} One study reported that driving ability was significantly lower than before the cardiac arrest,¹⁴⁶ while others reported only 12–27% unable to

resume driving.^{153,164} However, many patients with cognitive impairment were still driving,¹⁴⁶ and one quarter reported that they did not recall being informed not to drive during a period after the cardiac arrest.¹⁶⁴

In a European multi-centre trial (n=270), predictors for decreased societal participation were depression, self-reported mobility problems, cognitive impairment and fatigue.¹⁶¹ Another study from the Netherlands (n=110) reported only pre-morbid function as a predictor for societal participation.¹⁶⁷ Cognitive impairment increases the risk for not being able to return to work.^{146,151,161} Predictors positively associated with return to work were male gender,¹⁸⁰ younger age,^{180,181} a higher level job, bystander-witnessed cardiac arrest with bystander CPR¹⁸⁰ or cardiac arrest that occurred at the workplace.¹⁸¹

Several observational and cohort studies have included detailed measures of recovery, but previous systematic reviews in this area describe limitations that risk bias in the reported results including: small and/or heterogeneous study samples; many missing data; differences in assessment types and time-points used.^{147,182–184} Logistical and ethical challenges with collecting detailed information beyond hospital discharge remains a critical issue for long-term recovery reporting.¹⁴¹

Rehabilitation

Planning for rehabilitation after cardiac arrest requires estimation of numbers and appreciation of the changing needs of survivors.¹⁴⁵ Rehabilitation interventions for cardiac arrest survivors are often provided within programs that include other patient groups e.g. myocardial infarction or other types of acquired brain injury, e.g. traumatic brain injury (TBI).^{185,186} Studies describing such interventions may include few cardiac arrest survivors within mixed samples, meaning the specific rehabilitation outcome for cardiac arrest patients is difficult to separate. This overview of the rehabilitation programmes in Europe therefore includes only studies specifically describing interventions for cardiac arrest survivors.

Survivors with 'poor' neurological outcome suffer profound and life-changing problems. In an Italian study, rehabilitation was provided by an interdisciplinary team for 180 min per day.¹⁸⁶ After a mean of 78 days (SD 55), 45% of patients with anoxic brain injury were able to return home. While anoxic patients had poorer recovery than other groups, they also had worse baseline cognitive impairment and functioning. A similar individualised, multidisciplinary approach was provided in a Turkish rehabilitation hospital.¹⁸⁵ This study found that when anoxic brain injured patients had similar baseline function to TBI patients, improvement rate was still slower, but the difference in rehabilitation outcome was not statistically significant. French researchers described a therapeutic intervention for institutionalised patients (n=27) with anoxic brain injury (average 8 years since event).¹⁸⁷ The intervention consisted of medication, psychotherapy, support group, and therapeutic activities provided over six months, and improved quality of life and social participation.

The rehabilitative outcome for cardiac arrest survivors with prolonged disorders of consciousness is poor although some may improve, albeit rarely. A Dutch study estimated that over 50% of patients with vegetative/unresponsive wakefulness syndrome (most because of hypoxia during cardiac arrest) received no rehabilitation services.¹⁸⁸ In Germany, in-patient rehabilitation was provided to 113 cardiac arrest survivors with disorders of consciousness.¹⁸⁹ Most improvement was observed within the first eight weeks. A minority (6.2%) of the patients achieved a good functional outcome while

80.5% remained in a persistent unresponsive state. In another German study, early neurological rehabilitation of 300 min of daily therapy (e.g. physiotherapy, occupational therapy, speech/swallowing therapy and specialised nursing care) was provided to 93 survivors with hypoxic-ischaemic encephalopathy (mostly caused by cardiac arrest).¹⁹⁰ After a mean of 46.4 (SD68.2) days, 24.7% were discharged with a good outcome, but in common with the previous study, 82.1% of those comatose at admission remained comatose. Finally, an Italian study, reported that even patients with improved consciousness remained severely neurological impaired at two years follow-up.¹⁹¹

For patients with 'good' neurological outcome the need for rehabilitation may not be recognised during the acute hospital stay.²⁷ A Swedish survey showed that in 59 out of 74 hospitals, the most common follow-up was a patient visit to a cardiac reception unit (n = 42, 70%), with neurological and psychological support not often provided in a structured format. There were also major variations in follow-up.¹⁹² In the 2015 European Resuscitation Guidelines on post-resuscitation care structured follow-up to screen for potential cognitive and emotional problems is recommended to identify those individuals in need of further support and rehabilitation.²⁷ National guidelines have been developed in e.g. Sweden.¹⁹³

The effects of follow-up and screening were described by Moulart and colleagues in a randomised-controlled trial (n = 185).^{194–198} The intervention was performed by a trained nurse at an outpatient clinic or the patient's home and included screening for cognitive and emotional problems, provision of information and support, promotion of self-management strategies and referral to further specialised care if indicated. The first one-hour session was provided soon after discharge, with shorter follow-up sessions offered. Patients who received this intervention had better mental HRQoL one year after arrest and an earlier return to work compared with the control group. The intervention was also found to be cost-effective.¹⁹⁴

The Essex Cardiothoracic Centre in the United Kingdom describes a similar follow-up intervention including systematic psychological, cognitive and specialised medical support for survivors and their carers for the first six months post-arrest.¹⁶⁶ Before hospital discharge, patients (n = 21) were assessed by an ICU nurse and cardiologist and provided with written and video information, and social media links. A multidisciplinary appointment was provided at eight weeks, and follow-up appointments at six and twelve months. Of the patients included, 26% needed further psychological support. Overall health improved during follow-up, but no control group was included to evaluate the effect of the intervention.

A single centre in the Netherlands provides an integrated rehabilitation pathway for restoration of exercise capacity and optimal cognitive functioning.¹⁹⁹ All cardiac arrest patients eligible for rehabilitation were screened for cognitive and emotional problems approximately one month after cardiac arrest. Patients without cognitive impairment followed cardiac rehabilitation programs 'as usual', while patients with cognitive impairments followed the cardiac rehabilitation in smaller groups. After cardiac rehabilitation, a continued program with cognitive rehabilitation was offered. The program was not evaluated, but of 77 cardiac arrest survivors referred for cardiac rehabilitation, 23% had cognitive problems.²⁰⁰

There is currently no comprehensive evaluation of the types or numbers of rehabilitation interventions and programmes available to cardiac arrest survivors across Europe, and there is limited evidence of effect. This may be because there are few programmes, but it may

also reflect a need for more comprehensive reporting on interventions. Finally, some studies group cardiac arrest survivors with other cardiac or brain-injured patients for rehabilitation, meaning that unless the inclusion of cardiac arrest patients is explicitly stated, the types and frequency of rehabilitation available to cardiac arrest survivors may be underestimated. It is also of note that no paediatric rehabilitation studies were identified.

Genomic variations and sudden cardiac arrest

One of the major opportunities to further reduce mortality from sudden cardiac arrest lies with individual prevention (www.escape-net.eu).²⁰¹ This requires public education and early recognition of individual patients and families at increased risk for sudden cardiac arrest. At an individual level, genomic risk factors are most probably important²⁰² but understanding of their relevance is limited (www.escape-net.eu).²⁰³ However, in cases of unexplained cardiac arrest, genomic testing may result in more than 60% diagnostic yield of pathological genomic variations.²⁰⁴ Unfortunately, with the exception of selected cases in families with Brugada and long-QT syndrome (LQTS),²⁰⁵ individuals are most often not aware of their genomic disposition because of the relative lack of cardiogenetic screening.^{206,207}

Population-based systematic studies suggest a strong genetic component to cardiac arrest in general^{202,208} and of autopsy-negative, unexplained cardiac arrest in particular.^{209–213} An individually unique pathophysiological interaction of environmental (smoking, social stress, air pollution, chronic noise exposure, etc.) acquired (obesity, hypertension, diabetes, myocardial ischaemia and myocardial infarction, Takutsubo syndrome, medication used, etc.^{214–216} and genomic factors (Brugada syndrome, LQTS, arrhythmogenic right ventricular cardiomyopathy (ARVC), catecholaminergic polymorphic ventricular tachycardia, short QT syndrome, etc.^{205–207,217–227}) and their combinations²²⁸ determine the individual risk of sudden cardiac arrest. Moreover, genetic susceptibility to long-term alcohol effects, drug- and drug-drug interactions induced sudden cardiac arrest i.e. pharmacogenetics may be relevant at an individual level (www.escape-net.eu).^{229–232}

Research in recent years has most specifically focused on patients and families with rare inherited arrhythmia syndromes and episodes that are associated with an increased risk of cardiac arrest. Several molecules and mechanisms that control cardiac electrophysiology have been identified.^{205–207,233,234} Most genes and their variants discovered thus far are involved in regulating electrophysiology and putting the heart at a higher risk for VF.^{202,235–237} Specific genetic predispositions leading to cardiac arrest most often affect younger patients (e.g. Brugada syndrome; Long QT Syndrome). In older patients, genetic predisposition may interact with acquired and accumulated risk factors, medication, social stress and specific diseases.^{238,239} Different levels of risk will also be associated with different genetic variations. For example, Long-QT Syndrome can result from genetic variations in at least 12 different genes causing mutations that give rise to different degrees of negative QT prolongation which are subsequently associated with varying risk of cardiac arrhythmias.^{206,217} In addition to the primary gene variant, modifier genes may also determine disease severity.²⁴⁰ Gender disparities in genetic risk factors have also been proposed. Data suggest that women are at higher risk for QT prolongation.^{216,241} Females may also have lower expression levels of genes controlling repolarisation.²⁴² In contrast, males are at higher risk for Brugada

syndrome, arrhythmia syndromes that are associated with reduced depolarisation of myocytes, and medication-induced conditions that are associated with a reduced depolarisation reserve.²⁴³ Other data suggest that male gender may have lower expression levels of genes controlling depolarisation.²⁴⁴

Typically, genetic studies have focused on rare gene variants in highly selected populations. However, Milano et al. were the first to demonstrate that genetic mutations are associated with increased risk of sudden cardiac arrest in the general population.²³⁶ Huge amounts of DNA samples in cardiac arrest patients and their further individual risk factors and portfolios are needed to allow further insights into sudden cardiac arrest genomic risk stratification, arrhythmia development and individualised prevention as well as treatment strategies.

Current recommendations following the occurrence of sudden cardiac arrest include screening for genetic disorders in first-degree family members. Screening may identify relatives who might benefit from lifestyle modification and avoidance of certain drugs. Some relatives may benefit from medical therapy and implantation of cardiac defibrillators may be appropriate in a selected group of patients and family members.²¹⁰ Family screening is particularly recommended if the cardiac arrest was exercise-induced,²⁴⁵ occurred at a younger age; occurred in a young athlete with Long-QT Syndrome;²⁴⁶ and/or was associated with a positive family history of sudden cardiac arrest.^{203,204,209,223,247–257}

It is expected that the clinical role of genetic and epigenetic factors will be increasingly understood as research in this area continues to grow. There are currently no specific resuscitation recommendations for patients with known genomic predispositions. There are some instances where genotype-driven resuscitation strategies may theoretically be appropriate e.g., in patients with Brugada syndrome or similar conditions that are associated with reduced depolarisation, the use of amiodarone or lidocaine may facilitate the occurrence of asystole. However, there are no systematic studies that support such treatment.

Conflict of interest

JTG declared speakers honorarium from Weinmann, Fresenius, Ratiopharm, Zoll; he is Scientific Advisor for Zoll Temperature management.

BB declared speakers honorarium from Baxalta, BayerVital, BoehringerIngelheim, ZOLL, FomF, Bard, Stemple, NovartisPharma.

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